Celiac Disease and Coronary Artery Disease: Is There an Association? A Pilot Study

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A. Introduction/Background

Celiac disease (celiac sprue) is a malabsorptive syndrome that results from gluten dependent inflammation of the small bowel. Although the disease is typically characterized by diarrhea, flatulence and weight loss, more subtle symptoms such as non-specific bloating and malaise can be characteristic. Subgroups of patients can present with iron deficiency alone. A variety of pathological entities are associated with celiac disease. Folate, iron, vitamin K and vitamin D deficiencies are often present and can be explained by the malabsorptive process itself. Other conditions such as peripheral neuropathy, cerebellar ataxia and dermatitis herpetiformis are also associated but the pathogenesis is not as well understood. Autoimmune diseases including type 1 diabetes mellitus and autoimmune thyroiditis are also seen with increased frequency in patients with celiac sprue.

Much work has been done on the epidemiology of celiac disease. Although commonly thought of as a pediatric disease, the condition often first presents in adulthood. Many earlier studies underestimated the frequency of celiac disease because only cases with typical presenting symptoms were identified. However, with an increased awareness that celiac disease can present with much more subtle and varied symptoms, more cases are being recognized. Coupled with new serologic tests including antigliadin and antiendomysial antibodies, the prevalence has been found to range from 1:100 to 1:600 (1).

The pathogenesis of celiac disease involves an autoimmune reaction triggered by the ingestion of gluten (2). This phenomenon typically occurs in susceptible patients who possess the HLA-DQ2 cell surface antigen. Gluten derived gliaden proteins are expressed in conjunction with these antigens to T cells in the lamina propria of the small bowel. Tissue transglutaminase facilitates this process by deaminating gliadin peptides, thus evoking a stronger T-cell response. A localized inflammatory state ensues characterized by the generation of various cytokines. Tissue transglutaminase also acts as an autoanitgen itself, inducing the formation of autoantibodies that perpetuate the inflammatory response.

B. Hypothesis/Rationale

As previously mentioned, celiac disease has been found to be associated with a variety of autoimmune diseases such as type 1 diabetes mellitus and autoimmune thyroiditis. Although not as well documented, celiac disease has also been seen with increased frequency in certain cardiac conditions including idiopathic cardiomyopathy and heart block. A recent article in the Lancet examined 52 patients with idiopathic cardiomyopathy and found an increased incidence of celiac disease compared with normal controls (3). The diagnosis of sprue was based on both antibody studies and small bowel biopsy. A case report recently published in the American Journal of Gastroenterology described a celiac patient with dilated cardiomyopathy and complete heart block (4). It has been postulated that in celiac disease, gluten ingestion can trigger an immune response against autoantigens in cardiac tissue resulting in myocarditis and conduction disturbances.

Given the above information, the question is raised as to whether or not there may be an association between celiac disease and coronary artery disease. There is very little information in the literature concerning such an association. A study published in the Lancet in 1976 showed that patients with sprue actually had a lower mortality from coronary artery disease than the normal population (5). However, a repeat study published in Gastroenterology in 1989 showed no difference in mortality from atherosclerosis in celiac patients compared with the general population (6). The authors postulated that the decrease in mortality cited in the earlier study could be explained by the greatly increased proportion

of deaths due to malignant disease. There have been no studies examining the prevalence of coronary artery disease in patients with celiac sprue.

Based on the understanding of the pathogenesis of sprue, it is certainly plausible that gluten may trigger an immune response against coronary endothelial tissue. Atherosclerosis is seen in other autoimmune diseases including SLE and represents a significant cause of morbidity and mortality. A recent article in Trends in Immunology described antibody and cell mediated reactions against heat shock proteins in coronary endothelial cells triggered by homologous proteins in bacterial pathogens (7). Such autoimmune reactions are believed to play are large role in early atherogenesis. Supporting a possible association between celiac disease and coronary artery disease is the fact that tissue transglutaminases, which are involved in the pathogenesis of celiac disease, have been implicated in the development of atherosclerosis (8). These proteins are present in coronary endothelial cells and normally function to cross link fibronectin and facilitate cell matrix assembly. Increased transglutaminase activity and it's cross linked products have been noted in atherosclerotic plaques. Perhaps transglutaminase, in a similar manner to its role in the pathogenesis of celiac disease, also functions as an auto antigen that triggers inflammation in the coronary endothelium.

Finding an association between coronary artery disease and celiac disease would be important. If gluten in fact plays a role in the pathogenesis of atherosclerosis, the initiation of a gluten free diet might contribute to the regression of disease. As coronary artery disease is a leading cause of morbidity and mortality and rates of celiac disease have been shown to be as high as 1:100 in certain populations, the number of people that could be aided by initiation of a gluten free diet would be significant.

