

NIH Consensus Development Conference on Celiac Disease

June 28–30, 2004

**William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland**

Sponsored by:

- National Institute of Diabetes and Digestive and Kidney Diseases
- Office of Medical Applications of Research

Cosponsored by:

- U.S. Food and Drug Administration
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U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Introduction

Background

Celiac disease is a disorder primarily affecting the gastrointestinal tract that is characterized by chronic inflammation of the mucosa, which leads to atrophy of intestinal villi, malabsorption, and protean clinical manifestations that may begin either in childhood or adult life. Symptoms can include abdominal cramping, bloating, and distention, and untreated celiac disease may lead to vitamin and mineral deficiencies, osteoporosis, and other problems. The disease is also strongly associated with the skin disorder, dermatitis herpetiformis. Celiac disease's major genetic risk factors (HLA-DQ2 and HLA-DQ8) and environmental triggers (specific peptides present in wheat, rye, and barley) have been identified, and most patients experience complete remission after exclusion of these grains from the diet. Thus, there has been considerable scientific progress in understanding this complex disease and in preventing or curing its manifestations by dietary interventions.

At the present time, celiac disease is widely considered to be a rare disease in the United States. However, recent studies, primarily in Europe but also in the United States, suggest that its prevalence is much higher than previous estimates, raising the concern that the disease is widely under-recognized. Recent progress in identification of autoantigens in celiac disease have led to the development of new serological diagnostic tests, but the appropriate use of testing strategies has not been well defined. Some patients with celiac disease may be at risk for non-Hodgkin's lymphoma, a rare cancer affecting the gastrointestinal tract. It is not yet clear, however, what the impact of this observation should be on diagnostic and treatment strategies.

Conference Process

To address these issues, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Office of Medical Applications of Research (OMAR) of the National Institutes of Health (NIH) are sponsoring a consensus development conference to explore and assess the current scientific knowledge regarding celiac disease. The conference will be held June 28–30, 2004, at NIH in Bethesda, Maryland. Specifically, the conference will address the following key questions:

- How is celiac disease diagnosed?
- How prevalent is celiac disease?
- What are the manifestations and long-term consequences of celiac disease?
- Who should be tested for celiac disease?

- What is the management of celiac disease?
- What are the recommendations for future research on celiac disease and related conditions?

During the first 1 1/2 days of the conference, experts will present the latest celiac disease research findings to an independent panel. After weighing all of the scientific evidence, the panel will prepare a consensus statement answering the questions above. On the final day of the conference, the panel chairperson will read the draft statement to the conference audience, and invite comments and questions. A press conference that afternoon will allow the panel to respond to questions from the media.

General Information

Conference sessions will be held in the Natcher Conference Center, NIH, Bethesda, Maryland.

The conference may be viewed live via Webcast at <http://videocast.nih.gov/>. Webcast sessions will also be available after the conference.

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, level B1, across the street from the main entrance to the Natcher Conference Center.

The telephone number for the message center at the Natcher Conference Center is 301-594-7302.

Conference Sponsors

The primary sponsors of the conference are NIDDK and OMAR of the NIH, a component of the U.S. Department of Health and Human Services. The conference is cosponsored by the U.S. Food and Drug Administration, the U.S. Department of Agriculture, the National Institute of Child Health and Human Development, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases.

The National Library of Medicine (NLM) and the Agency for Healthcare Research and Quality (AHRQ) provided additional support to conference development.

Financial Disclosure

Each speaker presenting at this conference has been asked to disclose any financial interests or other relationships pertaining to this subject area. Please refer to the material in your participant packet for details.

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

AGENDA

Monday, June 28, 2004

- 8:30 a.m. Opening Remarks
Allen M. Spiegel, M.D.
Director
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
- 8:40 a.m. Charge to the Panel
Susan Rossi, Ph.D., M.P.H.
Deputy Director
Office of Medical Applications of Research, Office of the Director
National Institutes of Health
- 8:50 a.m. Conference Overview and Panel Activities
Charles O. Elson, M.D.
Panel and Conference Chairperson
Professor of Medicine and Microbiology
Vice Chair for Research, Department of Medicine
University of Alabama at Birmingham

I. How Is Celiac Disease Diagnosed?

- 9:00 a.m. Overview and Pathogenesis of Celiac Disease
Martin F. Kagnoff, M.D.
Professor of Medicine and Pediatrics
Cancer Biology Program
University of California at San Diego
- 9:20 a.m. The Pathology of Celiac Disease
Paul J. Ciclitira, M.D., Ph.D., FRCP
Professor
The Rayne Institute
St. Thomas' Hospital
United Kingdom
- 9:40 a.m. What Are the Sensitivity and Specificity of Serological Tests for Celiac Disease?
Do Sensitivity and Specificity Vary in Different Populations?
Ivor D. Hill, M.D.
Professor of Pediatrics
Wake Forest University School of Medicine

Monday, June 28, 2004 (continued)

I. How Is Celiac Disease Diagnosed? (continued)

- 10:00 a.m. Discussion
Participants with questions or comments for the speakers should proceed to the microphones and wait to be recognized by the panel chair. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted at the registration desk. Please be aware that all statements made at the microphone or submitted later are in the public domain.
- 10:30 a.m. Clinical Algorithm in Celiac Disease
Ciaran P. Kelly, M.D.
Director, Celiac Center
Herrman L. Blumgart Firm Chief
Director, Gastroenterology Fellowship Training
Associate Professor of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
- 10:50 a.m. Genetic Testing: Who Should Do the Testing and What Is the Role of Genetic Testing in the Setting of Celiac Disease?
George S. Eisenbarth, M.D.
Executive Director
Barbara Davis Center for Childhood Diabetes
University of Colorado Health Sciences Center
- 11:10 a.m. Evidence-Based Practice Center Presentation: Serological Testing for Celiac Disease
Alaa Rostom, M.D., M.Sc., FRCPC
Assistant Professor
Division of Gastroenterology
University of Ottawa
The Ottawa Hospital – Civic Campus
- 11:30 a.m. Discussion
- 12:00 p.m. Lunch

Monday, June 28, 2004 (continued)

II. How Prevalent Is Celiac Disease?

- 1:00 p.m. Epidemiology of Celiac Disease: What Are the Prevalence, Incidence, and Progression of Celiac Disease?
Marian J. Rewers, M.D., Ph.D.
Professor
Clinical Director
Barbara Davis Center for Childhood Diabetes
University of Colorado Health Sciences Center
- 1:20 p.m. What Are the Prevalence and Incidence of Celiac Disease in High-Risk Populations: Patients With an Affected Family Member, Type 1 Diabetes, Iron-Deficiency Anemia, and Osteoporosis?
Joseph A. Murray, M.D.
Professor of Medicine
Mayo Clinic
- 1:40 p.m. Evidence-Based Practice Center Presentation: Incidence and Prevalence of Celiac Disease
Alaa Rostom, M.D., M.Sc., FRCPC
Assistant Professor
Division of Gastroenterology
University of Ottawa
The Ottawa Hospital – Civic Campus
- 2:00 p.m. Discussion

III. What Are the Manifestations and Long-Term Consequences of Celiac Disease?

- 2:30 p.m. Clinical Presentation of Celiac Disease in the Pediatric Population
Alessio Fasano, M.D.
Professor of Pediatrics, Medicine, and Physiology
Director, Mucosal Biology Research Center
Center for Celiac Research
University of Maryland School of Medicine
- 2:50 p.m. The Many Faces of Celiac Disease: Clinical Presentation of Celiac Disease in the Adult Population
Peter H.R. Green, M.D.
Professor of Clinical Medicine
Division of Digestive and Liver Disease
Columbia University

Monday, June 28, 2004 (continued)

**III. What Are the Manifestations and Long-Term Consequences of Celiac Disease?
(continued)**

- 3:10 p.m. Association of Celiac Disease and Gastrointestinal (GI) Lymphomas and
Other GI Cancers
Carlo Catassi, M.D., M.P.H.
Co-Medical Director
Division of Pediatric Gastroenterology and Nutrition
Center for Celiac Research
University of Maryland School of Medicine
- 3:30 p.m. Skin Manifestations of Celiac Disease
John J. Zone, M.D.
Chairman and Professor of Dermatology
University of Utah Health Sciences Center
- 3:50 p.m. Neurological/Psychological Presentation of Celiac Disease: Ataxia, Depression,
Neuropathy, Seizures, and Autism
Khalafalla O. Bushara, M.D.
Assistant Professor
Department of Neurology
University of Minnesota
Veterans Administration Medical Center
- 4:10 p.m. Discussion
- 5:00 p.m. Adjournment

Tuesday, June 29, 2004

IV. Who Should Be Tested for Celiac Disease?

- 8:30 a.m. Should Children Be Screened for Celiac Disease? Is There Evidence To
Support the Strategy of Screening All Children?
Edward J. Hoffenberg, M.D.
Associate Professor of Pediatrics
Director, Center for Pediatric Inflammatory Bowel Disease
Children's Hospital Denver
University of Colorado School of Medicine
- 8:50 a.m. Should Adults Be Screened for Celiac Disease? What Are the Benefits and
Harms of Screening?
Pekka Collin, M.D., Ph.D.
Assistant Professor
Medical School
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Tuesday, June 29, 2004 (continued)

IV. Who Should Be Tested for Celiac Disease? (continued)

- 9:10 a.m. Evidence-Based Practice Center Presentation: Consequences of Testing for Celiac Disease
Ann Cranney, M.D., M.Sc.
Associate Professor
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Ottawa Health Research Institute
Civic Hospital Site
- 9:30 a.m. Discussion

V. What Is the Management of Celiac Disease?

- 10:00 a.m. Dietary Guidelines for Celiac Disease and Implementation
Cynthia Kupper, R.D., C.D.
Executive Director
Gluten Intolerance Group of North America
- 10:20 a.m. How To Provide Effective Education and Resources: Gluten-Free Diets
Shelley Case, R.D.
Case Nutrition Consulting
- 10:40 a.m. The Followup of Patients With Celiac Disease—Achieving Compliance With Treatment
Michelle Maria Pietzak, M.D.
Director, Center for Celiac Research—West
Childrens Hospital Los Angeles
Assistant Professor of Pediatrics
University of Southern California
Keck School of Medicine
- 11:00 a.m. Discussion
- 11:30 a.m. Adjournment

Wednesday, June 30, 2004

- 9:00 a.m. Presentation of the Consensus Statement
- 9:30 a.m. Public Discussion
The panel chair will call for questions and comments from the audience on the draft consensus statement, beginning with the introduction and continuing through each subsequent section in turn. Please confine your comments to the section under discussion. The chair will use discretion in proceeding to subsequent sessions so that comments on the entire statement may be heard during the time allotted. Comments cannot be accepted after 11:30 a.m.

Wednesday, June 30, 2004 (continued)

11:00 a.m. Conference Adjourns

Panel meets in executive session to review public comment. Conference participants are welcome to return to the main auditorium to attend the press conference at 2:00 p.m.; however, only members of the media are permitted to ask questions during the press conference.

2:00 p.m. Press Conference

The panel's draft statement will be posted to consensus.nih.gov as soon as possible after the close of proceedings, and the final statement will be posted 3 to 4 weeks later.

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Abstracts

The following are abstracts of presentations to the NIH Consensus Development Conference on Celiac Disease. They are designed for the use of panelists and participants in the conference and as a reference document for anyone interested in the conference deliberations. We are grateful to the authors, who summarized their materials and made them available in a timely fashion.

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Overview and Pathogenesis of Celiac Disease

Martin F. Kagnoff, M.D.

Celiac disease (CD) is characterized by small intestinal mucosal inflammation and mucosal injury. Disease is seen in genetically susceptible individuals following enteric encounter with proteins in wheat, rye, and barley and often is accompanied by nutrient malabsorption. Mucosal damage, which is most marked in the proximal small intestine, is characterized by a spectrum of pathology that ranges from minimal to complete villous atrophy, an increased infiltrate of lymphocytes and plasma cell infiltrate in the lamina propria, increased numbers of intraepithelial lymphocytes, and varying degrees of crypt hyperplasia accompanied by increased crypt mitoses.

CD was once considered a rare disorder in the U.S., occurring in as few as 1/10,000. However, with the advent and broader application of antibody tests as a screening tool over the past decade, it has been recognized to be far more common. Indeed, the prevalence of CD in the United States and in Europe appears to be in the range of 1:250 to 1:150, with increasing numbers of studies supporting the latter estimate.^(1,2) Concurrently, the presenting clinical picture of CD has changed. The former classic “textbook description,” in which patients with CD presented with marked diarrhea, steatorrhea, and weight loss, is now overshadowed by the more frequent presentation with one or more complaints such as abdominal bloating, lethargy, a lack of energy, irritability or depression, menstrual abnormalities, growth disturbances in children, or neurological complaints compatible with peripheral neuropathy. In some patients, the only laboratory abnormalities may be evidence of iron deficiency or osteopenia.

The pathogenesis of CD involves environmental, genetic, and immunologic factors.⁽³⁾ For clarity of defining key factors in disease pathogenesis, the events contributing to the pathogenesis of CD can be viewed as luminal events and events that occur in the intestinal mucosa, including the eventual activation of immune cells and ensuing tissue damage. The key environmental factor known to be essential for the development of CD is enteric exposure to certain proline and glutamine rich proteins in the dietary grains wheat, rye, and barley. Often simply referred to as “gluten,” the actual proteins that can activate disease are the gliadins and, to a lesser extent, glutenins^(4,5) in wheat, the hordeins in barley, and the secalins in rye. Peptides in these proline rich proteins are poorly digested into free amino acids or very small peptides (i.e., di, tri, and tetrapeptides) by pancreatic and intestinal brush border proteases in the human intestine.^(6,7) Current models of disease envision that the larger remaining peptides ultimately lead to the activation of disease-associated mucosal T-cells. The latter is more efficient when those peptides are acted on by tissue transglutaminase to yield more negatively-charged peptides, which are more efficient in activating disease relevant T-cells and T-cell-mediated immune responses in genetically susceptible individuals.

What are the relevant genes that contribute to susceptibility to CD? It is known that genes within the HLA class II DQ subregion on chromosome 6 are necessary, but not sufficient, to develop CD. Approximately 95 percent of patients with CD have a DQ2 heterodimer comprised of DQB1*02 and DQA1*05 and most of the remaining 5 percent have a DQ8 heterodimer comprised of DQB1*0302 and DQA1*03.^(8,9) A small number of individuals lacking either of those heterodimers have either DQB1*02 or DQA1*05 alone.⁽¹⁰⁾ Gene dosage also affects CD

susceptibility (e.g., DR17 homozygous individuals who carry DQB1*02 and DQA1*05 in cis on both chromosomes have a greater risk of disease).⁽¹¹⁾ CD is concordant in approximately 70 percent of monozygotic twin pairs and approximately 30–40 percent of HLA identical siblings, and it has been estimated that HLA class II genes are responsible for about 40 percent of the genetic contribution to disease.⁽¹²⁾ There is no clear definition of what other genes contribute to disease or how they do so, although linkage studies suggest disease-associated genes in a region of chromosome 5 and perhaps a region on chromosome 19 in some populations.⁽¹³⁾

What is the link between the DQ2 and DQ8 heterodimer, the disease activating peptides and T-cell-activated immune injury. CD4⁺ T-cell populations that recognize putative disease activating peptides are present in the intestinal mucosa of CD patients. Moreover, these peptides bind more efficiently in the peptide binding groove of the DQ2 or DQ8 heterodimer when specific glutamine residues are deamidated to negatively-charged glutamic acid by tissue transglutaminase.^(14,15) Nonetheless, a broad array of peptides derived from gliadins, glutenins, hordeins, and secalins likely can activate disease^(16,17) and their deamidation does not appear to be an absolute requirement, at least for initiating this disease.⁽¹⁷⁾

In summary, significant progress has been made at the protein, genetic and immunologic level in understanding the pathogenesis of CD. However, significant questions have not been answered and a great deal remains to be discovered regarding early luminal events that effect disease susceptibility and pathogenesis, the more complex and perhaps subtle genetic factors and mechanisms that enhance disease susceptibility, and the pathways involved in the mucosal entry and processing of disease activating peptides and the activation of T-cells and other cells that lead to the immune tissue injury.

