Risk of Coronary Artery Disease in Celiac Disease Patients

1. Study Purpose and Rationale

Celiac disease (CD) is an inflammatory, autoimmune disorder triggered by gluten intolerance, a protein found in wheat. It classically presents as a malabsorptive enteropathy, although recently has been found to present subclinically as anemia, osteoporosis, hypolipidemia, or other laboratory abnormalities. CD is currently under-diagnosed and has an estimated prevalence in the US of approximately 1%, although this is higher in other countries. Treatment and remission of CD require patients to switch to a gluten-free diet (GFD).

The risk of coronary artery disease (CAD) in patients with CD compared to the general population is unclear. It has been observed that CD patients often have hypolipidemia, which may be protective against CAD. However, CD patients tend to also have lower HDL levels as the intestine is a major producer of HDL and apo-A1, with relatively higher LDL:HDL ratios. Additionally, CD is an inflammatory process, which could also increase the risk of thrombosis in general. Previous studies are conflicted in their results, with conclusions ranging from decreased to increased risk of CAD, while some studies indicate no significant difference.

Whorwell PJ et al 1976 was a study that looked at cause of death in 77 members of the Coeliac Society for England and Wale and found a significant decrease in death from ischemic heart disease in men and non-significant decrease in women, overall 40% reduction.

Peters U et al. 2003 looked at the cause of death for 10,032 Swedish hospitalized patients with CD and found a 60% increase in mortality risk for cardiovascular diseases.

West et al. 2004 studied 3790 patients with CD from the UK's general practice research database and found decreased rates of hypertension and hypercholesterolemia, but similar rates of myocardial infarction, HR 0.85, 95% CI 0.63 to 1.13.

Ludvigsson JF et al 2007 was a Swedish national hospital based study looking at 13,358 CD patients, which found increased MI (HR 1.27, 95% CI 1.09 to 1.48) and angina pectoris (1.46, 1.25 to 1.70).

This is a retrospective study that will examine the risk of CAD in patients with CD based on their Framingham risk score, as measured by myocardial infarction (MI) or death from CAD. Previous studies have not look at CAD incidence using Framingham risk scores, nor did they account for the effect of a GFD, which may have confounded previous results. It is our hypothesis that patients with CD on a GFD will be at baseline risk for CAD, whereas patients with CD not on a GFD will be at increased risk.

2. Methods:

Study Design:
The primary outcome that will be measured is rates of CAD events, either MI or death from cardiac ischemia. Additional outcomes include rate of events before and after GFD. Expected rates of CAD events, ie: short term cardiovascular risk for 10 years, will be estimated by the patient's Framingham risk score, which includes age, sex, total cholesterol, HDL cholesterol, tobacco use, systolic blood pressure, treatment for HTN.

This will be a retrospective study using a cohort obtained from clinic patients diagnosed with biopsy proven CD. Patients' historical Framingham risk scores (for 10 year risk) will be calculated and the expected rate of cardiac events will be compared to the actual rate of cardiac events, as measured by subject self-recall during a telephone interview. Patients will be stratified according to their adherence to a GFD, defined as having a GFD throughout the 10 years with resolution of presenting CD symptoms/laboratory abnormalities.

Statistical Analysis
Baseline demographics will be analyzed in a sex specific manner, using chi-sqaure and t tests. The overall and sex specific predicted and actual cardiac event rate (subdivided as event and mortality) will be calculated and analyzed with a two-tailed t-test for an alpha of 0.05. A separate analysis will be performed for patients based on their GFD status. A c-statistic, analogous to the area under a receiver operating characteristic curve or a measure of concordance, will be calculated to quantify the discriminative ability of the Framingham score to correctly predict risk of CAD in those at high risk of CAD, where a c-statistic of 0.5 = no discriminative ability and 1 = perfect prediction. Calibration, which refers to agreement between predicted and observed predicted outcomes, will be assessed overall by sex (calibration in the large) and then by age, basically the slope of the curve generated by plotting predicted versus actual risk. Other variables that will be examined include a diagnosis of diabetes, if the patient's total cholesterol was at goal vs hypolipidemia vs hyperlipidemia, and whether the patient's CD was controlled/severity of CD.

Power analysis
This is a single group study comparing to the gold standard of the Framingham population. Given an estimated risk of 10% coronary disease over 10 years, this study would require 237 celiac disease patients to be 80% powered to detect difference of 5% in 10 year risk.

4. Subject Selection:
237 patients with biopsy proven CD with age > 50 and < 80 years old will be enrolled from a cohort derived from a CD clinic (Columbia Celiac Disease Center). Exclusion criteria include prior CAD or vascular disease. Patients will be contacted by mail or in clinic to be consented for the study inviting them to participate in a survey. Patients agreeing to participate would have the option of either filling out a survey by mail, email, or request to have a telephone interview, which would have standardized questions to assess if they have had a cardiac event over the last 10 years. Since the patients are from

a CD clinic, we do not anticipate significant difficulty with recruitment. There will not be any compensation for participation.

5. Misc:
Study questionnaire:
- Name
- Age
- Sex
- Race
- Patient living or deceased?
- If deceased, was the cause cardiac in nature (ie: heart attack)?
- CD biopsy confirmed? Y or N
- Gluten Free Diet? Y or N
- When was GFD started (year)?
- Symptoms vs ASX? Y or N
- If symptomatic, which ones (prior to and after GFD)?
- Over the last 10 years, hospitalized or told you had a heart attack? Y or N
- Over the last 10 years, any chest pain? Y or N
- Was chest pain from your heart, not from your heart, or unknown?
- Tobacco use (in years)? Current (by year)?
- Any history of diabetes? Y or N
- On medication for diabetes? Oral vs insulin?

Confidentiality:
Neither names or identities will be used for publication or publicity purposes. Patient identifying information with be coded for anonymity. Research records may be reviewed and/or copied by the investigators or the IRB.

Risks and benefits:
There are no risks or benefits.