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Celiac Disease

Summary

Introduction

Celiac disease (CD) is a disorder of small bowel malabsorption. It is characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to gluten, and clinical and histological improvement with withdrawal of gluten from the diet.[1-4] CD—also referred to as celiac sprue, gluten-sensitive enteropathy, non-tropical sprue, in addition to a host of other names—is thought to result from the activation of both a cell-mediated (T-cell) and humoral (B-cell) immune response upon exposure to the glutens (prolamins and glutenins) of wheat, barley, rye, and oats, in a genetically susceptible person.[5,6] Genetic susceptibility is suggested by a high concordance among monozygotic twins of close to 70 percent,[7] and an association with certain type II human leukocyte antigens (HLA).[8,9] HLA DQ2 is found in up to 95 percent of CD patients, while most of the remaining patients have HLA DQ8.[8-10] However, there is only a 30 percent HLA concordance among siblings, suggesting that other genetic factors are also at play.[11] More recent evidence suggests that the presence of auto-antibodies to a connective tissue element surrounding smooth muscle called endomysium is highly specific for CD. The target of this autoantibody is now known to be an enzyme called tissue transglutaminase (tTG). This enzyme may play a prominent role in the pathogenesis of CD by modifying gliadin, resulting in a greater proliferative response of gliadin specific T-cells, which contributes to mucosal inflammation and further B-cell activation.[5,6,12,13]

CD appears to represent a spectrum of clinical features and presentations. Although "classical" CD (i.e., fully developed gluten-induced villous atrophy and classical features of intestinal malabsorption) is most commonly described, it appears that most patients have atypical CD (i.e., fully developed gluten-induced villous atrophy found in the setting of another presentation such as iron deficiency, osteoporosis, short stature, or infertility) or silent CD (i.e., fully developed gluten-induced villous atrophy discovered in an asymptomatic patient by serologic screening or perhaps an endoscopy for another reason). Other authors describe a latent form of CD that is characterized by a previous diagnosis that responded to a gluten-free diet (GFD) and retained a normal mucosal histology upon later introduction of gluten. Latent CD can also represent patients with currently normal intestinal mucosa who will subsequently develop gluten-sensitive enteropathy.[13,14]

The true prevalence of CD is difficult to estimate because of the variable presentation of the disease, particularly since many patients can have little or no symptoms. With this limitation in mind, the prevalence of the disease is highest in Celtic populations where estimates of 1:300 to 1:122 have been described. The prevalence of CD in North America has been estimated to be 1:3000, but a recent American study found the prevalence among the general not-at-risk population to be 1:105, while the prevalence in at-risk groups such as first-degree relatives of CD patients was 1:22, suggesting that CD is greatly under diagnosed. CD can affect persons of many ethnic backgrounds, but appears to rarely affect persons of purely Chinese, Japanese, or Afro-Caribbean decent.[13]

The diagnosis of CD in adults is classically made on the basis of clinical suspicion—that is, recognizing atypical presentations such as isolated iron deficiency, combined iron and folate deficiency, and osteoporosis—compatible with a duodenal biopsy while taking a gluten-containing diet, followed by clinical and histological improvement following commencement of a GFD.[2,4] However, several serologic markers have become available that have altered the classic

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diagnostic pathway. The sensitivity of IgA anti-gliadin antibodies (AGA) is reported to range from 70 to 85 percent, whereas the specificity ranges from 70 to 90 percent. IgA anti-endomysial (EMA) and anti-tissue transglutaminase (tTG) antibodies have sensitivities in excess of 90 percent and specificities of over 95 percent.[14] Significant variability seems to exist in the reported values among the different studies, and these IgA-based tests can be negative in IgA-deficient patients, accounting for about 3 percent of CD cases.

The sensitivity and specificity of the anti-EMA and anti-tTG antibodies, along with the perceived under diagnosis of CD, has led to suggestions of using these tests for population screening. Aside from the recognized influence of CD prevalence on the predictive value of a serologic test result, little consensus exists regarding the value of population screening. Furthermore, specific questions regarding clinically important outcomes resulting from screening remain unclear. In particular, little data is available on adherence to a GFD in asymptomatic CD patients detected by screening.

The major complications of CD include intestinal and extraintestinal malignancies, ulcerative jejunoileitis, and collagenous sprue. Unlike most gastrointestinal (GI) lymphomas that are typically of B-cell origin, lymphomas associated with CD appear to be most commonly of T-cell origin. Unfortunately, the prognoses for patients with CD-associated T-cell lymphomas, ulcerative jejunoileitis, and collagenous sprue, appear grim. It is widely believed that strict adherence to a GFD reduces the risk of these complications. It is suggested that by 5 years of dietary adherence the risk of lymphoma in CD patients approaches that of the general population.[14]

The challenge of CD remains to determine which patient populations should be screened, the best means of screening, and whether early detection of patients with CD leads to improved patient outcomes. For patient outcomes to improve as a result of screening, the degree to which "positively" screened individuals, particularly those who were asymptomatic, adhere to the stringent GFD, needs to be determined.

