

SHORT REPORT

Inflammatory bowel disease and coronary artery disease

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Abstract Chronic inflammation with the presence of excess serum acute-phase proteins, cytokines and cell adhesion molecules is increasingly being implicated in atherosclerosis. The association between inflammatory bowel disease (IBD) and coronary artery disease (CAD) is unstudied. This is a preliminary, thesis-generating cross-sectional study aimed at evaluating the presence of traditional atherosclerotic risk factors in patients with IBD and CAD compared with the control population. The medical records of 42 consecutive IBD patients with CAD from 1999 to 2005 (27 men) were reviewed for the Framingham risk factors. The Framingham risk score (FRS) is calculated based on age, sex, hypertension, diabetes and hyperlipidemia. FRS of patients with IBD and CAD was compared with the FRS of 137 age- and sex-matched (102 men) consecutive patients with CAD (controls). When the Framingham risk score adjusted for group and gender with age as a covariate, the adjusted total FRS score was higher in patients with CAD alone (10.0 [3.75]) as compared to those with IBD and CAD: (8.1 [3.47]; $p = 0.001$). FRS is lower in cases (patients with IBD and CAD) when compared with the controls (CAD alone).

Keywords Framingham Heart Study · Multivariate models · Pathogenesis of atherosclerosis

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Introduction

Premature and accelerated development of atherosclerotic heart disease has been well studied in diseases with chronic inflammation like diabetes mellitus (DM), systemic lupus erythematosus, end-stage renal disease, rheumatoid arthritis, anti-phospholipid antibody syndrome, systemic sclerosis and gingivitis.^{1–4} Chronic inflammation may act independently or synergistically with traditional atherosclerotic risk factors in the pathogenesis of atherosclerosis. The association between the diffuse systemic inflammation of inflammatory bowel disease (IBD) and coronary artery disease (CAD) is unstudied.

Recurrent flares of ongoing activation of intestinal mucosal inflammation leads to presence of excess pro-inflammatory cytokines and serum soluble adhesion molecules in IBD.⁵ The possibility of IBD being atherogenic through chronic activation of the immune system forms the hypothesis of this study.

Methods

The Framingham Heart Study with multivariate models forms a basis for CAD risk detection and prevention programs.⁶ The Framingham risk score (FRS) is calculated based on the presence of risk factors: age, hypertension (HT), DM, tobacco use, total cholesterol and high-density lipoproteins or hyperlipidemia (HDL) values. Points are assigned for values of all these factors and the 10-year risk for CAD is calculated.^{6,7} Total score is used to categorize patients as having low (<10%), intermediate (10–20%) or high (>20%) 10-year CAD risk.⁶

The medical records of 127 consecutive patients with documented IBD and CAD discharged from Aultman Hospital between 1999 and 2005 were reviewed for age, HT, DM, smoking status, total cholesterol and HDL values. The diagnosis of IBD and CAD was confirmed after reviewing admission notes, consultation notes (gastrointestinal and cardiology), and diagnostic studies including endoscopy, pathology and cardiac catheterization reports. Patients with incomplete data were excluded. Records of 137 age- and gender-matched consecutive patients (controls) with diag-

nosis of CAD were also reviewed for FRS. The FRS system is available online at <http://www.nhlbi.nih.gov/about/framingham/riskabs.html>.

The study has a power of 39% to yield a statistically significant result. The sample size would need to be increased to 195 per group to have a power of 80% to yield a significant result. SYSTAT® 11 (Richmond, CA) was used for statistical analysis. Values are expressed as means (SD). The two groups were compared using Student's *t*-test. The effects of age and gender on FRS were controlled using analysis of covariance (ANCOVA). The alpha level was set at 0.05. Categorical variables were compared using chi-square (χ^2) analysis and continuous variables using Student's *t*-test.

The Aultman Health Foundation Human Research Review Board approved this study

Results

The FRS was calculated for the study population (IBD+CAD) and the control population (CAD alone). The study population included 27 men and 15 women with complete laboratory data and confirmed IBD and CAD diagnosis. Crohn's disease was present in 27 patients and ulcerative colitis in the remaining 15. Consecutive patients with

CAD alone (102 males and 35 females) were age and gender matched to the IBD+CAD group and studied as controls.

Table 1 summarizes the Framingham risk information for the two groups. IBD activity index, body mass index (BMI) and C-reactive protein (CRP) were not recorded and are not included in the analysis. The FRS for presence of DM is scored higher in females than males. There was no statistically significant difference in proportion of females between study population and controls, which could have influenced the final risk score ($p=0.062$). However, there was an excess of males in the CAD population, which was unintended.