C. Methods

a. StudyVariables

The prevalence of celiac disease will be determined in patients with coronary artery disease versus normal controls. Measurement of antiendomysial antibodies, which have been shown to have a high sensitivity, will be used to screen patients for celiac disease. Patients with positive antibody studies will undergo small bowel biopsy to confirm the results. Presence of coronary artery disease will be defined by patients with a chest pain syndrome and evidence of atherosclerotic disease on exercise or adenosine thallium scanning.

b. Study Design

There will be two arms in this cross-sectional study. Arm 1, the control group, will consist of patients recruited from the AIM clinic. These patients will have no chest pain syndrome and will undergo (or will have already undergone) thallium scanning to exclude the presence of atherosclerotic disease. They will also be tested for antiendomysial antibodies and will undergo small bowel biopsy if antibody tests are positive. Thus the prevalence of Celiac Disease will be determined in patients who have been shown not to have underlying coronary artery disease.

Arm 2 will consist of patients also recruited from the AIM clinic. These patients will have known chest pain syndromes and have evidence of coronary artery disease on thallium scanning. Patients with chest pain syndromes but negative thallium testing will be excluded from the study. Arm 2 patients will also be tested for antiendomysial antibodies and will undergo small bowel biopsy if antibody tests are positive. Thus, the prevalence of celiac disease will be determined in patients with known coronary artery disease.

c. Statistical Analysis

Chi-squared testing will be used to analyze the categorical data sets, namely the presence or absence of celiac disease and the presence or absence of coronary artery disease. An odds ratio will be generated comparing the prevalence of celiac disease in patients with coronary artery disease versus the prevalence of patients without coronary artery disease.

d. Sample Size

The prevalence of celiac disease in the general population has been estimated to range from 1:100 to 1:600. The recent study in the Lancet already cited above ("Prevalence of Celiac Disease in Idiopathic Dilated Cardiomyopathy") used a baseline prevalence of 1.79 per 1000 (0.179%) for statistical analysis. This number is based on a study conducted by Corazza and colleagues in which the prevalence of CD was determined in 2237 adult patients between the ages of 20 and 87 (9). Assuming that the AIM clinic population has a similar prevalence of celiac disease, a value of 1:50 (2%) in the coronary artery disease population will be considered significant and will be used for power calculations. Thus, for 80% power, testing at P=0.05, 614 patients will be required in both arms of the study. If the AIM clinic population carries a different rate of celiac disease, than a prevalence ten times higher in the coronary artery disease population will be considered significant. Although the choice of these values is somewhat arbitrary, given the high rates of both coronary artery disease and celiac disease, a 10 fold increase in prevalence would represent a significant patient population. If an association is indeed found, this may justify screening all future patients with coronary artery disease for antiendomysial antibodies.

e. Subjects Selection

Patients in arm 1 and arm 2 will be recruited from the AIM clinic. Recruitment will occur by both reviewing charts of already established patients and by recruiting new patients who meet criteria and are seen in the AIM clinic for the first time. Patients will range from 40 to 60 years of age as patients younger than 40 will have low rates of coronary artery disease. Recruiting patients from the same clinic population will ensure that racial differences between both arms of the study are relatively matched. As previously mentioned, patients in arm 1 will be included in the study only if they have no evidence of coronary artery disease on thallium scanning. Patients in arm 2 will be included if thallium scanning demonstrates evidence of coronary artery disease.

Importantly, as some studies have demonstrated lower cholesterol levels in celiac patients compared with the general population (secondary to malabsorption), patients will be tested for hyperlipidemia. Patients with high LDL levels (i.e. greater than 160 mg/dl) will be excluded from the study. This will ensure that a greater proportion of celiac patients are included in the investigation. In addition, as hyperlipidemia plays an important role in the pathogenesis of coronary artery disease, a possible confounding variable will be eliminated from the study.

As previously mentioned, testing for celiac disease will be based on antibody studies and on confirmatory small bowel biopsy when antibody testing is positive. Informed consent will be obtained prior to enrollment in the study and prior to any test or procedure. Given the imperfect specificity of thallium scanning, patients in arm 1 who test positive will be excluded from the study and referred to cardiology for possible cardiac catheterization.

D. Study Drugs

There will be no study drugs used in this investigation

E. Study Device

There will be no study devices used solely for the purpose of this investigation.

F. Study Questionnaires

There will be no study questionnaire used in this investigation.

G. Confidentiality

All data in this study will be confidential and will only be available to patients and their health care providers.

H. Location of Study

Patients will be recruited from the AIM clinic at Columbia-Presbyterian Medical Center.

I. Risks and Benefit

Baseline risks for upper endoscopy and small bowel biopsy will apply to applicable patients. Benefits may include the new diagnosis of celiac disease in previously undiagnosed patients.

J. Alternative Therapies

This investigation does not include the use of experimental therapies.

K. Compensation and Cost

Patients will incur no additional cost by participating in the study. There will be no compensation offered.

L. Minors as Research Subject

No minors will participate in this investigation.

M. Radiation and Radioactive Substance

Patients will not be exposed to any additional radiation beyond that of routine testing in the hospital.

N. Potential Difficulties

There are a number of potential problems in the above outlined study design. Importantly, the coronary artery disease population will likely have different characteristics than the controls. Prevalence of co morbid conditions including diabetes, hypertension and tobacco use will likely be higher than in the control group. It is unclear as to whether or not any of these concurrent conditions may affect the prevalence of celiac disease in the study. If an association between celiac disease and the coronary artery disease population is indeed found, further studies will need to be undertaken in order to elucidate which specific variables are related to the increased prevalence of celiac sprue.

O. References

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