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The Pathology of Celiac Disease

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Celiac disease (CD) was first described in a lecture by Samuel Gee in 1887. He noted the classical symptoms of diarrhoea, lassitude, and failure to thrive and commented from his observations that the cure might lie in the diet. The first accurate description of the celiac lesion was provided by Paulley in 1954, who examined full-thickness biopsies taken at laparotomy. He referred to broad villi and a chronic inflammatory cell infiltrate in the small intestinal mucosa. A detailed study of large numbers of intestinal biopsies was carried out by Marsh, who proposed a classification of different types of coeliac lesion.⁽¹⁾ He described distinct features characterizing pre-infiltrative, infiltrative, hyperplastic, destructive, and atrophic lesions (termed Marsh types 0–4). The majority of patients with CD have features distributed between Marsh types 1 and 3 and, although this terminology is used by some pathologists, its use is not universal.

The pathological lesion in CD is an inflamed and flattened small intestinal mucosa with impaired function. However, this inflammation results in highly variable clinical expression, particularly as the small intestine has a large amount of reserve functional capacity. The spectrum of severity extends from individuals with no symptoms to individuals presenting with critical malnutrition. The most common symptoms in adult patients are abdominal pain, lethargy, increased bowel frequency, and failure to maintain weight. These symptoms are often indolent and a significant latency may exist between their onset and diagnosis. Abnormal clinical signs are usually not seen. Severe cases do occur with generalized malabsorption resulting in steatorrhea, gross abdominal distension, and protein–energy malnutrition. More commonly and less dramatic, specific nutrient deficiencies arise which lead to anemia and low bone mineral density, which may also go unrecognized for a considerable time prior to eventual diagnosis of CD.

The gold standard for diagnosis of CD remains the small bowel mucosal biopsy. Fortunately, the abnormalities are typically more pronounced in the proximal small intestine and are sufficiently diffuse to be identified in random samples taken endoscopically from the second part of the duodenum or beyond. There is a spectrum of abnormalities seen on biopsy with varying degrees of villus atrophy, crypt hyperplasia, and lymphocytic infiltration. These changes correspond to enterocyte damage, tissue inflammation, and increased epithelial proliferation in response to injury. Quantification of mucosal morphometry can be made by taking measurements of villus height, crypt–depth ratio, enterocyte height, and intra-epithelial lymphocyte cell counts. Although CD is the most common cause, these morphological changes can be induced by other causes of enteropathy. Therefore, central to the diagnosis of CD is the demonstration that these changes improve on a gluten-free diet, although in practice this is not always deemed necessary.

The role of the pathologist is critical in the diagnosis of CD, as there are pitfalls in the assessment of biopsy specimens. It is vital to ensure correct orientation of the biopsy specimen as this can result in incorrect diagnosis. There are further difficulties if there are no architectural abnormalities and the changes are limited to an increase in number of intra-epithelial lymphocytes, which is generally accepted to be the earliest change detectable by light microscopy. There is debate over the accepted normal count with arbitrary values between

25 and 40 lymphocytes per 100 enterocytes being used. The significance of an isolated intra-epithelial lymphocytosis together with positive serology is not fully understood and recommended treatment will depend on the circumstances of clinical presentation. The term “latent” CD is sometimes applied to these individuals, although this also includes those with entirely normal biopsies and positive serology.

In active CD, the lamina propria is expanded in volume, which is due, in part, to recruitment of T-lymphocytes, plasma cells, and dendritic macrophages expressing HLA molecules, ICAM-1, and CD25 (IL-2 receptor α -chain)—an infiltrate indicative of a T-cell-mediated immune response. Although we know the toxic trigger (gluten) results in pathological changes in the small intestine, the intervening events remain unclear.

There are several distinct populations of T-lymphocytes in CD. Within the lamina propria, a population of DQ2 restricted CD4+ T-cells can be isolated that become stimulated when cultured with gluten. These gluten sensitive T-cells express a memory phenotype and the predominant cytokine secreted is interferon- γ . Supernatant from isolated gluten specific lymphocytes induces damage to the normal intestine. The mucosa also contains an excess of fibroblasts with increased expression of matrix metalloproteinases that activate degradation of extracellular matrix proteins.

A separate population of intra-epithelial lymphocytes is present, but their function remains unclear. The majority are CD8+ and express natural killer markers such as CD94, suggesting that they may be cytotoxic to enterocytes.⁽²⁾ A smaller percentage of these lymphocytes are both CD4/CD8 negative and express the primitive γ/δ T-cell receptor. Unlike the CD8 intra-epithelial lymphocytes or lamina propria infiltrate, this population does not regress on gluten withdrawal. It has been proposed that these γ/δ lymphocytes form part of innate rather than acquired immunity. They do not appear to require HLA for antigen recognition and recognize stress proteins such as MICA and MICB expressed on epithelial cells, subsequently recruiting polymorphs and monocytes.

The earliest changes in CD after gluten challenge can be seen at 1 hour, and this has led to the suggestion that the primary mechanism of injury is not related to a CD4+ T-cell response. Changes in intestinal morphology and membrane expression of HLA molecules and activation markers can be detected within 1 hour of gluten challenge, which precedes lymphocyte infiltration. CD4+ T-cell reactivity results in a delayed-type response, which would be expected to take days to effect significant cellular recruitment and an inflammatory response. Although much of the work has focused on these gluten sensitive T-cells, it is possible that they are a product of mucosal injury rather than the primary mechanism. It has recently been shown that IL-15 expression in the intestinal mucosa is significantly upregulated in active CD.⁽³⁾ IL-15 is expressed by cells from the innate immune system such as enterocytes and monocytes within the lamina propria. This indicates a role for the innate immune system at an early stage in disease pathogenesis, which might suggest an alternative toxic mechanism for gluten.

In this regard, the transport pathway for gliadin may be relevant. In rat intestine, gliadin administration results in increased permeability of tight junctions, mediated by zonulin, which is likely to facilitate the delivery of gliadin to the lamina propria via the paracellular route. In human celiac mucosa, zonulin expression is increased. Further studies have examined the transcellular pathways in enterocytes using labeled monoclonal antibodies to a gliadin peptide.⁽⁴⁾ In patients with CD, staining was found to be granular, with gliadin located within apical vesicles and in larger vacuoles together with Class II MHC antigens. In controls, the staining was uniform with no such localization. It is known that antigens within endosomal compartments have a tendency to be processed and presented to CD4+ T-cells, which might explain the varied gluten epitopes that have been identified. Recent work has shown that several of the major epitopes remain largely undigested on delivery to the lamina propria.⁽⁵⁾

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What Are the Sensitivity and Specificity of Serological Tests for Celiac Disease?

Do Sensitivity and Specificity Vary in Different Populations?

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Clinical practice serological tests for celiac disease (CD) are useful for identifying individuals who require an intestinal biopsy to diagnose the condition, are supportive of the diagnosis in those with characteristic small intestinal histological changes, and may be used to monitor response to treatment. Tests most commonly offered by commercial laboratories include IgG- and IgA-based antigliadin antibodies (AGA-IgG and AGA-IgA), IgA endomysium antibody (EMA-IgA), IgA tissue transglutaminase antibody (TTG-IgA), and IgA antireticulin antibody (ARA-IgA).

The sensitivity and specificity of these tests have been studied largely in research settings and their accuracy may not be as good in clinical practice. Reasons for this include (1) lack of test standardization between laboratories; (2) problems defining a “gold standard” for diagnosing CD; and (3) study populations in the research settings usually differ from those in clinical practice. The sensitivity and specificity for each test are illustrated in table 1. These values are based on studies comparing patients with biopsy-confirmed CD to those with normal small intestinal histology and/or disease controls.

Table 1. Sensitivity and Specificity of Individual Serological Tests

Test	Age Group	Sensitivity	Specificity
AGA-IgG	Adults/Combined ^{*(1,4,5,11)}	57–100%	69–87%
	Children ^(2,3,7–10,12)	88–100%	47–94%
AGA-IgA	Adults/Combined ^(1,4,6,14,18)	54–100%	79–100%
	Children ^(2,3,7–10,12,13,15–17)	52–100%	71–100%
EMA	Adults ^(5,17,25,27,28)	87–95%	95–100%
	Children ^(2,8,9,15,17,19,24,25)	88–100%	90–100%
	Combined ^(1,4,20–23,26)	91–98%	99–100%
TTG	Children ^(19,25,33,34)	90–100%	94–100%
	Combined ^(20–32)	84–100%	91–100%
ARA	Children ^(7,8,36)	65–94%	93–100%

*Combined—refers to studies involving both adults and children

Both sensitivity and specificity for AGA tests are highly variable. In general, AGA-IgG in children has good sensitivity but poor specificity. Adult data is less reliable due to the relatively small number of studies in this age group. Sensitivity of AGA-IgA is lower than that

for the IgG-based test, while specificity is higher. Based on a small number of studies, sensitivity and specificity for AGA can be improved using a combination of the IgG and IgA tests.

EMA-IgA is both highly sensitive and specific. Most studies demonstrate EMA sensitivities in excess of 94 percent in children and 90 percent in adults with specificities above 97 percent in both age groups. Studies comparing the use of human umbilical cord with monkey esophagus as substrate for the EMA tests show no difference in their performance values.

TTG-IgA is also highly sensitive and specific. Initial studies on TTG used guinea pig protein as antigen while most recent studies have used human recombinant protein. In two comparative studies, human-derived assays were shown to have improved sensitivity and specificity over guinea pig-derived tests.^(26,35) One study found TTG-IgA by RIA to be more sensitive than by ELISA but with identical specificity.⁽¹⁹⁾ In general, TTG-IgA and EMA-IgA tests have similar sensitivity and specificity.

ARA-IgA is less frequently used in clinical practice and fewer studies are available to assess the sensitivity and specificity of this test. One study demonstrated a sensitivity of only 64 percent⁽⁸⁾ while others have found higher figures (table 1).

Selective IgA deficiency is more common in individuals with CD and occurs in approximately 2 percent of those with the condition. IgA-based tests for AGA, EMA, and TTG are unable to identify individuals with IgA deficiency who require a biopsy to diagnose CD. AGA-IgG tests are most often used for this purpose but are poorly predictive for positive histological findings.^(37,38) IgG-based tests for EMA and TTG may be more accurate for identifying symptomatic individuals with CD. Sensitivity and specificity of TTG-IgG in non-IgA-deficient individuals with CD range from 84–97 percent and 91–93 percent, respectively.^(39–41) There was good concordance between TTG-IgG and EMA-IgG in one study.⁽³⁹⁾

Good comparative studies on the sensitivity and specificity of the serological tests in different ethnic populations are not available. A few studies have compared results between children and adults. One study suggested AGA tests were better for identifying children under 5 years of age while EMA-IgA were better for those over 5 years of age.⁽¹⁾ Similarly, sensitivity and specificity for TTG-IgA was higher for adults (95 percent and 100 percent) than children (93 percent and 97 percent).⁽²⁵⁾ It is also possible that EMA-IgA is less reliable in children under 2 years of age.⁽²⁾

Summary

TTG-IgA (human recombinant) and EMA-IgA are the most sensitive and specific serological tests available for identifying individuals who require an intestinal biopsy for CD diagnosis. Their accuracy in clinical practice may not be as good as that reported from the research setting. Therefore, a positive diagnosis of CD should not be made on the basis of a serological test alone without intestinal biopsy confirmation. Serological tests may be less reliable in very young children. AGA tests are no longer recommended as a screening test because of the variable sensitivity and specificity associated with this test. There is no advantage to using a panel of tests incorporating AGA, EMA, and TTG antibodies over a single test using EMA or TTG.

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Clinical Algorithm in Celiac Disease

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Celiac disease is characterized by inflammatory injury to the small intestinal mucosa that results from an aberrant immune response to specific ingested dietary peptides derived from cereals such as wheat, barley, or rye. Celiac disease is common in both the United States and Europe and affects 0.5 to 1 percent of the population. The variety of clinical presentations of celiac disease is broad and ranges from chronic and severe diarrhea with weight loss and malnutrition to symptomless disease with minimal or no clinically evident malabsorption. The fact that celiac disease is common and has protean manifestations means that the diagnosis is easily missed unless physicians and other health care providers include celiac disease in the differential diagnosis of common conditions such as iron deficiency anemia, mild chronic diarrhea, recurrent abdominal discomfort, failure to thrive as well as less common manifestations such as skin rashes, hair loss, neurological disorders, vitamin deficiency states, or infertility. In brief, the first and most critical step in making a diagnosis of this commonly overlooked disorder is to think of celiac disease as a diagnostic possibility.

The primary diagnostic criterion is the identification of an enteropathy that is consistent with the inflammatory intestinal injury seen in celiac disease. This requires that a small bowel biopsy be obtained prior to effective treatment with a gluten-free diet. Changes of celiac enteropathy may be visually evident at endoscopy. These include: a reduction in the number or height of duodenal mucosal folds, mucosal nodularity, a mosaic pattern of mucosal fissures, and scalloping of the duodenal folds where the mucosal fissures cross the apex of a fold. These endoscopic findings, alone or in combination, are quite specific for celiac disease but are not sensitive. Thus, visualization of the duodenal mucosa at endoscopy cannot replace microscopic examination of duodenal biopsy tissue for diagnosis. Although intestinal histopathology remains the gold standard for diagnosis of celiac disease, the enteropathy may be mild and patchy and therefore missed on biopsy. Even when an inflammatory enteropathy is present, the histological features—while characteristic—are not pathognomonic since other disorders can result in a similar or identical histopathologic picture. In this regard, the diagnosis of celiac disease is aided or reinforced by the demonstration of serum IgA tissue transglutaminase autoantibody.

