The Prevalence of Silent Celiac Disease: A Prospective Multicenter Trial

Julian Abrams

A. Rationale

The true prevalence of celiac disease in the United States is not known. Estimates have ranged from 1:300 to 1:10000.[1] The difficulty with determining the prevalence is that there have not been any screening endoscopy studies. It is felt by many gastroenterologists that celiac disease is probably significantly more prevalent than 1:10,000 due to underdiagnosis. An iceberg model has been proposed stating that, based on the genetic makeup of the study population and the physicians' level of clinical suspicion, celiac disease is much more or less underdiagnosed in various parts of the world.[2]

Prevalence studies to date have relied on serologic testing of large groups of random patients. Many papers in the literature have reported sensitivity and specificity of the antiendomysial antibody test, the most commonly used "diagnostic" test, of greater than 90%.[3,4] However, only patients with total villous atrophy on duodenal biopsy were included in the celiac disease groups. The results of a recent study that we performed here at Columbia indicate that the sensitivity of the antiendomysial antibody test is very poor among celiac disease patients with partial villous atrophy. (not yet published) A significant proportion of these patients (approx. 40%) had asymptomatic "silent" celiac disease.

We feel, therefore, that there are likely a large number of patients with asymptomatic celiac disease that would not be detected by serologic screening. Celiac disease has been associated with an increased prevalence of many other autoimmune conditions (e.g. type I diabetes mellitus, autoimmune thyroiditis) and even some malignancies (e.g. intestinal lymphoma).[5] In the case of some of these conditions, starting a gluten-free diet not only corrects the celiac disease but also reduces the severity/risk of developing these associated conditions. One study of adolescents with silent celiac disease reported subjective physical and psychological improvement after starting a gluten-free diet.[6] The primary purpose of this study is to determine the prevalence of silent celiac disease in the United States. This would help determine whether or not any kind of an endoscopic screening program would be beneficial.

B. Hypotheses

- The prevalence of silent celiac disease is significantly higher than previously reported in the literature.
- The overall sensitivity of the antibody tests for celiac disease is the same in silent celiac disease and in classical celiac disease.
- The sensitivity of the antibody tests for celiac disease is significantly lower in patients with partial villous atrophy compared to total villous atrophy.

C. Conceptual And Operational Definitions

The primary outcome is whether or not the study subject has silent celiac disease. For the purposes of this study, any degree of villous atrophy on duodenal biopsy will be used as a surrogate for the above diagnosis. There are other conditions (tropical sprue, eosinophilic enteritis, collagenous sprue) that can also present with duodenal villous atrophy, but these are relatively rare. Technically, to be diagnosed with silent celiac disease, there would have to be histologic normalization on a gluten-free diet. However, this would require an additional endoscopic procedure for each patient with villous atrophy.

D. Study Design

Patients to be included in the study will be recruited from Columbia Presbyterian Medical Center and New York Hospital. All patients undergoing elective upper endoscopies will be eligible for the study. All patients enrolled will have duodenal biopsies taken at the time of their scheduled endoscopies. These patients will also have blood tests drawn for the following: celiac disease antibodies (anti-EMA, anti-tTG, IgA and IgG AGA, and total serum IgA levels), HLA analysis, complete blood count, iron studies, and thyroid studies. Comorbidities and demographic data will be recorded for all patients in the study.

Exclusion criteria include the following: (1) age <18; (2) known history of celiac disease; (3) symptoms of malabsorption at the time of endoscopy (including diarrhea and malabsorption); (4) known history of tropical sprue, collagenous sprue, or eosinophilic enteritis; (5) any individual who is unable to give informed consent for him/herself.

Informed consent will be obtained prior to the endoscopy. Patients will be enrolled continuously at both centers until the desired number of subjects has been attained (see below).

Biopsies will be interpreted by a pathologist at each of the two participating institutions, each of whom will be blinded to the other's reading. If there is disagreement over a specimen, a third pathologist will provide the definitive interpretation. Specimens will be classified as having total villous atrophy, partial villous atrophy, or no atrophy.

E. Statistical Analysis

Using the chi-square test for sample size (for 80% power and testing at p=0.05), the number of subjects needed to demonstrate a prevalence of 1% while showing a significant difference of 0.5% is 2501. Once data has been collected, standard chi-square tests will be used to analyze patients with and without celiac disease.

F. Study Procedure

No additional endoscopies will need to be performed. The only additional procedures include duodenal biopsies (to be performed during an already planned endoscopy) as well as one set of phlebotomies for the various blood tests (described above).

G. Recruitment Of Subjects

Eligible patients who are already scheduled for upper endoscopies will be approached about participating in the study either by phone prior to the study or in person on the day of the study.

H. Confidentiality OF THE STUDY DATA

Random numbers will be assigned to each study participant by a computer.

I. Location Of The Study

The study is to be performed in the respective endoscopy suites of the participating institutions. Blood tests will be analyzed at preselected laboratories. Biopsy specimens will be analyzed by pathologists at Columbia and Cornell.

J. Potential Risks

The most common complication of duodenal biopsy is bleeding, although this is usually localized and minimal. The most serious complication is intestinal perforation and death, although the risk of this is very small. The endoscopy itself also has a low incidence of complications, and these include aspiration and adverse reactions to the sedative medications used.

K. Potential Benefits

If a subject is identified as having silent celiac disease, he/she may benefit from a gluten-free diet. Relatives of these individuals could also benefit by being identified as being at increased risk for having or developing celiac disease. Subjects may not benefit from participation in the study.

L. Compensation To Subjects

No compensation will be provided to the study subjects.

M. Costs To Subjects

Subjects will not incur any additional costs as a result of participating in the study.

N. References:

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5. Fasano et al. Current approaches to diagnosis and treatment of celiac disease: An evolving spectrum. Gastroenterol. 2001;120:636-51.
6. Fabiani et al. Dietary compliance in screening-detected celiac disease adolescents. Acta Paediatr Suppl. 1996;412:65-67.