Consequences of Testing for Celiac Disease

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Population screening studies have identified that up to two thirds of celiac disease (CD) cases are asymptomatic. The aim of this study was to conduct a systematic review of the expected consequences of testing for CD in the following populations: (1) patients with symptoms suggestive of CD, (2) asymptomatic at-risk populations, and (3) general population. Standard systematic review methodology was used. A comprehensive literature search was conducted in MEDLINE (1996–2003), EMBASE (1974–2003), CAB (1972 forward), PsychINFO (1840–2003), AGRICOLA (1970–2003), and Sociological Abstracts (1963 forward); searches were conducted in December 2003. Pooled summary estimates were not calculated. The majority of the included studies were before-after studies, case control, or retrospective cohorts. The quality of evidence for the before-after studies is weaker. The overall strength of the evidence for this issue was fair to good. This area of research is relatively new, and further high-quality studies are required. The consequences of testing for celiac disease in symptomatic individuals appears to have a positive impact on patient-relevant outcomes. The data are less clear for those with silent CD or those with lower grade histologic lesions in small bowel biopsy. The literature suggests that compliance is less than ideal in these individuals, especially if diagnosed when adults. Long-term outcomes have not been extensively studied in those with silent CD.

Recent, large, screening programs have noted a high prevalence of celiac disease (CD) in the general population and, of those who test positive, up to two thirds are asymptomatic.[1] Prior to recommending population screening for CD, the consequences of testing and risk of long-term complications in individuals with clinical silent CD, especially those with low-grade histologic lesions on small bowel biopsy, need to be clarified.

Our objective was to conduct a systematic review of trials evaluating the expected consequences of testing for CD in (1) patients with symptoms suggestive of CD, (2) asymptomatic at-risk populations, and (3) general population.

Materials and Methods

This paper was part of a multipart systematic review conducted for the Agency for Healthcare Research and Quality (AHRQ).

Data Sources

A comprehensive literature search was conducted by the National Library of Medicine in collaboration with the University of Ottawa Evidence-Based Practice Center (UO-EPC). The searches were run in MEDLINE (1996–October 2003), EMBASE (1974 to December 2003), PsychINFO (1840–2003), AGRICOLA (1970–2003), CAB (1972–December 2003), and Sociological Abstracts (1963–2003). Reference lists from eligible studies were reviewed for other relevant studies.

Study Selection and Data Extraction

The comprehensive search strategy included potential studies that dealt with consequences of testing for celiac disease; 1199 potentially relevant citations were identified. Study selection was performed by 2 independent reviewers, using 3 levels of screening with gradually increasing stringent criteria to ensure that all relevant articles were captured. Articles were excluded if they did not identify one of the consequences of screening for celiac disease such as false-positives, cases diagnosed, or response to treatment. Studies were excluded if there was no control group, unless the studies

Abbreviations used in this paper: AGA, antigliadin; AMA, arm muscle area; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; CD, celiac disease; EMA, antiendomysial IgA antibody; FAI, fat area index; FN, femoral neck; GFD, gluten-free diet; HbA1c, hemoglobin A1c; IRR, incidence rate ratio; IUGR, intrauterine growth retardation; LS, lumbar spine; OR, odds ratio; PY, person years; SDS, standard deviation score; SMR, standardized mortality ratio; SSSF, suprascapular skin fold area; TSF, triceps skin fold; tTG, tissue transglutaminase IgA antibody; WHI, weight for height index.

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were a before-after design. Studies that used antigliadin (AGA) without commercial ELISA or that were published before 1990 were excluded. After 3 levels of screening, 51 published studies met the eligibility criteria. Full data extraction was conducted by 2 independent reviewers (R.S. and A.C.). Quality of case control and cohort studies was evaluated with the Ottawa-Newcastle Scale.[2] Outcomes included test performance and outcomes related to identifying patients and the subsequent response to the gluten-free diet (GFD), including (1) body composition and anthropometrics, nutritional status, and diabetic control; (2) compliance with a gluten-free diet; and (3) costs, factures/osteoporosis, and mortality.