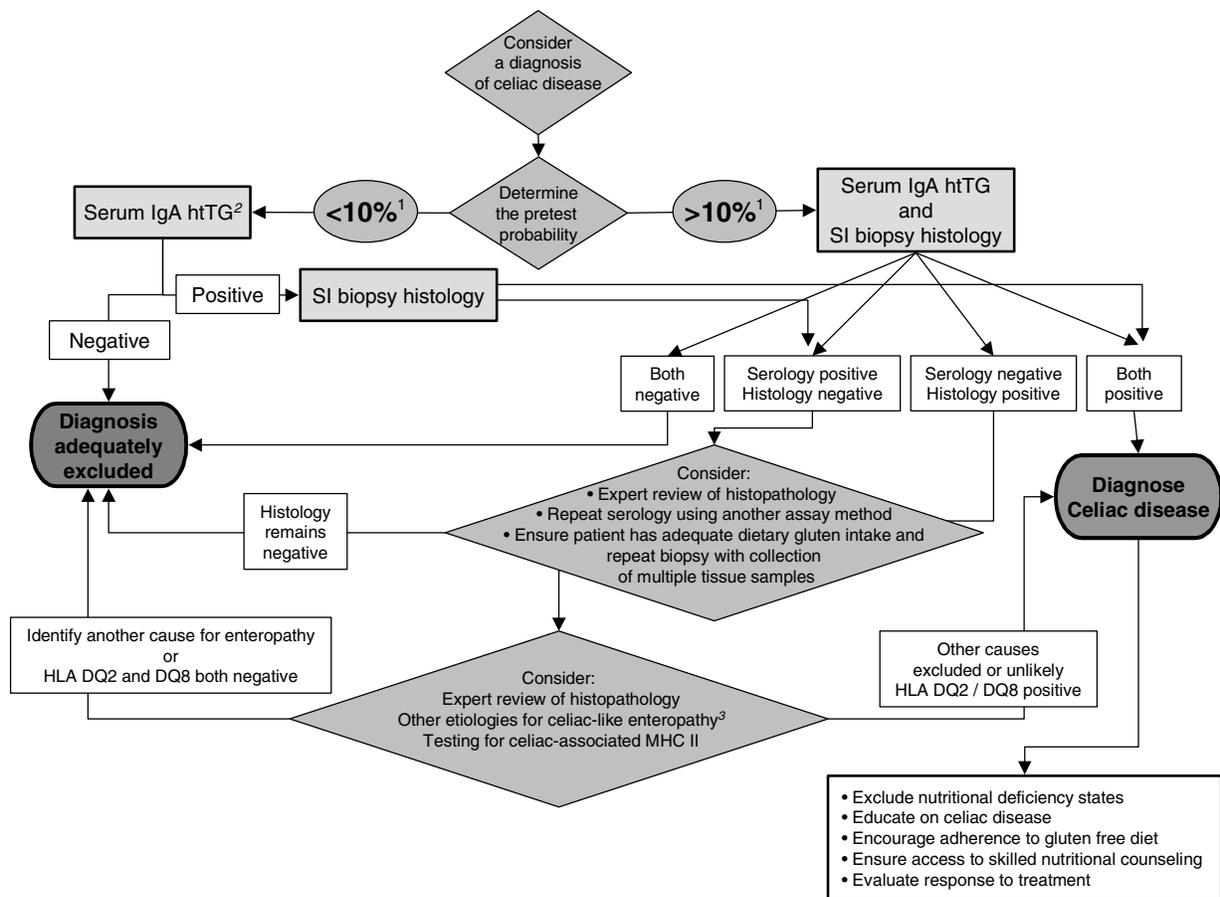
The identification of human tissue transglutaminase (htTG) as a celiac autoantigen has revolutionized our understanding of celiac disease pathogenesis. Simultaneously, it has greatly enhanced our ability to identify individuals with untreated celiac disease by accurate and minimally invasive serologic testing. Measurement of serum IgA against htTG has now become the serologic test of choice for diagnosis or exclusion of untreated celiac disease. IgA htTG serology is far more specific than the older gliadin-based immunoassays, to the point that the antigliadin assays are now of minimal clinical utility. The identification of serum IgA endomycial antibodies (EMA) remains a sensitive and highly specific marker of untreated celiac disease. However, IgA EMA testing by indirect immunofluorescence is more cumbersome, expensive, and operator dependent than IgA htTG enzyme immunoassay.

Serum IgA htTG in concert with small intestinal histology are a powerful diagnostic duo, and when both are performed correctly and are positive, provide a near absolute diagnosis of untreated or incompletely treated celiac disease. As a result, other diagnostic criteria such as clinical response to a gluten-free diet, histological response to a gluten-free diet, and gluten challenge now play lesser roles in diagnosis.

The remarkably high positive predictive value of IgA EMA or high-titer IgA htTG serology has led to debate as to whether endoscopy with biopsy is required for diagnosis—especially in instances where the pretest probability of celiac disease was already high. Each patient must be the final and individual arbiter of this debate, however, most expert celiac clinicians advocate strongly for histological confirmation of a diagnosis of celiac disease for the following reasons: (1) celiac disease is defined by an enteropathy, not by the presence of a serum autoantibody; (2) positive serology in the absence of significant enteropathy does occur and does not predicate lifelong treatment with a gluten-free diet; (3) endoscopy with biopsy is readily available in the United States and is relatively simple and safe; (4) it is difficult to either confirm or refute the diagnosis after dietary treatment is initiated; and (5) the cost of a false-positive diagnosis is enormous in that a patient may needlessly and fruitlessly adhere to an inconvenient and expensive gluten-free diet for decades while the actual etiology of their initial symptoms and signs remains undiagnosed.

A suggested clinical algorithm for diagnosis of celiac disease is shown in figure 1. The first and essential step is to consider the diagnosis. The next is to determine—on the basis of the patient’s clinical presentation, medical and family history, and available laboratory data—whether a diagnosis of celiac disease is highly likely (e.g., greater than 10 percent pretest probability) or less likely. For those with a lower pretest probability, IgA htTG serology is the current test of choice. A positive IgA htTG serology indicates the need for small bowel biopsy to diagnose celiac disease prior to lifelong treatment with a gluten-free diet. For those who are negative by IgA htTG, a serum IgA level may be checked to exclude IgA deficiency; however, but this additional test has a relatively low diagnostic impact. Antigliadin serology is largely counterproductive especially in individuals older than 2 years because of the plethora of false-positive results in low-risk populations. For high-risk populations (e.g., greater than 10 percent pretest probability), the likelihood of a false-negative IgA htTG serology may be unacceptably high; therefore, both serology and endoscopy with biopsy should be performed at the outset. Additional diagnostic steps are needed in instances where IgA htTG serology is positive but biopsy histology is reportedly normal, or where IgA htTG serology is negative but the small intestinal morphology and inflammatory infiltrate are consistent with a celiac lesion. There is no place for a trial of a gluten-free diet prior to diagnostic testing for celiac disease. Unfortunately, in some instances, patients present on treatment with a gluten-free diet in the absence of diagnostic pretreatment serology or histopathology. In such circumstances, gluten challenge followed by serology and biopsy is needed to establish a secure diagnosis.

When celiac disease is diagnosed, there should be an evaluation for deficiencies in nutrients such as iron, folic acid, vitamin B12 and vitamin D. The patient should be educated on the cause of intestinal injury and malabsorption in celiac disease, encouraged to adhere to a lifelong gluten-free diet, and provided with access to expert nutritional counseling. The clinical and serologic response to treatment should be monitored and reversal of any identified nutritional deficiencies confirmed. With accurate diagnosis and appropriate treatment the substantial morbidity associated with unrecognized symptomatic celiac disease can be avoided completely.



1. The pretest probability level at which both IgA htTG serology and small bowel histology should be examined will vary in individual circumstances depending upon the severity of the presenting complaint, the age and general health of the patient, and the patient's willingness to undergo endoscopy with biopsy versus risking a false-negative diagnostic evaluation.
2. Some clinicians also test for total IgA concentrations to identify IgA deficiency.
3. These include: tropical sprue, postinfectious enteropathy, peptic duodenitis, Crohn's disease, cow's milk and other dietary protein intolerances, eosinophilic enteritis, small intestinal bacterial overgrowth, giardiasis, immunodeficiency states including common variable immunodeficiency, severe malnutrition, graft versus host disease, refractory sprue, and intestinal lymphoma.

Figure 1: Clinical algorithm for diagnosis of celiac disease (based on references 1 and 2 below)

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Genetic Testing: Who Should Do the Testing and What Is the Role of Genetic Testing in the Setting of Celiac Disease?

George S. Eisenbarth, M.D.

At present, there is public health screening for a series of disorders that can be identified shortly after birth. These disorders are all relatively infrequent, but include diseases such as hypothyroidism (1/4,000 newborns) and phenylketonuria (1/13,500 to 1/19,000), and for some U.S. States and France, even diseases such as cystic fibrosis are assessed with newborn screening. The major driving force for screening is the ability to identify a treatable disorder with significant incidence such that there is a public health risk. Essentially all of the disorders are identifiable as a neonatal disorder requiring immediate therapy (e.g., neonatal hypothyroidism) or are Mendelian disorders with high penetrance (e.g., cystic fibrosis). The threshold for determining the cost-effectiveness of screening for a given disease is very much influenced by the infrastructure put into place for newborn screening due to the almost universal screening for phenylketonuria and hypothyroidism. As we consider celiac disease, we are considering a very common disorder of children and adults, a disease that at present usually does not manifest (expression of transglutaminase autoantibodies) until after 2 years of age, and most important, a complex genetic disorder. For complex genetic disorders that do not manifest in neonates and in particular immune-mediated diseases, which is determined by HLA alleles, we lack a public health screening infrastructure. It is likely that if the paradigm of screening for celiac disease is developed, it will provide an infrastructure that would affect and lower the threshold for public health intervention for a series of disorders including type 1A diabetes and Addison's disease.

In many ways, celiac disease is an ideal HLA-associated disorder for public health screening consideration. The disease is common (approximately 1 percent of children in Colorado, 6 percent of children with type 1A diabetes, 16 percent of children who are DQ2 homozygous with type 1A diabetes). Specific HLA class II alleles (DQ2 or DQ8) are present in approximately 95 percent of affected individuals. The disease is asymptomatic and thus not diagnosed in the majority of children. The transglutaminase autoantibody assay is inexpensive, sensitive, and specific, and small-bowel biopsy confirms diagnosis. There is an effective therapy (gluten-free diet). Major caveats include (1) whether the bulk of asymptomatic individuals with celiac disease would have morbidity/mortality, and whether early diagnosis and treatment are useful in preventing such morbidity/mortality; (2) only a subset of those identified with HLA-determined genetic risk will develop transglutaminase autoantibodies and biopsy-confirmed celiac disease (0.3 percent with no DR3/DQ2 allele develop persistent transglutaminase autoantibody by age 7 versus approximately 3 percent for those with DR3/DQ2); and (3) public health infrastructure is not in place for screening diseases that manifest by the expression of autoantibodies followed by diagnosed pathology in infancy, childhood, and adulthood.

There are populations at particularly high risk of developing celiac disease, including individuals with multiple different autoimmune disorders and with type 1A diabetes. Figure 1 (from barbaradaviscenter.org Web book on immunology of diabetes) illustrates the risk of expression of transglutaminase autoantibodies (TGA) amongst patients and their relatives with type 1A diabetes subdivided by DR3 haplotypes containing DQ2.

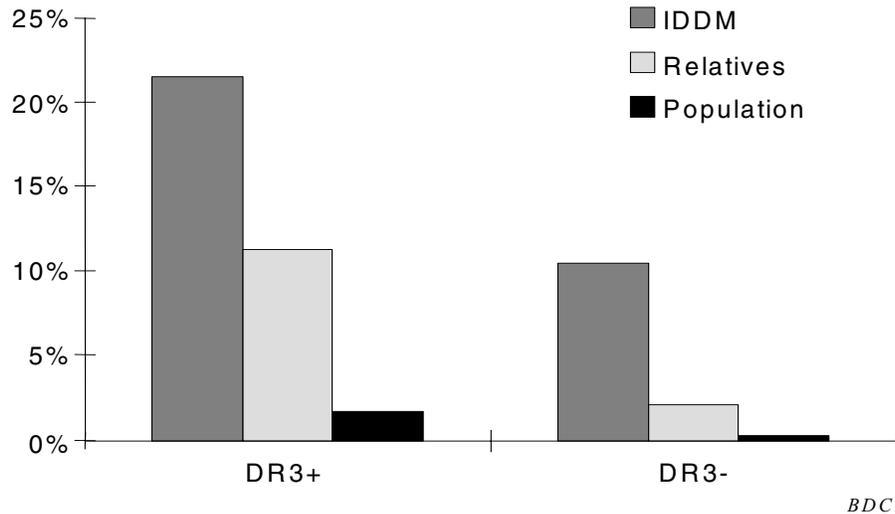
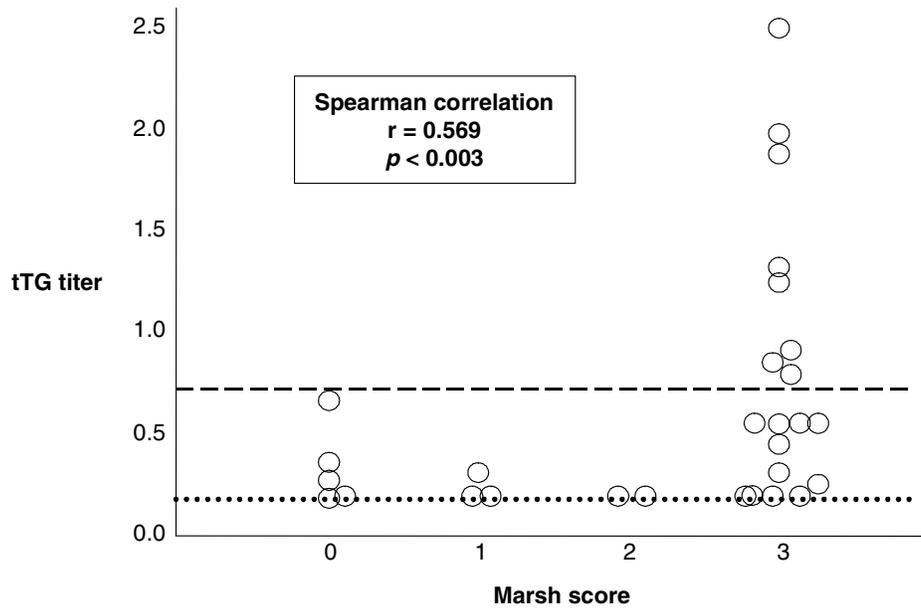


Figure 1. Prevalence of TGA by HLA-DR Amongst Patients With Type 1 Diabetes Mellitus, Relatives of Patients with Diabetes Mellitus, and the General Population

Of newborns evaluated in the DAISY study, headed by Marian Rewers of the Barbara Davis Center, 39.5 percent have either DQ2 and/or DQ8. At present, this is the primary genetic locus that can be relied upon for determining risk at birth. Individuals not expressing DQ2 or DQ8 are at low risk. These same two alleles determine risk for type 1A diabetes and Addison’s disease but their negative predictive values (ability with celiac disease to “exclude” 60 percent of population) are lower. It is a difficult task to ascertain additional loci determining celiac disease given the development of complications such as intestinal T-cell lymphoma. At present only MHC alleles can be considered for genetic analysis.

Given the ability to define a higher- and lower-risk group with relatively simple class II HLA typing, an important question is whether therapy would need to be instituted in early infancy. Prospective epidemiologic questions, in particular studies of diet headed by Jill Norris of the CEDAR study, are evaluating whether timing of introduction of, for instance, gliadin will influence the eventual development of celiac disease. If such a dietary influence is found and has a life-long benefit, it would be a major impetus for newborn screening.



Hoffenberg, *J. Peds* 2000;137:356.

Figure 2. Transglutaminase Autoantibodies and Marsh Score (Disease Severity)

Given genetic susceptibility, current TGA assays provide inexpensive, specific, and sensitive markers of the presence of celiac disease pathology with high levels of the autoantibody associated with intestinal biopsy-positive celiac disease.

In summary, celiac disease is an important candidate for public health newborn genetic screening based upon HLA DQ alleles. Outside of the newborn period, and particularly for populations at increased risk (autoimmune disorders such as type 1A diabetes and their relatives), HLA analysis can contribute to defining a population not needing repeated testing over time to identify the development of TGAs. Such testing from a public health perspective is likely to be useful given the prevalence of celiac disease and the potential for altering relatively simple factors such as the timing of introduction of gliadin.

Serological Testing for Celiac Disease

Alaa Rostom, M.D., M.Sc., FRCPC

Context

Mounting evidence suggests that celiac disease (CD) is much more common than previously suspected. Furthermore, with the availability of increasingly more sensitive and specific serological tests, it has become apparent that the majority of CD patients do not demonstrate the classically described features of symptomatic intestinal malabsorption, and an important proportion have milder histological grades that do not necessarily fit with commonly used histological criteria cut-offs for defining CD (i.e., requirement of some degree of villous atrophy). These findings have important implications for the assessment of the diagnostic performance of the available serological tests, since there is an inherent interdependence between the performance of these tests, and the clinical and histological criteria used to define CD.

Objectives

(1) To conduct a systematic review of the diagnostic performance of antigliadin antibody (AGA), endomyseal antibody (EMA), and transglutaminase antibody (tTG) and their subtypes for the screening and diagnosis of CD. (2) To assess the performance of these tests in unselected general populations; patients with suspected CD; and populations at high risk of CD.

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 (1966 to Oct 2003) and EMBASE (1974 to Dec 2003) databases.