Methods

We completed a series of systematic reviews on five areas of CD: (1) sensitivity and specificity of serological tests; (2) prevalence and incidence of CD; (3) CD-associated lymphoma; (4) consequences of testing for CD; and (5) interventions for the promotion and monitoring of adherence to a gluten-free diet (GFD). Staff at the National Library of Medicine performed a series of searches in support of the literature review of CD. Searches were run in the MEDLINE® (1966 to Oct 2003) and EMBASE (1974 to Dec 2003) databases for each of the five objectives and their respective sub-objectives separately. Furthermore, for the 4th and 5th objectives, PsycINFO (1840 forward), AGRICOLA (1970 forward), CAB (1972 forward), and Sociological Abstracts (1963 forward) database searches were run in December 2003. Study selection for each objective was performed using three levels of screening with predetermined increasingly more strict criteria to ensure that all relevant articles were captured. Following a calibration exercise, two reviewers independently screened all studies using a Web-based system that allowed automatic identification of review disagreements. These disagreements were resolved by consensus. For each CD objective, a detailed and standardized data abstraction form was developed. For each objective, data abstraction was conducted by one reviewer and verified by another. The extracted data was further verified by one of the principal investigators. Quality assessments were performed using specific instruments for each of the included study types. The data obtained from this review fell into several broad categories, which correspond in large part to the individual study objectives. Data for the sensitivity and specificity of each serological marker was considered separately, and studies were further divided according to the age group of the study population. Attempts were made to identify, explain, and minimize clinical and statistical heterogeneity in the included studies. A Pearson's Chi Square with n-1 degrees of freedom, where n represents the number of included studies in an analysis, was calculated to assess statistical heterogeneity. Pooled estimates were only calculated, if clinically and statistically appropriate. In situations where pooling was not performed, a qualitative systematic review was conducted.

To produce clinically useful pooled statistics, a weighted mean of the overall sensitivity and specificity from the included studies was calculated, along with 95 percent confidence intervals (CIs). The pooled estimates for the sensitivity and specificity were compared with a summary receiver operating characteristic (ROC) curve, calculated for the same group of studies as a second check of the estimates.

Results and Discussion

Perhaps one of the most important findings of this report is the significance of how one chooses to define CD in the era of serological testing, and how this apparently clear-cut task has profound implications on all the results presented in this report. Specifically, can CD be diagnosed solely on the basis of serology? Is some degree of villous atrophy necessary for a diagnosis of CD? These questions have important implications downstream of the diagnosis as well. For example, do CD patients without symptoms or villous atrophy have the same risk of complications as those with villous atrophy? Is serological improvement on a GFD sufficient to reduce CD complications, or Must there be documented histological improvement? What degree of histological improvement is necessary?

Out of 3,982 citations identified by the search strategy for the Celiac 1 objective, 60 studies fulfilled the level 3 inclusion criteria. Overall, the quality of the diagnostic studies assessed in the Celiac 1 objective was quite good, due largely to our stringent inclusion criteria. However, 59 percent of the

included studies reported using a selected patient population that may not be representative of a clinically relevant population. This is likely related to study design. In addition, only 11 percent of the studies reported on whether the reference test was reported without knowledge of the index test. However, we felt that this was not a major threat to the validity of the studies.

Two other factors that affect the interpretation of these results, are (1) the threshold effects for determining the positivity of a serological test and (2) the high prevalence of CD in these studies (see above). With these considerations in mind, the overall strength of the evidence is quite good.

To minimize clinical and statistical heterogeneity, the included articles of a particular antibody test were divided into groups by age of the included population (adults, children, mixed), the study design (case control, or relevant clinical population/cohort), by antibody type (IgA or IgG), and by test methodology (e.g., monkey esophagus [ME] or human umbilical cord [HUC]). Within these groups, further differences in study population, country of origin, and biopsy definitions (especially whether or not mild grades without villous atrophy were included) were assessed systematically. Studies that reported using the ESPGAN criteria for the diagnosis of CD were categorized as including patients with some degree of villous atrophy. Other potential causes of heterogeneity, such as the cut-offs used to define a positive test, were assessed. The results of the Celiac 1 objective suggest that in the era of EMA and tTG antibody testing, AGA antibody testing in both children and adults has a limited role. The sensitivity and specificity of EMA and tTG are quite high (over 95 percent for sensitivity, and close to 100 percent for specificity), as are their positive and negative predictive values; however, the reported diagnostic parameters are taken from studies in which the prevalence of CD was, for the most part, much higher than that seen in usual clinical practice. The positive predictive values reported for these tests will certainly not be as high as that reported when these tests are used to screen the general population. The bulk of the evidence on the diagnostic characteristics of these tests was derived from studies that defined CD as having at least some degree of villous atrophy.