Data Synthesis

The search strategy did not identify studies that allowed us to address specific benefits and harms of testing with different strategies for CD. Many of the included studies relevant to response to treatment dealt with small populations of symptomatic individuals. Most studies did not report outcomes according to clinical presentation, so it was difficult to ascertain whether outcomes differed in asymptomatic or silent CD cases when compared with symptomatic CD cases. Few studies correlated the histologic grade at biopsy with outcomes, such as improvements in bone mineral density (BMD), anemia, and diabetic control. We did not pool results from the observational trials because of differences in methodologies and the potential for selection bias and heterogeneity.[3]

Results

The search identified 1121 citations from bibliographic databases, and 123 potentially relevant citations were nominated by reviewers. Twenty-nine duplicate records were removed, resulting in 1199 potential citations that were evaluated for inclusion. Out of 1199 citations, 1164 failed to meet the specified inclusion criteria; 1148 were not about the consequences of testing, and 7 were review articles. Thirty-six articles satisfied the inclusion criteria.[4–39] Fifteen other relevant studies were identified by hand searching of references,[40–54] for a total of 51 studies. Outcomes related to the identification of patients and response to treatment, including: (1) consequences based on test performance; (2) response to treatment in terms of anthropometrics, body composition, and diabetic control; (3) compliance with the GFD; and (4) other relevant clinical outcome such as osteoporosis, costs, pregnancy, and mortality. Based on results from recent population-based screening results, the number of potential subclinical and silent celiac cases may be 8 times that of classically symptomatic cases. It is important to determine whether clinical outcomes vary according to the clinical presentation. Most studies included in this review were studies that assessed the response to treatment in newly diagnosed patients after commencing a gluten-free diet (GFD).

Outcomes Related to Test Performance

False-positive results and cases diagnosed with testing are dealt with extensively in the paper of serologic testing by Rostom et al.[55] However, it is important to emphasize that the prevalence of CD in the test populations has an important impact on the diagnostic parameters of the screening tests used. For example, the sensitivity of screening tests is lower for histologic grades below Marsh IIIa by approximately 30%.[55] In addition, the prevalence of CD in study populations in which the diagnostic test studies of serologic testing were conducted is higher than the prevalence of CD in most clinical situations. The positive predictive value, which is influenced by both the specificity and prevalence of CD, falls from the reported value to much lower values in typical clinical populations, resulting in an increased chance of false-positives. Conversely, the negative predictive value increases as the prevalence of CD decreases but will remain over 90%, provided the sensitivity of the test is >50%. Although currently recommended serologic screening tests (EMA, tissue transglutaminase IgA antibody [tTG]), have a high specificity in low-prevalence populations, the use of these tests results in much higher false-positive rates (as high as 30%–35%) in low-prevalence populations.

Outcomes Related to Response to Treatment: Type 1 Diabetes and Celiac Disease

Four studies evaluated diabetes and celiac disease in children.[5,14,16,27] Two were case-control studies,[5,14] and 2 studies had CD patients act as their own controls.[16,27] All studies assessed the impact of a GFD (range, 3–12 months) on the diabetic control of type 1 diabetics. The United Kingdom study[5] included 230 type 1 diabetics who were screened for celiac disease with serologic tests. Children with positive serology had small bowel biopsies. Eleven children were diagnosed with celiac disease and followed longitudinally. Controls included type 1 diabetic children with negative serology, and 2 controls per case were matched for age, sex, and duration of diabetes. Baseline weight standard deviation score (SDS), body mass index (BMI) SDS, and HbA1c of the cases were statistically lower than the controls. No statistical difference was noted for height SDS, C-peptide level, and insulin requirements. Cases received significantly less intensive insulin regimens compared with controls. Six type 1 diabetic children with celiac disease participated in the GFD. After 12 months of a GFD, the differences seen in the BMI SDS reversed between the cases and controls. HbA1c levels did not improve sig-