Study Selection and Data Extraction

This study was conducted using accepted systematic review methodology. Study selection was performed by two independent reviewers using three levels of screening with increasingly more strict criteria to ensure that all relevant articles were captured. Articles passing the third level screen fulfilled all the inclusion/exclusion criteria, allowed actual extraction of the sensitivity and specificity data, and did not have fatal methodological flaws. Articles were excluded if the control group did not have the gold standard test (biopsy) applied; no description of biopsy criteria given; celiac group known to be positive for test under evaluation; control group known to be negative for the test under evaluation; control groups included patients with Marsh I or II biopsy lesions; or AGA test performed without commercial ELISA kit or before 1990. Study data was abstracted using a predetermined electronic form by one reviewer, and

verified by another. The quality of reporting of the included studies was assessed using the QUADAS tool.

Data Synthesis

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 or human umbilical cord). Pooled estimates were only calculated if clinically and statistically appropriate. We calculated a weighted mean of the sensitivity and specificity from those of the included study. For each pooled estimate, a 95 percent confidence interval (CI) was calculated using both a fixed and random effects model, the results of which were compared as a further test for heterogeneity. The pooled estimates for the sensitivity and specificity were also compared to a summary ROC curve calculated for the same group of studies as a second check of the estimates.

Results and Conclusions

Out of 3,982 citations identified by the search strategy, 907 met level 2 screening criteria. Of these, 204 diagnostic test studies of one or more of the serological markers of interest (AGA, EMA, tTG) were identified. Fifty-five studies fulfilled the level 3 inclusion criteria.

The results of the systematic review demonstrate that in the studied populations IgA-EMA and IgA-tTG have sensitivities and specificities each in excess of 90 percent in both children and adults. The pooled specificity of EMA was 100 percent in adults using either EMA-ME or EMA-HU. In studies of children, the specificity of EMA using these two substrates was 97 percent and 95 percent, respectively, with overlapping 95 percent CIs, suggesting no statistical difference between these values. In adults, the pooled specificity of tTG-GP and tTG-HR were 95 percent and 98 percent, respectively, with overlapping CIs. Similarly, in children, the specificities were 96 percent and 99 percent, again with overlapping CIs. Among the three studies in adults, and four studies in children that assessed both EMA and tTG, the specificities were nearly identical. Overall, these results suggest that EMA and tTG antibodies demonstrate extremely high specificities in both adults and children.

We identified a tendency towards greater variability in sensitivity between studies and between antibodies, compared with specificity. IgA-EMA-ME demonstrated sensitivities of 97 percent and 96 percent in adults and children, respectively. EMA-HU demonstrated a similar sensitivity of 97 percent in children, although the pooled estimate in adults was somewhat lower at 90 percent. Two studies assessed both EMA-ME and EMA-HU in adults, one demonstrated identical sensitivities of 95 percent, whereas the other showed a lower sensitivity of HU compared with ME (90 percent versus 100 percent). None of the included mixed-age studies assessed both of these antibodies. Heterogeneity existed in the analyses of sensitivity of tTG-GP in the adult, but it is likely close to 90 percent. In children, the pooled estimate was 93 percent. The sensitivity of tTG-HR was 98 percent in adults and 96 percent in children, although in both cases the CIs included a low of 90 percent. In studies of mixed-age populations, the sensitivity was 90 percent.

Estimates of the sensitivity of the IgG class antibodies of EMA and tTg suggest that these tests have poor sensitivities around 40 percent, although the specificities were high at around 98 percent. These findings suggest that this class of antibody would be inappropriate as a single test for CD, but may be useful in IgA deficient patients, or in combination with an IgA class antibody. One study that assessed the use of IgA-tTG-HR with IgG-tTG-HR found a sensitivity of 99 percent and a specificity of 100 percent for the combination.

The analyses of all the AGA subgroups demonstrated significant heterogeneity, and no statistical pooling was undertaken. The sensitivity of IgA-AGA in adults is likely not much higher than 80 percent, but seems somewhat higher in children. The specificity likely lies between 80 and 90 percent in adults and children, although the studies of serial testing of AGA followed by EMA or tTG in the prevalence section of this report suggest that the specificity is low as well. Even if one considers an optimistic range, the performance of IgA-AGA in both adults and children is inferior to that of the other antibodies discussed above.

The analyses of IgG-AGA suffered from significant clinical and statistical heterogeneity making even general summary statements difficult. The typical sensitivity of this test likely lies below 80 percent in adults, and between 80 and 90 percent in children. The specificities are likely close to 80 percent in adults and between 80 and 90 percent in children with the same warning coming from the prevalence studies, suggesting that in the era of EMA and tTG, testing for CD with AGA has a limited role.

The sensitivity of the studied serological tests appears to be lower than reported when milder histological grades are used to define CD. Several studies demonstrated sensitivities for EMA and tTG well below 90 percent when histological grades milder than Marsh 3 were considered. If true, then the nearly perfect negative predictive value of these tests would drop. Furthermore, the majority of studies assessed the performance of these antibodies in situations of high CD prevalence. Therefore, the positive predictive value of these tests is likely lower than reported when the tests are applied in general population screening.

Abbreviations: ME—monkey esophagus; HU—human umbilical cord; GP—guinea pig liver; HR—human recombinant.

Epidemiology of Celiac Disease: What Are the Prevalence, Incidence, and Progression of Celiac Disease?

Marian J. Rewers, M.D., Ph.D.

Definition of Disease

Celiac disease (CD) is a chronic, systemic, autoimmune disorder induced by gluten proteins present in wheat, barley, and rye. Genetically susceptible persons develop autoimmune injury to the gut, skin, liver, joints, uterus, and other organs. The classical definition of CD includes gastrointestinal manifestations confirmed by a small bowel biopsy (SBB) with findings of villous atrophy, crypt hyperplasia, and normalization of the villous architecture in response to gluten-free diet.^(1,2) However, the clinical manifestation of CD has become more subtle and affects mostly older children or adults.⁽³⁾ SBB is poorly accepted by a majority of patients with mild or no symptoms, and the pathological examination of biopsy material is suboptimal in most settings. SBB is also hardly a “gold standard”—occasionally false-negative due to patchy mucosal changes, often most severe in proximal jejunum, and typically not reached by endoscopic biopsy. This has led some to propose a new definition of CD, based on the presence of serum IgA autoantibodies to tissue transglutaminase (IgA TG) and HLA-DQB1*0201 or *0302 alleles.⁽⁴⁾ These markers are increasingly used in screening for CD, but their true sensitivity and specificity is debatable due to problems with some IgA TG assays and verification bias—overestimation of sensitivity and underestimation of specificity due to lack of SBB studies in TG-negative screenees.

Prevalence

Prevalence of childhood CD has been reported to be as high as 1 in 77 among Swedish 2 ½-year-olds,⁽⁵⁾ 1 in 99 (using SBB as criterion) or 1 in 67 (using presence of IgA TG and HLA-DQB1*0201 or *0302) in Finnish schoolchildren,⁽⁴⁾ and 1 in 230 in Italian school-age children.⁽⁶⁾ In the United States, the frequency of CD among adults varies from 1 in 1,750 (with CD defined as clinical cases including dermatitis herpetiformis)⁽³⁾ to 1 in 105 (CD defined by presence of IgA TG in blood donors⁽⁷⁾). The estimates based on sero-epidemiological studies suggest that for each diagnosed case of CD, there may be 3–7 undiagnosed cases.

Incidence

Cumulative incidence of SBB-confirmed CD in children has been reported between 1 in 285 in Sweden⁽⁸⁾ and 1 in 588 in New Zealand.⁽⁹⁾ In Colorado, the risk estimate for developing CD—defined as IgA TG positivity by the age of 5—was 1 in 104 (95 percent CI 1:49–221).⁽¹⁰⁾ Population-based estimates of the incidence of SBB-confirmed CD in adults vary from 2–13/100,000.^(3,9) The recent increase in the incidence rates is likely due to increasing use of serologic screening, leading to diagnosis in milder cases. Infant and early childhood nutrition varies among populations. Differences in the prevalence of susceptibility HLA alleles may explain interpopulation variation in the incidence of CD. The effects of nutritional practices on

the risk and severity of CD may also account for geographic and temporal variation in the incidence of CF and may be of great public health importance.

Progression

While there is growing evidence for a remitting-relapsing pattern of CD autoimmunity in some patients,^(4,11) the disease process defined by current serological and histopathological techniques is remarkably persistent in the absence of gluten-free diet. A two- to threefold excess in all-cause mortality among CD patients, compared to the general population, has been reported in some studies^(12,13) and attributed to GI tract malignancies.^(14,15)

In summary, CD is a protean systemic disease affecting up to 1 percent of the general population. Appropriate screening, diagnosis, and treatment guidelines are being redefined using improved diagnostic methods that include IgA TG testing and HLA-DQB1 typing, in addition to SBB.

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What Are the Prevalence and Incidence of Celiac Disease in High-Risk Populations: Patients With an Affected Family Member, Type 1 Diabetes, Iron-Deficiency Anemia, and Osteoporosis?

Joseph A. Murray, M.D.

Outline

The presence of autoimmune conditions like insulin-dependent diabetes mellitus (DM), a family history of celiac disease (CD), or dermatitis herpetiformis may increase the risk of coexisting CD. The prevalence of CD may be increased in certain patient groups including the following: osteoporosis or low bone mass, or iron-deficiency anemia.

Family History of CD and Dermatitis Herpetiformis

Many early case reports documented the occurrence of CD in siblings, identical twins, parent and child pairs, as well as more extended kindreds. At least 20 percent of index cases will have an affected family member if screening is done. The exact degree of increased risk for specific family members has not been reliably ascertained but estimates have been made based on screening studies undertaken at one point in time. Identical twins have a 75–100 percent concordance rate for the disease. Siblings are at the next highest risk at 7–20 percent concordance rate. It has been suggested that if siblings share the same HLA disease risk haplotype, their risk approaches 40 percent. It is less so for parents or children of the proband. Most of these studies were in homogenous populations where the background risk for CD was high. A recent multicenter study in the U.S. identified a rate of 4–5 percent of first-degree relatives had CD based on endomysial antibody testing, a rate significantly greater than the rate in the not-at-risk individuals.

These studies have based their risk estimations on the numbers of relatives that were screened, not necessarily the number of first-degree relatives. Many of these studies are subject to the selection bias of family members coming forward or agreeing to screening. Additionally, there often is incomplete followup of family members to determine if the screening at one point in time is an adequate estimation of the risk over time. Not all studies were so positive. Two of 100 first-degree family members underwent biopsy and only 2 had CD. Five others appeared to have transient changes. Occasional cases of progression to CD have been reported in a few cases initially negative for CD. In our ongoing community study, 10 percent of tested first-degree relatives are found to have undiagnosed CD. A further 2 percent had possible CD with subtle histopathological changes on intestinal biopsies. Almost as many family members were diagnosed clinically for CD via screening, usually because of a heightened awareness of the risk in a symptomatic relative. Serological testing detected most, but not all, screened-found patients with CD, however 4/41 patients were found to have CD based on biopsy alone. This was due to the protocol that included biopsying symptomatic family members who had the at-risk HLA type despite negative serology. While most screen-found patients had little or no symptoms, compliance with a gluten-free diet was good.

Type 1 Diabetes Mellitus

An association between CD and type 1 DM has been recognized for more than 40 years. Several studies, both in children and adults, have shown that there is a 1.5–7 percent prevalence of CD in type 1 diabetics. There is some evidence that undiagnosed CD may not only coexist with diabetes but may precede it. It has been suggested that delayed diagnosis of CD is associated with an increased risk for subsequently developing diabetes. Patients in whom CD was identified and treated in early childhood had a lower rate of developing diabetes than children in whom CD was diagnosed later in childhood or as adults. Autoantibodies directed against islet cells are frequently present in untreated CD but disappear with the gluten-free diet.

Studies of American children with type 1 DM revealed a prevalence of CD of 4–6 percent and studies of adult American patients with type 1 DM reported a prevalence of CD of 4–6.4 percent. These studies have largely been based in tertiary referral centers or specialized diabetic clinics and therefore may not be representative of the prevalence of CD in the type 1 DM community. Studying the occurrence of CD in a pediatric group alone may underestimate the lifetime risk of the disease that requires extended followup. We have undertaken a community-based study of CD in residents of Olmsted County, MN, who have type 1 diabetes encompassing all ages. The prior incidence of CD in this cohort of approximately 502 individuals was just 3 individuals. Unlike many prior studies that focused on just adults or children, we endeavored to study all ages. Two hundred and five type 1 diabetics have been tested, of whom a total of 12 have CD. We estimate that there should be 30 cases of CD within the type 1 diabetic cohort within the community. The prevalence of CD in the type 1 diabetics is substantially higher than expected in the general population. Fifty percent of subjects did not have gastrointestinal (GI) symptoms. It would seem that DM is a rich source for discovering CD. Indeed, many diabetic patients undergo endoscopy to investigate the frequent GI symptoms that afflict type 1 diabetics. It would require little extra effort or cost to obtain duodenal biopsies at least once to identify CD, and the biopsy result may explain the GI symptoms for which the procedure has been done. It is not clear what impact that discovery may have on diabetic control or complications, though GI symptoms seem to improve on a gluten-free diet. Certainly our data do not support the hypothesis that CD is a significant risk factor in the subsequent development of DM.

Iron-Deficiency Anemia and CD

Iron is absorbed by the proximal small intestine, the site of the greatest damage in CD. Active CD is also associated with heme-positive stools. It is not surprising, therefore, that iron-deficiency anemia is a common finding in newly diagnosed CD. It also usually resolves with the institution of a gluten-free diet. Several studies from Europe and North America have suggested that iron-deficiency anemia may be the sole manifestation of CD in the absence of diarrhea. The association of CD may be especially high in those unresponsive to oral iron therapy. An Italian study of 200 consecutive adult patients presenting with iron deficiency revealed a 5 percent prevalence of CD. The prevalence of CD in patients referred to GI endoscopy for investigation of iron deficiency varies from 3 to 12 percent. These studies may be subject to selection bias due to referral patterns.

Iron deficiency may be present in as many as 50 percent of individuals at the time of diagnosis of CD but rarely is the reason for referral. If it occurs in young women it is often

ascribed to excess menstrual loss. The persistence of anemia after menopause is a frequent precipitant for investigation that leads to the detection of CD. Indeed patients have undergone hysterectomies to treat the iron deficiency that persisted until the correct diagnosis was made. If the majority of subjects with CD have iron malabsorption, then many of the undiagnosed subjects with CD should present and be detectable in this population of anemic individuals. We have identified a total of 529 prevalent cases of diagnosed iron-deficiency anemia residents in Olmsted County in 2001. One hundred sixty-one community residents with otherwise unexplained anemia have undergone testing for CD, of whom 6 have been found to have CD. Two additional patients had possible CD based on subtle pathologic changes. Anemia was rarely sought or diagnosed in children. However, iron-deficiency anemia is a very common illness in primary care and often does not spur investigation in the younger patient. In fact hemoglobin is not measured routinely in children. A potential confounder is the association between haemochromatosis (HFE) genes and CD. 282Y was more common in CD and was associated with higher Hgb and iron stores. Clinicians should consider CD as a possible though not common cause of unexplained anemia, and gastroenterologists should biopsy the duodenum when endoscopic patients with iron-deficiency anemia.

Low Bone Mass and CD

Individuals with bone mineral density more than 2.5 standard deviations below the sex-specific peak bone mass are presumed to have osteoporosis. Low bone mass is common in subjects with newly diagnosed CD. The mechanism for this effect may be due to malabsorption of vitamin D and calcium and decreased intake of calcium due to lactose intolerance. However, low bone mass may be due not only to osteoporosis but also to osteomalacia. While osteomalacia would therefore be expected to be the bone consequence of malabsorption, osteoporosis been described in CD on bone biopsy. A raised alkaline phosphatase and other stigmata of osteomalacia may not always be present. It is possible that low bone mass is the only manifestation of CD in a significant proportion of patients with this disorder and consequently, CD may be an underdiagnosed cause of low bone mass in the general population. There are two ways in which the epidemiology of CD and osteoporosis has been examined.