The two groups did not differ with respect to age ($p=0.616$), total cholesterol ($p=0.557$). However, proportion of patients with DM ($p=0.958$) or HT ($p=0.573$), and smoking status ($p=0.211$). HDL concentration was higher in the study group ($p<0.001$). There was no significant difference in the treatment for CAD between the two groups ($p=0.995$).

There was no difference in the unadjusted FRS between the two groups. When the risk score was adjusted for the group and gender with age as a covariate, there was the adjusted FRS was higher in controls ($p=0.002$).

Table 1 Comparison of various parameters in patients with inflammatory bowel disease and coronary artery disease and controls with coronary artery disease alone

	IBD+CAD	CAD	Pearson χ^2	<i>p</i> -value
Total (<i>n</i>)	42*	137		
Age (years)	56.21 (9.52)	57.15 (10.91)		0.616
Gender (M/F)	17/25	35/102	3.476	0.062
Diabetes mellitus	13/42	43/137	0.003	0.958
Hypertension	21/41	77/137	0.317	0.573
Cholesterol (mg/dL)	182.33 (47.22)	187.69 (52.87)		0.557
HDL (mg/dL)	47.17 (18.23)	37.81 (10.25)		<0.001
Smoking status				
Current	17	54	3.109	0.211
Former	13	27		
Never	12	56		
Treatment received for CAD				
CABG	10	33	0.011	0.995
Medical therapy	12	40		
PTCA	20	64		
Unadjusted Framingham total risk score (Student's <i>t</i> -test)	7.43 (4.93)	8.7 (4.18)		0.100
Adjusted Framingham total risk score (ANCOVA)	8.1 (3.47)	10.0 (3.75)		0.002

Values are as mean (SD). *27 Crohn's disease and 15 ulcerative colitis.

CABG Coronary artery bypass graft; PTCA Percutaneous transluminal coronary angioplasty.

Discussion

Approximately 20% of CAD occurs in the absence of traditional risk factors, such as smoking, HTN, DM and hypercholesterolemia.⁷ Pro-inflammatory cytokines promote atherosclerosis-related inflammation, alter lipid metabolism, and contribute to plaque instability and rupture. This formed the hypothesis for our preliminary, thesis-generating study aimed at identifying the traditional atherosclerotic risk factors in patients with IBD and CAD.

FRS score based on traditional atherosclerotic risk factors was lower in patients with IBD compared with the general population raising the possibility of IBD being atherogenic through chronic activation of the immune system and inflammation. Inflammatory cytokines especially IL-6 inhibits lipoprotein lipase (LPL) enzyme activity leading to atherogenic lipid profiles consisting of elevated levels of very low-density lipoproteins (VLDL), triglycerides and low levels of HDL in patients with SLE.⁴ Interestingly with small study numbers, we could not replicate a similar lipid profile in IBD.

Our results should be interpreted in light of some potential limitations. The study is a cross-sectional review of the clinical information recorded in the patient's medical records. Conditions not recorded in the medical records would have been missed. Also the cross-sectional design does not permit an estimate of lifelong inflammatory burden, and hence, the influence of confounding factors like use of corticosteroids, IBD activity, malnutrition, BMI and CRP could not be completely evaluated.

Morbidity and mortality studies in patients with primary diagnosis of IBD revealed shock, volume depletion, protein calorie malnutrition and anemia as the most frequent comorbid conditions.⁸ Surgical interventions resulting in septicemia and peritonitis are the systemic complications associated with death.⁸ However, patients with secondary diagnosis of IBD were excluded from this study.

Understanding the mechanisms and mediators of endothelial dysregulation and inflammation will yield new targets to predict, prevent and treat CAD.³ Clinical trial using humanized monoclonal antibodies against IL-6 has shown promise in Crohn's disease.⁹ Similarly, the anti-TNF antibody (infliximab) therapy decreased the levels of acute-phase proteins and resulted in clinical improvement.¹⁰

Prospective cohort studies are needed to study the incidence of CAD in patients with IBD. Studies similar to The

Prevention of Accelerated Atherosclerosis in SLE (PASS) are required to evaluate the role of IBD, exposure to anti-inflammatory medications in the clinically relevant endpoints of CAD. In addition to prospective management of traditional atherosclerotic risk factors, aggressive control of IBD activity is recommended, as chronic inflammation is a driving force for premature atherosclerosis.

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