HLA DQ2/DQ8 testing appears to be a useful adjunct in the diagnosis of CD. The test has high sensitivity (in excess of 90 to 95 percent); however, since approximately 30 percent of the general population, and an even higher proportion of "high-risk" subjects (e.g., diabetics and family members) also carry these markers, the specificity of this test is not ideal. The greatest diagnostic utility of this test appears to be its negative predictive value.

Biopsy itself, when used with a strict cut-off requiring villous atrophy, appears to have high specificity, but poor sensitivity. Using a lower grade cut-off clearly improves sensitivity, but because of the wide differential of causes of histological lesions similar to Marsh I to IIIa, the specificity suffers. The use of histomorphometric measures such as quantification of gamma delta positive intraepithelial lymphocytes (gd+ IELs) are likely to allow for the use of lower grade cut-offs, while maintaining reasonable specificity. Ultimately, a trial utilizing multiple diagnostic tests in an attempt to capture as many CD patients in a clinically relevant population as possible, along with a time dimension such as a response to a GFD or gluten challenge, is required to fully assess the diagnostic characteristics of biopsy alone. This type of study would be able to characterize the false-positive and false-negative rates, provided that all studied patients are followed forward in time.

The literature search yielded 2,116 references to address the Celiac 2 objective. Studies were included if they reported the prevalence and/or incidence of CD in the following groups: (1) general populations from North America or Western Europe; (2) first-degree relatives of patients with CD; (3) patients with type 1 diabetes; (4) patients being investigated for anemia; (5) patients with osteoporosis or osteopenia; and (6) patients with suspected CD on the basis of their clinical presentations. We did not use any geographic restriction for the studies of populations at risk (first-degree relatives and type 1 diabetics) or of associated clinical presentations (suspected CD, anemia, or metabolic bone disease). Studies of prevalence or incidence that used AGA tests conducted prior to 1990 were excluded after discussion with AHRQ because of potential problems with the reliability of older AGA assays. One hundred and nineteen studies were included.

The overall quality of reports of the included studies in the Celiac 2 objective was found to be marginal to fair. For example, most of the studies did not report on whether the patients were consecutively enrolled, a factor that could contribute to selection bias. However, setting aside the quality of individual studies, from a policy perspective, the strength of the evidence is fairly good in that the study populations were selected to reflect that of a North American/Western European descent, that should reflect the demographics of the U.S. population.

The crude incidence of CD in adults varied from lows of 1.27 in Denmark[15] and 3.08 in England,[16] to a high of 17.2 cases per 100,000 patient years in Finland,[17] where specific efforts had been untaken to encourage screening for CD (see Table 34). The crude incidence of CD in children age 0 to 15 years varied from 2.15 to 51 cases per 100,000 patient years.[18-20,21,16,22] When reported, the relative risk (RR) of CD was greatest for the 0- to 2-year age group, as well as for women, and varied from 32.26 to 42.4 [18,19,22] and from 1.9 to 3.34, [23,18,20] respectively. The cumulative incidence at age 5, when reported, varied between 0.089 and 9 cases per 1,000 live births.[23,24,25,26]

The included prevalence studies demonstrated important differences between the studies including execution, tests for prevalence assessment, and patient sampling. Thus, results have to be interpreted in light of some of the limitations that have been identified regarding the diagnostic performance of the tests for CD. Nonetheless, the results of this report suggest that

CD is a very common disorder with a prevalence in the general population that is likely close to 1:100 (1 percent). Several high-risk groups with a prevalence of CD greater than that of the general population have been identified and include: (1) those suspected of having CD; (2) family members of CD patients; (3) type I diabetics; and (4) those with iron-defiency anemia (IDA) or low bone mineral density (BMD). Additionally, the review identified many other high-risk groups, including those with Down Syndrome, short stature, and infertility, to name a few. Their inclusion was, however, beyond the scope of this report.

Out of 379 references resulting from the literature search on CD and lymphoma, our third objective, eight cohort studies and one case-control study were selected for data extraction. The studies included in the Celiac 3 objective were found, overall, to be of good quality. Again, the overall strength of the evidence is due largely to the stringent inclusion criteria, such as the requirement for the reporting of standardized rates for the outcomes based on rates from the local general population, and the overall good quality of the included studies.

Out of 1,199 citations that were identified by the search strategy for the Celiac 4 objective, 35 articles satisfied the screening criteria. The majority of studies included in this objective were single group "before–after" studies, although some also had a comparative healthy control group. We could not identify any quality instruments for this type of study design and, in general, this type of study is considered weak, particularly in the absence of a control group. Overall, however, the strength of the evidence for this objective is fair to good and suggests that the results can be used for policy decisions with the understanding that this area of CD research is still relatively new and requires further high-quality studies.