The first is the screening of patients with osteoporosis for CD. A limited number of screening studies for CD among patients with low bone mass have been performed in Europe. CD was found in 3.4 percent of adults with low bone mass. One Scandinavian study screened a pediatric population with low bone density and demonstrated a 5 percent prevalence of CD. However, a carefully performed Canadian study in predominantly postmenopausal women with osteoporosis has not identified an increased prevalence of CD. Why the difference? The early studies were predominantly based in serology alone without biopsy confirmation. It is also not clear if referral bias may have been factor.

Our studies in a population-based setting have not identified an increased rate of CD in over 290 patients with osteoporosis. Initial serological tests had a high rate of low-level positivity to tissue transglutaminase antibodies, however followup serological tests and biopsies only conformed CD in 2/25 initially seropositive persons. This yielded an overall positive rate of only 2/290, which is close to the expected general population by screening but greater than that of the diagnosed rate.

The second way the association has been examined is the screening of a large population for CD and relating it to measured bone density. The single best study is the Cambridge health study, which suggested a 3-fold increased risk of osteoporosis in seropositive individuals. However, the attributable risk to CD was low.

It seems, therefore, that screening those postmenopausal osteoporosis patients defined by World Health Organization (WHO) criteria is unhelpful. By contrast, when patients with CD are screened for bone disorders, many have elevated parathyroid hormone (PTH) and low calcium; it would be in these patients whose Z-scores are low that CD should be considered. The real problem lies in how osteoporosis is defined.

While low bone mass may remain unrecognized in many individuals with CD, bone pain is a common symptom in untreated adult patients with CD and may reflect more subtle osteomalacia (see preliminary results). It is not known what consequences of low bone mass may occur in CD. Low bone mass usually responds to the introduction of a gluten-free diet with a gradual restoration of bone over 2 years. However, it remains to be known if using the Z-score as a guide would be a better method to determine risk of CD in this population. The finding of low bone density in a young person may well be a risk factor for CD but bone densitometry is not a routine test at this age. There is no clear increase in fracture risk in patients diagnosed with CD. What effect undiagnosed CD has on lifelong fracture risk is not known.

Conclusions

Case finding of CD is feasible in some high-risk situations. Family members are often the most accessible and most likely of any of these groups to have the disease. Subjects with symptoms suggesting CD should not only have serologic testing done but also should be considered for intestinal biopsy, as some family members may have intestinal damage without serologic evidence of the disease. Type 1 diabetics and those with iron-deficiency anemia have a small but significant risk of CD. What impact screening these at-risk groups will have on the overall detection of CD is unknown but most likely represents only a small proportion of the prevalent cases overall.

Screening for CD by any method or even case finding in asymptomatic people is not clearly justified without data on outcome. We do not know the outcome of undiagnosed CD as it is present in either the at-risk groups or the larger reservoir of undetected CD in the general population. As CD makes such a small impact on the overall risk of osteoporosis and fractures, it seems unjustified to undertake systematic searching for CD to reduce the burden of bone disease. The Cambridge study suggests, however, that our data based on diagnosed CD may underestimate the impact of CD on bone disease and anemia as most CD goes undiagnosed and untreated. Confirmation of these results with biopsy and studies on the long-term consequence of undetected or untreated CD is needed. To truly understand the potential consequences of CD, followup may need to be lifelong or at least extend into late adult life. Such studies may be possible by focusing these efforts on finding CD in an older cohort or in those populations whose health history has been followed up long-term and serum-stored.

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Incidence and Prevalence of Celiac Disease

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Context

Celiac disease (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 (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 (fully developed gluten-induced villous atrophy discovered in an asymptomatic patient by serologic screening or perhaps an endoscopy for another reason). The true prevalence of CD is difficult to estimate because of this variable presentation, particularly when many patients may have little or no symptoms. With this limitation in mind, there appear to be important geographical and ethnic differences in the reported prevalence of CD. The prevalence appears highest in Celtic populations where estimates of 1:300 to 1:122 have been described. In North America, the prevalence has been estimated to be 1:3000, but a recent American study found it to be 1:105 among the general not-at-risk population suggesting that the disease is underrecognized.

Objectives

(1) To conduct a systematic review of the prevalence and incidence of CD in North American and Western European populations. (2) To assess differences in prevalence among different geographical regions/countries and in at-risk populations such as relatives and patients with type I diabetes.

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 (1966 to Oct 2003) and EMBASE (1974 to Dec 2003) databases.

Study Selection and Data Extraction

This study was conducted using accepted systematic review methodology. Study selection was performed by two independent reviewers using three levels of screening with increasingly more strict criteria to ensure that all relevant articles were captured. Articles passing the third level screen fulfilled all the inclusion/exclusion criteria, allowed actual extraction of the prevalence and/or incidence data, and did not have fatal methodological flaws. Articles were excluded if the studied population was non-North American or Western European; patients were

identified by surveys or through solicitation of celiac societies; or reported incidence without a population density denominator. Study data was abstracted using a predetermined electronic form by one reviewer, and verified by another. The quality of reporting of the included studies was assessed.

Data Synthesis

The prevalence and incidence data were anticipated to be quite heterogeneous considering the different, countries, age groups, and risk characteristics of the studied patients. Attempts were made to group studies by age group, study population, and serological screening method. If the grouped studies did not show evidence of heterogeneity, pooled estimates of the prevalence were produced for that group of studies; otherwise a descriptive presentation of the data with a qualitative systematic review was conducted. For pooled estimates, statistical heterogeneity was assessed along with 95 percent confidence intervals.

Results and Conclusions

The literature search yielded 2,116 references. Of these, 119 articles, were included in the review. Of these studies, 42 assessed the prevalence and/or incidence of CD in a general population. Twelve of the 42 reported on the incidence of CD, and 30 reported on the prevalence. Studies of the prevalence of CD in populations at risk were divided as follows: 18 studies of the first-degree relatives of CD patients and 34 studies in patients with type 1 diabetes. Studies of the prevalence of CD in patients with associated clinical presentations were divided as follows: 12 studies in iron-deficiency anemia, 4 studies in metabolic bone disease, and 13 studies of patients with suspected CD. Several studies included data for multiple at risk groups.

Incidence

The crude incidence of CD among western European and North American countries over the past 25 years has varied between 1 and 51 per 100,000, and the cumulative incidence by age 5 between 0.118 and 9 per 1,000 live births. Important methodological differences existed among the studies, from using patient registers to identify patients to actively screening at-risk groups. The true incidence of CD is likely greater than reported.

Prevalence

The included prevalence studies demonstrated important differences in execution, tests for prevalence assessment, patient sampling, rates of biopsy confirmation, and histological grade defining CD. The prevalence of CD in the general unselected populations of North America and Western Europe is quite high and likely falls within the range of 0.5–1.26 percent (1:200 to 1:79). Smaller sample-size studies tended to give wider estimates ranging from 0.17 to 2.67 percent. Among the studies from the United States, the range of prevalence was 0.4–0.95 percent in adults, and 0.31 percent in children. In Italy, the range of prevalence was between 0.2 and 0.8 percent, whereas the Scandinavian countries, Ireland, and the United Kingdom, tended to show a higher prevalence of CD of approximately 1.0–1.5 percent .

The prevalence of CD in patients with type 1 diabetes is higher than the prevalence in the general not-at-risk population. The prevalence of CD by serology varied greatly with lows near 1 percent and highs close to 12 percent. However, the majority of studies, and particularly those using EMA or tTG, demonstrated prevalence rates in the 4–6 percent range. Although the prevalence by biopsy also varied, and was usually lower than the prevalence by serology, the typical study with complete biopsy confirmation of serology-positive patients demonstrated a prevalence in the range of 3–6 percent.

The prevalence of CD in relatives of patients with CD is also higher than that of the general population, both in first- and second-degree relatives. That prevalence varied between 2.8 and 17.2 percent in first-degree relatives and between 2.6 and 19.5 percent in second-degree relatives. The prevalence remains elevated among first cousins, and was 17 percent in the single study of these subjects.

The prevalence of CD among patients with iron-deficiency anemia is highest (between 10 and 30 percent) in studies of patients with GI symptoms, or in patients who have no gross lesions seen at an initial investigation. CD appears to also be common in premenopausal women, both with (4.5 percent) and without (33 percent) heavy periods. Overall, in typical asymptomatic IDA patients assessed by serology or biopsy, the prevalence of CD was between 2.3 and 6 percent.

The studies of the prevalence of CD in patients with low BMD suggest that between 0.9 and 3 percent of patients with osteoporosis have CD. However, the included studies demonstrated important methodological weaknesses, and contradictory results making it difficult to draw any firm conclusions about the true prevalence of CD in this population.

Overall, CD appears common in the unselected general populations of North America and Western Europe with a prevalence in the range of 1:100 and a proportionally higher prevalence in various high risk populations such as relatives of CD patients. The true prevalence still requires further study based on some of the identified study limitations that include incomplete biopsy confirmation and reliance on serological tests whose performance has not been fully characterized in situations of low prevalence (<15–20 percent).

Clinical Presentation of Celiac Disease in the Pediatric Population

Alessio Fasano, M.D.

Introduction

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Gluten is a protein component in wheat and other cereals (rye and barley), and a staple food for most populations in the world. The major predisposing genes are located on the HLA system, namely the HLA-DQ2 and/or DQ8 genotypes found in at least 95 percent of patients.

CD can manifest with a previously unsuspected range of clinical presentations and can present at any age, including the elderly. However, typical cases often manifest in early childhood.

Clinical Spectrum of CD in Children

The clinical spectrum of CD in children is wide⁽¹⁻⁷⁾ (table 1). *Typical* forms of CD usually present in young children with impaired growth, chronic diarrhea, abdominal distention, muscle wasting and hypotonia, poor appetite, and unhappy behavior. Within weeks to months of starting to ingest gluten, weight gain velocity decreases and finally weight loss can be observed. Despite a wide variability between countries, classical CD still represents a common presentation in the pediatric age group.

Table 1. Clinical Manifestations of Celiac Disease in Pediatrics

Clinical Form	Histological and Clinical Manifestations
Typical	<i>Fully expressed enteropathy</i> Intestinal symptoms, e.g., chronic diarrhea, weight loss, abdominal distention
Atypical	<i>Fully expressed enteropathy</i> Extra-intestinal manifestations, e.g., iron deficiency, short stature, osteoporosis
Silent	<i>Fully expressed enteropathy</i> Minimal complaints or symptom-free (occasionally discovered by serological screening)
Potential	Minimal changes enteropathy or normal small intestinal mucosa Sometimes symptomatic

Atypical CD is characterized by unusual intestinal complaints (e.g., irritable bowel syndrome–like, nausea, vomiting) or by extra-intestinal manifestations (e.g., short stature,

pubertal delay, iron deficiency, dental enamel defects, and abnormalities in liver function test). Atypical presentation is usually encountered in association with the late onset of complaints, particularly in older children. Dermatitis herpetiformis, a blistering skin disease, is presently regarded as a variant of CD.

CD is defined as *silent* whenever a typical gluten-sensitive enteropathy is found in a subject who is apparently healthy. Large numbers of silent cases of CD have been reported in at-risk groups (such as subjects with insulin-dependent diabetes and first-degree relatives) and in general population samples enrolled in screening programs. An indepth clinical examination shows that many of these “silent” cases are indeed affected with a low-grade intensity illness often associated with decreased psychophysical well-being.

Finally, a *potential* form of CD is diagnosed in subjects showing positivity of EMA and/or anti-tTG antibodies, the typical HLA predisposing genotype (DQ2 or DQ8), but a normal or minimally abnormal mucosal architecture (increased IEL count) at the intestinal biopsy. These cases are at risk of developing a typical CD enteropathy later in life.

Untreated CD is associated with a list of diseases and complications⁽¹⁾ (table 2). The possible association with Down syndrome is well known. Two recent studies provided further evidence of an increased prevalence of CD in Down syndrome in the United States, with a reported frequency of this disease association of 3.2–10.3 percent, respectively.^(8,9) In Down syndrome children, CD is not detectable on the basis of clinical findings alone and is therefore underdetected. Even when there are symptoms, they may be considered clinically insignificant or possibly attributed to Down syndrome itself. Nevertheless, the reported resolution or improvement of gastrointestinal complaints on a GFD for all symptomatic patients suggest that identification and treatment can improve the quality of life for these children.

Table 2. Associated Diseases

Associated Diseases	Associated Diseases Possibly Secondary to Untreated CD
Down syndrome	Autoimmune diseases (e.g., type 1 diabetes, thyroiditis, hepatitis, primary biliary chirrosis)
Turner syndrome	Epilepsy with or without occipital calcifications
Williams syndrome	Ataxia and other neurological disturbances
IgA deficiency	IgA nephropathy

An increasing number of studies show that many CD-associated problems that were originally described mostly in adults can indeed be observed in children or adolescents.⁽⁷⁾ Osteoporosis is one of the well-known complications of untreated CD in adults. Several studies showed that bone mineral content, bone area, and bone mineral density could be significantly lower in CD adolescents than in controls. Further, it has been reported that a complete recovery of bone density can occur after 1 year of GFD, and maintenance of normal bone mineral density is achieved after long-term treatment. In the last decade, there has been an explosion of interest on the neurological manifestations associated with CD. The existence of a syndrome characterized by epilepsy, occipital calcifications, and CD is generally accepted. The strong association with autoimmune diseases, including type 1 diabetes^(10,11) and thyroid disease⁽¹¹⁾ has

been widely reported. The question regarding the possible role of an early treatment of CD on the development of autoimmune complications is still open for debate. While some studies suggest that children with untreated CD have higher than expected prevalence of organ-specific autoantibodies (apparently “gluten-dependent”), which tend to disappear after starting the GFD, others deny this cause-effect relationship.⁽⁷⁾

Conclusions

CD is a common disorder in children as well as in adults. The spectrum of clinical presentations is wide, and currently extra-intestinal manifestations (e.g., anemia or short stature) are more common than the classical malabsorption symptoms. A high degree of awareness among health care professionals and a “liberal” use of serological CD tests can help to identify many of the atypical cases. The primary care physician has a central role in this process of case finding.

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The Many Faces of Celiac Disease: Clinical Presentation of Celiac Disease in the Adult Population

Peter H. R. Green, M.D.

The presentation of adults with celiac disease can be broadly divided in two types: the *classical* diarrhea-predominate type and the *silent* type in which gastrointestinal symptoms are not prominent.⁽¹⁾ The latter group includes patients that may present with secondary manifestations of celiac disease (e.g., anemia or osteoporosis), associated autoimmune diseases (type 1 diabetes or peripheral neuropathy), or associated malignancies. The silent group includes those that are asymptomatic, and detected by screening relatives of patients with celiac disease.

The lag between the clinical prevalence⁽²⁾ and the serologic prevalence⁽³⁾ of celiac disease (the iceberg phenomenon) in the United States demonstrates that most people with celiac disease are currently not diagnosed and probably have the silent form of celiac disease. This was confirmed in a population-based screening study from England in which those with undetected celiac disease (1.2 percent of those screened) had mild anemia, osteoporosis, and low serum cholesterol values and considered themselves well, and had a trend to participate in less cardiovascular events.⁽⁴⁾

Celiac disease is a proximal small intestinal inflammatory disease that may involve a variable length of the intestine. The proximal intestine is the site of absorption of iron, calcium, fat-soluble vitamins, and folic acid, as well as the products of the digestion of fats, carbohydrates, and proteins. When limited to the proximal intestine, vitamins and minerals usually absorbed may be selectively malabsorbed; however, diarrhea may not occur because the distal small intestine can compensate and absorb the products of the digestion of fats and carbohydrates. The length of intestine involved is more important than the degree of villous atrophy present in duodenal biopsies in determining whether diarrhea will occur. Other factors contributing to diarrhea include a reversible pancreatic insufficiency, secondary lactose intolerance, and bacterial overgrowth.

In view of the lack of information about the clinical spectrum of celiac disease in the United States, we conducted a survey to obtain data. Information from more than 1,600 patients was obtained. This study confirmed a female predominance over males (3:1). The majority of patients were diagnosed in their fourth to sixth decades and 85 percent presented with diarrhea. The mean duration of symptoms prior to diagnosis was 11 years.⁽⁵⁾ This delay in diagnosis is not unique to the United States and is considered to be physician-based rather than due to delay in patients seeking health care.⁽⁶⁾ A contributing factor is that patients receive alternative diagnoses such as an irritable bowel syndrome.⁽⁷⁾

Two studies have shown a relative decrease in the percent of patients presenting with diarrhea, though it remains the most common mode of presentation accounting for about 50 percent of patients.^(2,8) The increasing availability of serologic testing may contribute to both the increased rate of diagnosis and to diagnosis of patients with nondiarrheal presentations. Despite an increased rate of diagnosis, patients still experience a long duration of symptoms

prior to diagnosis (4.4 ± 0.6 years for those diagnosed after 1993 compared to 9.0 ± 1.1 years for those diagnosed prior to 1993, $p < .0001$).⁽⁸⁾

The other major modes of presentation are screening of first-degree relatives of affected individuals, and the recognition of endoscopic signs of villous atrophy in patients undergoing endoscopy for symptoms not typically associated with celiac disease—for example, esophageal reflux symptoms⁽⁹⁾ or dyspepsia.⁽¹⁰⁾ These symptoms often improve after initiation of a gluten-free diet. Other major reasons for presentation are the evaluation of iron-deficiency anemia and reduced bone density.

While weight loss may be a presentation of celiac disease, many patients are in fact overweight.⁽²⁾ Females predominate although we found men had a shorter duration of symptoms, more severe osteoporosis, and lower serum cholesterol values compared to women, suggesting more severe malabsorption.

Celiac disease may be diagnosed at the time patients present with an associated malignancy. These malignancies include esophageal adenocarcinoma, small intestinal adenocarcinoma, or non-Hodgkin's lymphoma.^(9,11) The risk factors for the development of adenocarcinoma of the small intestine have not been established; however, the cancer appears to arise in adenomatous lesions rather than via dysplasia.⁽¹²⁾ Patients may present with neurological symptoms such as peripheral neuropathy or ataxia.⁽¹³⁾ Aphthous stomatitis, detection of dental enamel defects, and of abnormal liver chemistries are also modes of presentation.

Laboratory abnormalities may be the presenting manifestations of the disease. These include the presence of abnormalities in the blood film such as Howell-Jolly bodies or thrombocytosis, a manifestation of hyposplenism, hyperamylasemia due to macroamylasemia,⁽¹⁴⁾ and an elevated sedimentation rate.

Patients with celiac disease have a 10-fold prevalence of autoimmune diseases compared to the general population, suggesting that people with celiac disease have an increased burden of illness. Frequently the associated autoimmune disease is diagnosed first, with celiac disease diagnosed because of serologic screening of individuals with autoimmune disorders that have an increased incidence of celiac disease, such as type 1 diabetes, primary biliary cirrhosis, and peripheral neuropathy.

At presentation, not all patients have positive celiac serologies. Those with sero-negative celiac disease have identical clinical presentations, associated disorders, and response to a gluten-free diet as those with positive serologies.⁽¹⁵⁾ Negative serologic tests are seen more often in patients with lesser degrees of villous atrophy.⁽¹⁶⁾

The spectrum of presentations of celiac disease is great. The vast majority of patients have silent celiac disease, though the associated diseases may have severe manifestations. Many patients have associated autoimmune diseases.

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Association of Celiac Disease and Gastrointestinal (GI) Lymphomas and Other GI Cancers

Carlo Catassi, M.D., M.P.H.

The association between celiac disease (CD) and cancer is long established. The most frequent malignant complication of CD is a high-grade T-cell non-Hodgkin lymphoma (NHL) of the upper small intestine, usually defined as enteropathy-associated T-cell lymphoma (EATL). It has been suggested that patients with CD carry an increased risk of developing malignancies other than NHL, especially small-intestinal adenocarcinoma and oesophageal and pharyngeal squamous carcinomas.⁽¹⁾

Recent epidemiological studies have shown that CD is one of the most common life-long disorders in Western countries, affecting around 1 percent of the general population. Currently, most cases remain undiagnosed and are exposed to the risk of long-term complications.⁽²⁾ For this reason, the CD–cancer connection has gained a renewed interest, as this treatable disorder could theoretically represent a major risk factor for NHL and other malignancies.

CD-Associated GI Cancers

EATL is an intestinal T-cell lymphoma that peaks in the sixth decade of life. With an annual incidence rate of 0.5–1 per million people in Western countries, this is a rare form of cancer covering around 35 percent of all small bowel lymphomas.⁽³⁾ By definition, this NHL subtype arises in patients with either previously or concomitantly diagnosed CD. Occasionally, CD is recognized after the diagnosis of lymphoma has been made. The EATL immunophenotype is consistent with a derivation from a clonal proliferation of intraepithelial lymphocytes (IEL). In some cases EATL represents the end-stage evolution of refractory celiac sprue (RCS). RCS is defined as symptomatic villous atrophy not responding to gluten-free diet (GFD) in a subject initially showing diagnostic features of CD. In approximately 80 percent of RCS cases, an abnormal clonal IEL population can be shown, frequently diffused along the intestinal tract, characterized by a low ratio of CD_8^+/CD_3^+ and TCR gene rearrangement. This entity should be classified as “cryptic EATL” as it is associated with a high risk of ulcerative jejunitis and lymphomatous transformation.⁽⁴⁾

EATL commonly develops in the jejunum but may also be found in the ileum and lymph nodes, and less frequently in the stomach and the colon. It is often multifocal with ulcerative lesions. Extranodal presentations are not uncommon in the liver/spleen, thyroid, skin, nasal sinus, etc. Most patients present with malaise, anorexia, weight loss, and diarrhea, often associated with abdominal pain. Physical signs include fever, lymphadenopathy, skin rash, hepatomegaly, and a palpable abdominal mass. Approximately 50 percent of patients require laparotomy for complications of haemorrhage, perforation, or obstruction. The suspicion of EATL prompts an extensive diagnostic workup that may include upper and lower intestinal endoscopy, CT scan with enteroclysis, or small bowel follow through; either push or wireless video-capsule enteroscopy. The final diagnosis is made on either endoscopic biopsies or full thickness laparoscopic small bowel biopsies. The immunoistochemical study shows a large- or medium-size T-cell proliferation mainly expressing a CD_3^+ , CD_8^- , CD_{103}^+ phenotype. In most

patients, EATL is disseminated at diagnosis and the outlook is poor, though it may improve with chemotherapy and surgery. The 1-year survival has been estimated to be 30 percent while the 5-year survival is approximately 10 percent.⁽⁵⁾

Different studies have shown a significant association between adenocarcinoma of the small intestine and CD. In the largest series of this rare tumour, an associated CD was found in 13 percent of cases, CD being diagnosed first in 63 percent of cases (mean lag time of 8.2 years). CD-associated adenocarcinoma was characterized by proximal (duodeno/jejunal) localization and presentation with either acute (obstruction, haemorrhage) or chronic signs (anemia, abdominal pain, weight loss). In the majority of patients, complete surgical resection was possible, and the overall survival at 30 months was 58 percent.⁽³⁾

In a population-based cohort study from Sweden, an increased risk of oropharyngeal (standardized incidence ratio = SIR of 2.3) and esophageal (SIR = 4.2) carcinomas was found in patients with CD on long-term followup. This work also disclosed a minimal increase of the risk for colorectal cancer (SIR = 1.5) which was owing to an increased risk for ascending and transverse but not descending colon or rectal cancer.⁽⁶⁾

The Magnitude of the Cancer Risk

Pioneer studies suggested that the CD-associated relative risk (RR) of developing NHL or other malignancies was very high, in the range of 40–100. This issue has recently been reconsidered in the light of significant advances on CD epidemiology and diagnosis.

To quantify the risk for developing NHL of any primary site associated with CD, we performed a case control study on 653 Italian adults with NHL at the onset using the serum IgA class antiendomysial antibody as the screening test. CD was diagnosed in only 6 of 653 patients (0.92 percent) with lymphoma. Of the six cases, three were of B-cell and three were of T-cell origin. Four of six cases had lymphoma primarily located in the gut. The odds ratio (adjusted for age and sex) for NHL of any primary site associated with CD was 3.1 (95 percent CI 1.3–7.6), 16.9 for gut lymphoma (95 percent CI 7.4–38.7), and 19.2 for T-cell lymphoma (95 percent CI 7.9–46.6).⁽⁷⁾

The Swedish cohort study found a CD-associated overall SIR of 5.9 for malignant lymphoma (95 percent CI 4.3–7.9). The excess occurrence of malignant lymphoma was confined to adults, decreased with time of followup evaluation, and decreased over successive calendar periods. The analysis of the causes of death in the same cohort of CD patients showed that mortality from all malignant neoplasm combined was elevated 70 percent and was particularly high for cancer of the small intestine, NHL, and liver.⁽⁶⁾

In summary, these new studies seem to indicate that (1) CD is associated with a significantly increased risk for NHL, especially of the T-cell type and primarily localized in the gut (EATL), and other GI cancers; (2) the CD–lymphoma association is less common than previously thought, the RR being much lower than 10; and (3) the CD–cancer association is partially responsible for the increased mortality observed in patients with CD.

Does the Gluten-Free Diet Protect From Cancer Development?

Data on the protective effect of treatment with the GFD are somewhat conflicting. On the one hand, it is evident that a large proportion of EATL and other GI cancers develop in subjects who have been already treated for CD, sometimes for decades.^(3,8) It is, however, well known that complete avoidance of dietary gluten is difficult, and the possible link between the protracted ingestion of gluten traces and cancer development has never been investigated. By contrast, several studies provided indirect evidence for a protective role of the GFD. In 1989, Holmes reported that the RR of overall cancer was not significantly elevated among those on a strict GFD for at least 5 years.⁽⁹⁾ This view has found further support in studies from Finland,⁽¹⁰⁾ Sweden,⁽⁶⁾ and Italy.⁽¹¹⁾

Strict adherence to the GFD seems to be the only possibility of preventing, at least partially, a subset of rare but very aggressive forms of cancer.

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Skin Manifestations of Celiac Disease

John J. Zone, M.D.

Dermatitis herpetiformis (DH) is a cutaneous manifestation of celiac disease (CD). The spectrum of intestinal abnormalities in DH ranges from minimal lymphocyte infiltration of the small intestinal epithelium in some patients to complete villous atrophy in others. Only about 20 percent of DH patients have intestinal symptoms of CD. Both the skin disease and the intestinal disease respond to gluten restriction and recur with institution of a gluten-containing diet. It seems likely that the presence of skin disease in DH patients is a marker of CD that is independent of the severity of the histological CD or the severity of intestinal symptoms. The complications and course of CD, as manifested in DH patients, may represent the true spectrum of CD that would otherwise largely go undiagnosed. Study of DH therefore gives insight into the nature of the spectrum of CD. For this reason, I will review the consensus questions relative to DH and will propose that understanding DH holds the potential to a better understanding of the entire spectrum of CD.⁽¹⁾

How is DH Diagnosed?

Three findings support the diagnosis of DH: (1) pruritic papulovesicles on extensor surfaces; (2) neutrophilic infiltration of the dermal papillae with vesicle formation at the dermal-epidermal junction; and (3) granular deposition of IgA in the dermal papillae of clinically normal-appearing skin adjacent to a lesion. The last finding is present in greater than 98 percent of DH patients and is the gold standard for diagnosis.⁽²⁾ IgA tissue transglutaminase and IgA endomysial antibodies are found in 70–90 percent of patients, indicating that there is a population of CD patients who are negative for this serum antibody. IgA antibodies to epidermal transglutaminase have been proposed as the causative antibody in DH.⁽³⁾

How Prevalent is DH?

DH is most common in those of northern European descent. It is exceedingly uncommon in African Americans and Asians. According to a study in Finland in 1978, the prevalence of DH is 10.4 per 100,000 and the incidence is 1.3 per 100,000. The mean age of onset was in the fourth decade, but ranged from age 2 to 90. Adolescent and prepubescent children are infrequently affected. This later age of onset is believed to indicate a need for chronic stimulation of the mucosal immune system for production of the immune response that causes DH. In contrast to CD in the absence of DH, males outnumbered females 2:1.⁽⁴⁾ From 1979 to 1996, the familial incidence of DH was studied prospectively in Finland. DH was diagnosed in 1,018 patients. 10.5 percent of patients with DH had one or more affected first-degree relatives.⁽⁵⁾

Studies in Utah confirm that DH and familial DH in the United States are of comparable prevalence to European studies. A study of a Utah population reflects the predominant northern European ancestry in that area of the United States. The prevalence of DH in 1987 was 11.2 per 100,000. The incidence for the years 1978–1987 was 0.98 per 100,000 per year. The mean age of onset for males was 40.1 years. The mean age of onset for females was 36.2 years. The male to

female ratio was 1.44:1.⁽⁶⁾ In another study of a Utah population, affected DH patients were studied and first-degree relatives were identified with DH or CD. The increased prevalence of CD and DH in first-degree relatives further confirmed the familial nature of CD in a U.S. population.⁽⁷⁾

What Are the Manifestations and Long-Term Consequences of DH?

DH is associated with other disorders and complications that likely reflect the spectrum of CD. Autoimmune thyroid disease occurs in 20–30 percent of the cases.⁽⁸⁾ Insulin-dependent diabetes and lymphoma occur in less than 5 percent of cases, while other autoimmune diseases such as alopecia areata, Addison’s disease, vitiligo, and psoriasis occur infrequently. However, diseases such as psoriasis and alopecia areata have been reported to remit when patients adhere to gluten restriction, indicating a causative role for gluten in the related autoimmune disorder in some cases. Whether the long-term risk of autoimmune disease is reversed by gluten restriction is unknown.

DH patients are subject to complications of malabsorption such as anemia at a rate that is believed to be less than that of symptomatic CD without skin disease. This probably reflects the less severe nature of the malabsorption in DH patients, since the DH population includes those with histologic CD without intestinal symptoms.

Who Should Be Tested for DH?

Patients with otherwise unexplained skin disease that is characterized by intense pruritus should be tested for DH by biopsy for direct immunofluorescence. In addition, serologic testing for endomysial antibodies of first-degree relatives has yielded a CD prevalence of 12 percent in our patients. Serum IgA endomysial antibodies and IgA tissue transglutaminase antibodies represent an index of adherence to gluten restriction in individual patients.

What Is the Management of DH?

The treatment includes dapsone and a gluten-free diet. The pruritus of DH is relieved within 48 to 72 hours of instituting oral Dapsone (4’, 4’ diamino-diphenylsufone) therapy, and the lesions recur within 24 to 48 hours of discontinuation of therapy. Dapsone will adequately suppress but not cure the disease. It has no effect on the associated gluten sensitive enteropathy or its complications. Gluten restriction results in clearing of the skin disease and the intestinal abnormality over months to years. Reinstitution of a gluten containing diet results in recurrence of disease in weeks to months.⁽⁹⁾ The skin disease is known to spontaneously remit in the absence of gluten restriction on rare occasions.⁽¹⁰⁾

What Are the Recommendations for Future Research on DH?

Study of a large cohort of DH patients is likely to expand our understanding of CD. Since DH patients are definitively identified on the basis of their skin disease and not their intestinal disease, DH patients usually have mild or asymptomatic CD. Detailed study of these patients will

allow a better understanding of the complications of mild CD. Because of the response of the skin disease to Dapsone, many patients opt to take only Dapsone and not adhere to gluten restriction. This allows for longitudinal study of a population of CD patients not adhering to gluten restriction. Study of the pathogenesis of DH will yield further understanding of the mucosal immune response to gluten and the process by which IgA produces inflammation.

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Neurological/Psychological Presentation of Celiac Disease: Ataxia, Depression, Neuropathy, Seizures, and Autism

Khalafalla O. Bushara, M.D.