The results of this report confirm that, apart from a few limitations, there is a strong association between CD and GI lymphoma. The report identified standard incidence ratios (SIR) for lymphoma that ranged from 4 to 40, and standard mortality ratios (SMR) that ranged from 11 to 70. A diagnostic delay—and possibly a diagnosis of CD in adulthood as opposed to in childhood—may be associated with poorer outcomes. Fortunately, several studies suggest that adherence to a GFD reduces the risk of lymphoma in CD patients.

The consequences of testing for CD in at-risk and symptomatic patients appears to be more straightforward, since these patients appear to be more compliant with a GFD and would be expected to benefit from this intervention. The data are less clear for asymptomatic screen-identified patients, particularly those who have truly silent CD and/or don't have fully developed villous atrophy. On the one hand, the outcome of such patients has not been extensively studied; on the other hand, compliance with a GFD appears problematic, particularly for those diagnosed in adulthood.

Out of 502 citations identified by the search strategy for the Celiac 5 objective, 20 studies met level 3 inclusion criteria. The majority of studies in this objective were also of a "before–after" design. However, in this setting, this design may not pose a major limitation, since the purpose of the study is to assess the change in serology and histology after introduction of a GFD. In this regard, the strength of the evidence for monitoring adherence to a GFD is fairly good. However, there is almost a complete absence of studies of interventions for the promotion of adherence to a GFD.

No specific interventions have been identified that promote adherence to a GFD, but education of patients and family members about CD and about the intricacies of a GFD, and participation in local celiac societies, has been shown to improve compliance. Although somewhat controversial, biopsy monitoring of adherence to a GFD appears to be important, since improvement in histological grade has been associated with improved BMD, IDA, and nutritional status. The serological markers appear to be adequate for detecting gross dietary indiscretion and respond to a gluten challenge, but appear to have poor sensitivity for detecting lesser degrees of dietary indiscretion and inadequately correlate with histological improvement, at least in the short-term. Children, on the other hand, show more rapid and complete histological improvement on a GFD. Therefore, monitoring adherence using serology is reasonable in this age group. It should, however, be noted, that we could not identify a controlled study that objectively determined the level of histological improvement that would be associated with improved outcomes; this is an area for future study. Nonetheless, based on this report it would appear that followup biopsy at least 1 year after a GFD in adults to document improvement of the histological grade would be valuable.

This review has allowed us to identify several areas in need of future research. Perhaps the most important of these is a need for the development of a consensus on the definition of CD in the era of advanced serological testing. As discussed in the report, this distinction of what one calls CD has profound implications for each of the requested task order objectives. Do screen-positive patients without villous atrophy have CD? Certainly, the preliminary evidence suggests that this is the situation in many cases. However, what is required is a new definition of a gold standard for the diagnosis of CD. This new gold standard may include a combination of serology, biopsy, and HLA testing. Such a gold standard, when used in studies with a time dimension (e.g., response to a GFD or gluten challenge; extended followup), would help answer some of the uncertainties identified in this report including: the real performance of the serological tests when low-grade lesions are considered CD; the diagnostic performance of biopsy alone; the outcomes of patients with these low-grade lesions; and those that would be "missed" using current screening strategies. Even in the absence of a new gold standard, we could not identify a well-conducted study of the diagnostic performance of the various serological markers when applied to an average population (i.e., one with a prevalence of CD in keeping with the range identified for average risk), with the entire cohort

being investigated equally (i.e., all are biopsied). Such a study would at least be able to shed light on the performance of these tests in average-risk patients, and since all patients are biopsied, the relationship of histology to serology could be further assessed.

On a similar theme, we have identified multiple studies that suggest the importance of histological improvement on a GFD. This is a controversial area because in common clinical practice clinicians are moving away from routine followup biopsy. It seems reasonable to believe that improvement in clinical parameters with loss of serological markers is adequate evidence of response to a GFD. In children, this issue may be less important since histological improvement is much more rapid and complete than in adults, and correlation with serology seems better. However, we have identified multiple studies in adults that suggest poor correlation between serology and improvement of histology on a GFD, and other studies that suggest that serology is useful for detecting gross dietary indiscretion, but not minor occurrences. Therefore, the questions that arise are What constitutes adequate improvement on a GFD?, and What are the criteria to define this improvement? Based on the lymphoma literature that suggests that this malignancy may arise from chronic antigenic stimulation and immune activation, what are the outcomes of adults with clinical improvement, yet persistent histological abnormalities? Are some histological features, such as reduction of mucosal lymphocytes, more important markers of improvement and possibly prognosis than other features such as villous height?

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center, under Contract No. 290-02-0021. It is expected to be available in July 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 104, *Celiac Disease*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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