Celiac disease (CD) has long been associated with a wide spectrum of neurological and psychiatric disorders including cerebellar ataxia, peripheral neuropathy, myositis, epilepsy, dementia, psychosis, and depression.⁽¹⁻⁴⁾ Earlier reports have mainly documented the involvement of the nervous system as a complication of prediagnosed CD. However, more recent studies emphasized that neurological syndromes may be the presenting extra-intestinal manifestation of gluten sensitivity with or without intestinal pathology.^(5,6) These include migraine, encephalopathy, chorea, brain stem dysfunction, myelopathy, mononeuritis multiplex, Guillian Barre-like syndrome, and neuropathy with positive antiganglioside antibodies.⁽⁷⁻¹⁰⁾ It has further been suggested that gluten sensitivity (as evidenced by high antigliadin antibodies) is a common cause of neurological syndromes (notably cerebellar ataxia) of otherwise unknown etiology.⁽¹¹⁾ However, further studies showed high prevalence of gluten sensitivity in genetic neurodegenerative disorders such as hereditary spinocerebellar ataxia and Huntington's disease.^(12,13) It remains unclear whether gluten sensitivity contributes to the pathogenesis of these disorders or whether it represents an epiphenomenon.

The mechanisms of nervous system pathology in association with gluten sensitivity is currently unclear. Nervous system involvement is unlikely to be due to malabsorption-related deficiencies.⁽¹⁴⁾ Although few studies suggested immunological mechanisms, most studies showed no evidence for a direct immune-mediated insult to the nervous system.^(1,11,15)

Studies of gluten-free diet in patients with gluten sensitivity and neurological syndromes showed variable results. In few patients, gluten-free diet was reported to result in improvement of neurological deficits while in the majority of patients reported, gluten-free diet had no significant effect.^(1,11) Gluten-free diet trials have also been inconclusive in autism and schizophrenia; two diseases in which sensitivity to dietary gluten has been implicated.

Further studies are clearly needed to assess the efficacy of gluten-free diet and to address the underlying mechanisms of nervous system pathology in gluten sensitivity.

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Should Children Be Screened for Celiac Disease? Is There Evidence To Support the Strategy of Screening All Children?

Edward J. Hoffenberg, M.D.

The identification of accurate serologic markers for celiac disease (CD) provides a tool to study at-risk groups as well as whole populations. Although the ability to conduct widespread screening is evident, the wisdom of such an endeavor needs evaluation.

How should the question of screening children be evaluated? Guides published 30–40 years ago provide a framework still relevant today for CD screening.^(1,2) Adapting from these sources, eight criteria relevant to screening children for CD merit consideration.

Important Health Problem: Serious, Prevalent

The prevalence of CD approaches 0.5–1 percent of the U.S. general population.^(3,4) Most cases have no or mild symptoms and are identifiable only by screening. Whether all forms of CD have the same long-term consequences (i.e., osteoporosis, intestinal malignancy) has not been determined. Whether screening-identified CD represents a “serious” problem similar to that of clinically identified CD requires further study.

Diagnostic Criteria Accepted and Widely Available

The “ESPGN criteria” developed for the *clinical* diagnosis of CD requires characteristic histologic findings on small bowel biopsy plus a response to therapy with a strict gluten-free diet. This response may be improvement of symptoms or of intestinal injury.⁽⁵⁾ Problems with this definition include patchiness of intestinal injury; expertise in histologic interpretation; assumption of compliance with a strict gluten-free diet; subjectivity in the assessment of symptomatic improvement (and specific to screening-identified CD, absence of symptoms); and poor acceptance of followup biopsy.

Diagnostic criteria which incorporate autoantibody assays need updating. To address this need, algorithms for the evaluation of screening- and clinically-identified CD have recently been developed and will need validation and acceptance.⁽⁶⁾

Screening Tests Available, Acceptable, Reliable, and Valid

The antitransglutaminase antibody screening test (TG) is widely available. In the clinical setting, TG has a sensitivity of 95–100 percent for biopsy confirmation of CD. But in screening at-risk populations, the predictive value lingers around 75 percent.⁽⁷⁾ It is unknown whether biopsy negative cases represent false-positive TG results, false-negative biopsy results, mild disease (celiac autoimmunity without villous atrophy), or early “latent” CD. The significant variability among commercial tests is also an issue. Cutoffs, usually derived using well

characterized, clinically-identified adult cases, may require adjustment (i.e., higher cutoff values) for use in population screening.

There is some evidence that TG expression can be transient or intermittent, although this phenomenon seems to be rare.^(8,9) The significance of a single positive TG test should not be overestimated. An attractive model based on type 1 diabetes autoimmunity demonstrates that susceptible individuals may proceed through a period of TG expression and possibly even mild intestinal injury on the way to tolerance or frank disease.

Disease Natural History, Transition to Declared Disease

The natural history of screening-identified CD has not been determined, and tools do not exist for predicting or detecting the transition to declared disease. Initial prospective studies assessing the impact of TG seropositivity on growth and nutrition⁽¹⁰⁾ and on outcome in type 1 diabetes⁽¹¹⁾ are under way. Studies published to date are small, poorly controlled, underpowered, and provide no consensus.

Agreement on Whom To Treat, and Benefit of Earlier Treatment

The benefit of treating clinically identified CD includes normalization of intestinal absorptive function and bone mineralization as well as reduction in the risk for malignancy. It is assumed that this benefit also applies to screening-identified CD and provides the rationale for screening at-risk groups.⁽⁶⁾ Given the lack of information, the benefit of “early” or “preventive” treatment of CD is controversial.

Accepted Treatment

The gluten-free diet is effective and available, but requires ongoing commitment. Adolescents with screening-identified CD seem less likely to comply with this diet than those with clinically-identified CD.⁽¹²⁾ The benefit of reduced gluten intake and the likely compliance rates need to be factored into the decision to conduct screening.

Cost/Benefit

Cost/benefit analyses of early diagnosis and treatment of CD are lacking.

Repeat Testing

There is some data that seroconversion develops in childhood over time, at each increment in time.⁽³⁾ The optimal age at which to begin testing and the frequency of repeat testing are unclear. It seems likely that testing school-age children will identify a large proportion of cases, but that retesting to detect late cases will be needed.

Conclusions

In the clinical setting, serological screening of children for CD is highly accurate. Currently, there is no evidence to support screening all children for CD. Screening of at-risk children looks attractive but needs further study. Standardization of screening tests, assessment of appropriate cutoffs for screening, and algorithms for the evaluation of cases identified on screening are needed.

Areas for Further Study

(1) Clarify the natural history of CD and TG seropositivity (to assess the benefit of early or preventive treatment) in general, and on type 1 diabetes outcome specifically. (2) Standardize definitions and algorithms for evaluation of screening-identified CD. (3) Identify methods to predict progression to frank disease; possible factors include gene dosage, diet, modifier genes, environmental factors, TG quantitation, etc. (5) Analyze the cost/benefit/harm in screening, the optimal age to begin screening, and frequency of repeat screening. (6) Standardize methods for screening (tests, cutoffs) children.

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Should Adults Be Screened for Celiac Disease? What Are the Benefits and Harms of Screening?

Pekka Collin, M.D., Ph.D.

Recent epidemiological studies have shown that the prevalence of celiac disease (CD) is as high as 1 percent in both the United States and in Europe.^(1,2) The prevalence of detected disease is much lower, from 0.27 percent to 0.02 percent.^(3,4) This means that for every patient with a diagnosis of CD, 3–10 patients with CD remain undetected. Symptoms of the disorder are diverse, and the disease is often asymptomatic.^(1,2) Without active serologic screening, most cases of CD may remain undiagnosed. Recent serologic screening assays, especially the IgA-class tissue transglutaminase antibody test, are sufficiently inexpensive, sensitive, and specific to allow even mass screening for CD. The disease satisfies the criteria for mass screening and theoretically there are many standpoints favoring such an approach. CD is associated with many severe complications that can be prevented by gluten-free dietary treatment. The question remains whether we should apply screening to all adults or only to certain risk groups.

The risk of small-intestinal lymphoma is increased in CD.⁽⁵⁾ In retrospective and cross-sectional studies, dietary treatment has been shown to prevent the malignant development.⁽⁶⁾ However, there is no evidence as yet to suggest that patients with mild or only subtle symptoms run an increased risk of lymphoma. There is, in fact, indirect evidence to the contrary; undetected CD has not proved a significant factor in the etiology of lymphoma.⁽⁷⁾ Some cases may be detected by severe neurological disorders such as ataxia, without any symptoms indicative of CD.⁽⁸⁾ However, such complications are rare and prevention of neurological sequelae does not justify mass screening.

Screening has been advocated in order to prevent malabsorption. Again, the evidence is scarce. Subclinical osteoporosis occurs in undetected patients with CD, even in asymptomatic subjects.^(9,10) The prevention of osteoporosis seems to be the strongest indicator for widespread screening today. It has also been hypothesized that early gluten-free dietary treatment might prevent the development of autoimmune conditions in CD.⁽¹¹⁾ The issue is controversial,⁽¹²⁾ and does not therefore justify mass screening.

Screening asymptomatic individuals for CD may be harmful. A lifelong gluten-free diet is not easy to maintain, and the subject's quality of life may deteriorate. It is also debatable whether patients found by active screening adhere to a gluten-free diet similarly to symptomatic ones. In type 1 diabetes, it may be problematic to combine a diabetic and a celiac diet. Whether a gluten-free diet is of benefit or harm in celiac patients without symptoms and malabsorption is thus controversial. Screening is also costly; apart from serologic testing, even a small loss of specificity will result in numerous "useless" endoscopies. Compulsory testing would also entail ethical problems.

CD is a common disorder with a specific treatment. Increased alertness should be observed in at-risk patients. Serologic screening should be applied in individuals with even subtle indicative symptoms such as subclinical isolated iron deficiency. In various autoimmune conditions the risk of CD is approximately 5 percent,⁽¹³⁾ and in individuals with affected first-degree relatives, 15 percent. Infertility, neurological symptoms such as polyneuropathia,

ataxia, epilepsy with posterior cerebral calcification, and osteoporosis are conditions for which CD should be borne in mind. Elevated aminotransferases and possible liver failure can lead to a diagnosis of CD.^(14,15) The recommendation for screening is depicted in the table below.

Table 1. Screening for Celiac Disease in Adults

Screening indicated, small-intestinal biopsy in selected cases	Screening indicated, always when even subtle symptoms consistent with CD	Screening not indicated
Malabsorption, isolated iron deficiency	Family history of CD	Population in general (enrollment in clinical studies indicated)
Infertility	Autoimmune thyroid disease	Acute short-term abdominal symptoms
Osteoporosis	Sjögren's syndrome	Atopic symptoms
Ataxia and polyneuropathy	Type 1 diabetes*	Type 1 diabetes**
Arthritis of unknown etiology	Addison's disease	
Chronic liver disease of unknown etiology	Any gastrointestinal symptoms	
Suspicion of dermatitis herpetiformis (consider skin biopsy)		
Irritable bowel syndrome		

*With and **without any symptoms indicative of celiac disease.

In conclusion, evidence today does not support mass screening. More research is needed to assess the cost-effective benefits of mass screening. The occurrence of osteoporosis and the effects of a gluten-free diet should be investigated in a large group of symptom-free patients. Dietary compliance and quality of life before and after a gluten-free diet should likewise be evaluated.

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Consequences of Testing for Celiac Disease

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Context

The prevalence of silent cases of celiac disease (CD) may be eight times that of classically symptomatic CD, and it is important to determine if the consequences of testing and the response to treatment differs by mode of diagnosis, and clinical presentation.

Objective

To conduct a systematic review of the expected consequences of testing for CD in the following populations: (a) patients with symptoms suggestive of CD, (b) asymptomatic at-risk populations, and (c) the general population.

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 (1966–Oct 2003), EMBASE (1974–Dec 2003), CAB (1972–Dec 2003), PsycINFO (1840–2003), AGRICOLA (1970–2003), and Sociological Abstracts (1963–2003).

Study Selection and Data Extraction

This review was conducted using accepted systematic review methodology. Two independent reviewers selected the articles using three levels of screening. The strategy included articles that dealt with the consequences of testing for CD. We did not include articles that dealt with consequences addressed in celiac objectives one and two (e.g., cases diagnosed, false-positive results, invasive procedures [biopsies], and followup testing). Full data extraction was conducted on all articles that met the level 3 screening requirements by one reviewer and then verified by a second reviewer. The quality of the included studies was assessed. Outcomes included: (1) nutritional parameters (body composition and anthropometrics), anemia, and diabetic control; (2) compliance with a gluten-free diet (GFD); (3) costs; and (4) other clinical endpoints ([a] osteoporosis and [b] mortality).

Data Synthesis

The studies identified dealt primarily with small populations of symptomatic individuals and not all studies reported clinical presentation in detail. The number of studies evaluating outcomes in asymptomatic, screen-detected patients was small, and it was difficult to determine if outcomes differed by population and clinical presentation. The majority of studies evaluating

consequences in asymptomatic at-risk populations pertained to studies of type 1 diabetics screened for CD. Few studies correlated the histological grade at biopsy with a change in outcomes.

Results

The search identified 1,199 potentially relevant citations. After 3 levels of screening, 35 published studies fulfilled all the eligibility criteria. Sixteen relevant articles were identified from other celiac objectives in addition to a search on osteoporosis/CD, for a total of 51 studies. The search strategy did not identify any studies that would allow us to address the specific benefits and harms of testing with different strategies for CD.

Body Composition/Anthropometrics

In general, body composition and anthropometric parameters such as weight, body mass index (BMI), and fat mass improved after starting a GFD in symptomatic populations of CD. Individuals with CD on a strict GFD may have a lower BMI due to lower daily energy intakes.

Anemia

The studies evaluating the impact of a GFD on anemia demonstrated an improvement on a GFD with some studies linking recovery to improvement in villous atrophy. Iron-deficiency anemia improved 6–12 months after starting a GFD, but results indicated that iron deficiency (ferritin levels) may take longer to resolve.

Diabetic control

Diabetic control as measured by HbA1c levels did not improve after the institution of a GFD, although an improvement in body composition parameters was noted.

Compliance

Studies that assessed the outcome of compliance with a strict GFD in adolescent populations suggested that diagnosis in early childhood or symptomatic clinical presentation were associated with significant improvements in compliance with the GFD.

Costs

There were five studies that evaluated the costs of different screening strategies and only one contained the majority of the components that are recommended for the reporting of cost-effectiveness analyses.⁽¹⁾

Osteoporosis/Fractures

There were 11 articles that evaluated bone mineral density (BMD) in individuals with CD and 6 controlled studies that assessed the outcome of fracture. Most studies documented an increased prevalence of osteopenia in newly diagnosed celiacs. One study found that femoral neck BMD was significantly lower in symptomatic celiacs.⁽²⁾

In the majority of studies, a variable but significant increase in BMD was noted after 1 year on a GFD. The issue of fracture prevalence in CD was controversial with some studies finding an increased rate of fractures and other studies not noting an increased risk. Difference in methodologies including sample size, study populations, and ascertainment of fractures could account for differences in fracture risk. The risk of fracture appeared to be highest prior to the diagnosis of CD. Moreno et al. found that the risk of fracture was not increased in subclinical and silent cases of CD in contrast to symptomatic cases.⁽²⁾ Additional population based fracture studies in subpopulations of celiac individuals would help clarify risk of fracture.

Mortality

Seven studies evaluating mortality were included and the majority demonstrated an increase in the overall mortality rate for CD when compared with the general population (SMR = ≥ 2). Mortality rate was increased with longer delays in diagnosis and poor compliance with the GFD. Corraro et al. found that mortality was not increased when compared to the general population in those with mild symptoms or those who were asymptomatic at presentation.⁽³⁾

Conclusions

Based on our literature review, the consequences of testing and identifying symptomatic CD patients can have a positive impact on patient relevant outcomes such as improved body composition, nutritional status, bone mineral density, and fractures. This improvement is in part due to the superior compliance that is seen in individuals with symptomatic CD. The data on consequences are less clear for asymptomatic at-risk populations and individuals identified through population screening programs. Although some studies suggest a lower risk of complications in asymptomatic individuals identified through screening, it is premature to conclude that the risks of complications are lower. At present, there is inadequate evidence from the published literature on the magnitude of the benefits and harms of screening the general population and the potential risks of undetected CD. Further research, including comprehensive economic evaluations, are recommended to adequately address the consequences of screening in both asymptomatic at-risk groups and the general population.

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Dietary Guidelines for Celiac Disease and Implementation

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Medical nutrition therapy is the only accepted treatment for celiac disease (CD). It is a strict, gluten-free diet (GFD) for life. The GFD avoids the storage proteins from wheat, rye, barley, and hybrids of these grains, such as kamut and triticale. Historically, rice, corn, and potato were substitutes for gluten-containing grains. Today a number of nutrient-dense grains, seeds, legumes, and nut flours offer increased variety, improved palatability, and higher nutritional quality to the GFD. These grains and seeds include amaranth, buckwheat, flax, Indian rice grass, millet, tef, quinoa, and sorghum.

The inclusion of oats and wheat starch in the GFD is controversial with no clear-cut guidelines for their use. Short- and long-term studies involving children and adults during the last decade suggest oats can be included safely in the GFD.⁽¹⁻³⁾ Størsrud found the use of oats increased the patient's intake of iron, dietary fiber, thiamin, and Zn.⁽³⁾ However, oats in the GFD are not widely recommended in the United States and Canada, due to concerns of unacceptably high levels of cross-contamination. A study by Lundin in Norway confirms that contamination of commercial oats can vary widely. Lundin found contamination levels between <1.5 ppm to >400 ppm in commercial oats. In the sample with the highest levels, it was difficult to determine the source of contamination, but Lundin suspects barley, not wheat, as the source. Testing of the "bottom of the bag" of the same product found contamination of <1.5 ppm. Further, Lundin demonstrated that even pure oats caused villous atrophy and dermatitis in at least one patient. This may be a rare situation but does cause concern.⁽⁴⁾ Research supports that oats may be acceptable for the majority but not all patients with CD. At this time, there are no U.S. studies available to assess the potential contamination of commercial oats. Continued research is warranted.

Wheat starch is used in some European countries as part of the GFD. A food product is considered GF by Codex Standards if it contains less than 0.05 grams (g) nitrogen per 100 g dry product matter. GF products containing wheat starch therefore may contain as much as 40–60 mg gluten/100 g dry product. According to Codex Standards, wheat starch must contain not more than 0.3 percent protein in the dry matter. European GFDs containing wheat starch meet Codex Standards. Research on the use of strict GFDs containing wheat starch is limited; however, research by Peräaho et al. and Kaukinen et al. indicates no differences in villous architecture, density of intra-epithelial lymphocytes, serum antibodies, bone mineral density, or quality of life in patients choosing a strict wheat starch-containing GFD versus a natural GFD.^(5,6) Complaints of adverse gastrointestinal (GI) symptoms were limited but did not alter the patient's chosen diet. A study by Faulkner-Hogg et al. suggests the trace amounts of gluten allowed by the Codex Standards may be responsible for continued symptoms seen in some patients and that a "no-detectable" gluten GFD may be required in these patients.⁽⁷⁾ Selby et al. found no differences between patients on a Codex GFD and those on a no-added-gluten GFD. He suggests factors other than trace amounts of gluten may cause continued villous atrophy in some patients.⁽⁸⁾ Wheat starch is not currently accepted in the United States or Canada. Based on definition of GF and tolerance studies, its addition seems to be worth consideration.

Worldwide, there is debate about the accepted definition for what constitutes “gluten-free.” Canadian standards state less than 20 ppm gluten, while other countries use 200 ppm, and still others prefer a double standard for products rendered GF and those naturally GF. This debate fuels confusion about labeling products GF. The current Codex Standard for “Gluten-Free Foods” was adopted by the Codex Alimentarius Commission in 1976 and amended in 1983. In this document, gluten is defined as those proteins commonly found in wheat, triticale, rye, barley, or oats. The definition came under review in the 1990s. As of the 25th Session of the Codex Alimentarius Commission, the definition of gluten-free continues to remain at Step 7 while the committee awaits research on the scientific basis for the establishment of a tolerance level and a method of detection is clarified.^(9,10) The Working Group on Prolamin Analysis and Toxicity is currently evaluating a sandwich R5-ELISA system as proposed by the Codex Alimentarius Commission. This new system has good reproducibility (8.7 percent) and repeatability (7.7 percent). In a study by Valdés et al.,⁽¹¹⁾ the R5-ELISA was able to identify gliadins, hordeins, and secalins sensitivities of 0.78, 0.39 and 0.39 ng/ml, respectively. The assay’s detection limit was 1.56 ppm gliadins, 3.2 ppm gluten.⁽¹²⁾ Acceptance of R5-ELISA by the Codex Commission and results of ongoing research on tolerance levels will allow the Commission to advance towards a revised definition of gluten-free. The American Dietetic Association (ADA), in conjunction with the Dietitians of Canada, revised the GFD guidelines in 2000. These guidelines are based on the best available information at the time. Currently the ADA is involved in a National Gluten-Free Diet Project to review these guidelines and provide evidence-based analysis.⁽¹³⁾

Numerous studies document the impact of nutrient malabsorption caused from CD. Intestinal motor function caused by nutrient malabsorption may be partially responsible for the delayed gastric emptying seen in children in a study by Perri et al.⁽¹⁴⁾ Bona et al. shows low dietary intake or malabsorption of B-vitamins, iron, and folic acid appear partially responsible for delayed puberty in children with CD.⁽¹⁵⁾ Jameson⁽¹⁶⁾ reports a correlation between zinc deficiencies and the severity of villous atrophy in adults. He also reports that the more pronounced the lesion, the lower the levels seen for iron, copper, folate, and vitamin B-12. Hallert et al. assessed the total plasma homocysteine levels in patients following a GFD. Compared to controls, persons following a GFD showed poorer vitamin status for folate, vitamin B-6, and vitamin B-12, even when taking nutrient supplements.⁽¹⁷⁾ Studies report an incidence of 4 percent anemia in the patients with newly diagnosed CD in the United States. While vitamin B-12 deficiency is not unusual in CD, pernicious anemia is considered uncommon.^(18,19) Recovery from iron-deficiency anemia is possible with GFD alone.⁽²⁰⁾ Bone disease in CD of adults and children is well documented in the literature. Calcium, vitamin D, magnesium, and fiber are also limited in the GFD. In the United States, very few GF products are enriched, as are wheat-containing products, adding to the increased possibility of nutrient deficiencies. GF products, without enrichment, are lower in fiber, iron, folate, thiamin, riboflavin, and niacin.^(12,21) Some patients report additional food sensitivities.

In an Italian study of body composition and dietary intakes of adults with CD following a strict GFD, weight and body mass index of patients with CD was significantly lower than that of controls, as was fat and lean body mass. Bone mineral content of women diagnosed as adults was significantly lower than controls. The diet of these patients was unbalanced and had a higher percentage of calories from fat and less from carbohydrates.⁽²²⁾ A study by Mariani et al. showed similar results of the nutritional analysis of children with CD. They found the children complying with a strict GFD had significantly greater nutrition imbalance in their diet than did

children cheating on their GFD. More troubling is that the incidence of children overweight or obese in the strict GFD group was more frequent (72 percent), compared to the children not following a strict GFD (51 percent), and only 47 percent in the healthy age-matched control group.⁽²³⁾

Due to the nutritional inadequacies and potential health concerns caused by CD, a qualified dietitian must be an integral part of the health care team. When properly instructed by a dietitian with expert knowledge, the GFD can be nutritionally adequate, allow healing and return to good health, decrease risk of associated health conditions, as well as allow catch-up growth in children. Historically, training for dietitians in CD and GFD was limited. Because of the limited access of qualified dietitians, patient support organizations took on the role of making and revising diet recommendations, restrictions, and guidelines used in the United States, often without scientific, evidence-based qualifications for the changes. Over time, these modifications have caused a great deal of confusion for patients and may have added to increased noncompliance. Within the ADA today is a specialty group of dietitians involved in CD. It is important that patients receive medical nutrition therapy from dietitians knowledgeable about this disease. The diet is complicated and can be overwhelming if not presented using a proactive approach. A patient's current nutritional status, instruction in the GFD, and correction of nutritional deficiencies and complications must be addressed by nutrition experts to help minimize additional complications of malnutrition and malabsorption, as well as noncompliance. Studies indicate that compliance to the GFD is compromised by a number of factors, including a lack of education. In a study by Ciacci, dietary compliance and the extent of intestinal damage on followup examination could be predicted by baseline education.⁽²⁴⁾ This study supports the need for frequent reinforcement and accurate explanation of dietary recommendations. Medical nutrition therapy is currently the only treatment for management of CD. Maintaining an optimal nutritional state with a GFD and avoidance of potential complications caused from inadequate care and treatment can be difficult. It is important that regular nutritional therapy be a part of management of CD; that access to care is readily available to all patients; that initial and routine followup nutrition therapy not is limited; and that insurance reimbursement is available.

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How To Provide Effective Education and Resources: Gluten-Free Diets

Shelley Case, R.D.

A strict gluten-free diet (GFD) for life is the only treatment for celiac disease (CD). Successful management of CD requires (1) a team approach, including the person with CD, family, physicians, a registered dietitian, a celiac support group, and caregivers; (2) an individualized approach; (3) an understanding of quality-of-life issues; (4) use of evidence-based, current information and resources; and (5) regular followup to monitor compliance and nutritional status, as well as additional information and support.^(3,16)

Once a diagnosis is made, the physician must clearly communicate, with a positive and optimistic attitude, an overview of CD and strongly emphasize the importance of a GFD for life.⁽¹⁶⁾ It is essential that the physician initiate an immediate referral to a registered dietitian with expertise in CD for nutritional assessment, diet education, meal planning, and assistance with the social and emotional adaptation to the new gluten-free lifestyle.^(2,7,15,16) A delay in referral, or no referral at all, increases the likelihood of the patient obtaining inaccurate information from the Internet, health food stores, alternative health practitioners, family, friends, and other sources, often resulting in confusion and frustration. The physician and dietitian should also encourage the patient to join a local and/or national celiac group for ongoing support, as patients who are active members are usually more knowledgeable and compliant with their diet.⁽¹⁶⁾ The registered dietitian is the most qualified health care professional to provide medical nutrition therapy (MNT). Table 1 presents a summary of the nutritional assessment, education, and followup of newly diagnosed individuals with CD.

Gluten-Free Diet and Quality of Life

Dietary change requires modification of lifelong eating habits and adoption of new food habits. This can be a challenge for most patients with CD, as wheat and wheat-based products are major staples in the North American diet. Hectic lifestyles have resulted in more meals eaten away from home and reliance on prepackaged convenience foods. In addition, the cost of GF specialty foods is significantly higher than that of gluten-containing foods, and obtaining these specialty foods is difficult for some patients.

Many studies have investigated the impact of CD and following a GFD on the quality of life in adults^(4,6,8-10) and children^(11,17) with varying results. In addition, several studies have looked at specific lifestyle issues and their effect on the patient's ability to follow the GFD in adults^(5,8,12,14) and children with CD.⁽¹⁸⁾ A significant number of adults with CD report difficulties following the GFD, especially when eating out in restaurants, at social functions, and while traveling. Determining the GF status of foods, finding GF foods, and planning and cooking GF meals also interfere with their family life and career. Children often feel left out of activities at school or friends' homes, are embarrassed to bring GF foods to parties, and are angry about having to follow a special diet.

Table 1. Nutrition Assessment and Education For Celiac Disease

Complete Nutritional Assessment	
Anthropometrics	Height, weight, body mass index, pediatric growth charts, skin, hair, nails
Tests/Labs	Celiac antibody and endoscopy results, bone density results, Hgb, Hct, Iron, Transferrin, Ferritin, TIBC, B12, Folate, Albumin, Chol, HDL, LDL, Sodium, Potassium, Calcium, other tests (e.g., hydrogen breath test)
Symptoms Review	Abdominal pain, bloating, gas, diarrhea, constipation, fatigue, bone/joint pain, depression, other
Medical	Associated symptoms or related illnesses (e.g., lactose intolerance, osteopenia, osteoporosis, anemia, diabetes, other food intolerances), medications, supplements, herbs, alternative therapies, family history
Diet Hx./Food Record	(1) Nutrient composition (look for adequate kcal, protein, B complex, vitamin D, calcium, iron, fiber, fluids) (2) Lifestyle Issues: Shopping and food preparation issues, cooking experience, willingness and time to cook, use of convenience foods, food preferences, eating away from home (e.g., restaurants, school, work), financial determinants, ethnic and religious belief considerations
Social/Emotional Assessment	Query response to diagnosis and diet, knowledge, readiness to learn, motivation, family support, literacy level

Education
1. Explanation of celiac disease, definition and role of gluten
2. GFD instruction: <ul style="list-style-type: none">a. Grains and flours allowed/to avoidb. Label reading, including safe and unsafe ingredients and hidden sources of glutenc. Variety of foods allowed, meal planning guidelines, nutritionally balanced eatingd. Nutritional issues (e.g., iron, calcium, vitamin D, B vitamins, fiber, enrichment)e. Nutrition supplements as neededf. Shopping, cross-contamination issues, recipes, substitutions, how to use gluten-free grainsg. Eating out, travel, how to deal with family and friendsh. List of manufacturers of gluten-free foods and local stores that carry gluten-free foods
3. Resources: Books, cookbooks, newsletters, magazines, Web sites, celiac support group contact information (local and national)

Followup
1. Encourage patient to return for regular followup assessment, modifications to treatment plan, and further information
2. Schedule appointments based on patient's need and/or interest
3. Instruct patient to call with questions or concerns
4. Communicate pertinent information to physician(s)

Adapted from Anne Lee, R.D., Celiac Disease Center at Columbia University in the American Dietetic Association Clinical Connections, 2003.⁽¹⁵⁾

In order to effectively counsel individuals with CD, physicians and dietitians must understand the emotional and psychological impact of the disease and diet, as well as the complex quality-of-life issues patients and their families face on a daily basis, and offer practical advice and specific strategies to help them successfully follow the GFD.^(5,14)

Poorly Controlled/Nonresponsive Celiac Disease

It is critical to conduct a systematic review of nonresponsive CD, as several factors may be responsible for poor control, such as intentional and/or unintentional gluten ingestion and co-existing gastrointestinal conditions (e.g., lactose intolerance, bacterial overgrowth, microscopic colitis, collagenous colitis, enteropathy-associated T-cell lymphoma and refractory sprue).^(1,3,7,20) The most common cause of nonresponsive CD is gluten ingestion, either intentional or unintentional.^(1,4,7,13) Therefore, it is essential that the patient have ongoing followup and education with a dietitian experienced in CD. Better dietary compliance can reduce the risk of further complications and associated health care costs.

Sources and Quality of Information

Patients seek information on CD and the GFD from a variety of sources including health professionals, celiac support groups, health food stores, alternative health practitioners, the Internet, libraries, dietetic associations, food companies, and the media. Unfortunately, patients frequently receive outdated, inaccurate, and/or conflicting information from some of these sources, resulting in patients unnecessarily restricting certain foods and thus limiting the variety and nutritional quality of their diet. Several studies have reported on the perceived quality of information that patients receive from different sources.^(5,8,12,14,19) The majority of adults surveyed reported a high level of confidence in the information provided by celiac support groups; however, gastroenterologists, dietitians, and family physicians received significantly lower ratings.

Access to Information

As MNT is the only treatment for CD, it is essential that newly diagnosed patients be referred to a dietitian. Case (2004 unpublished) conducted an online and/or telephone survey of 96 dietitians in the United States and Canada to ascertain referral procedures and practices. Although CD is considered to be a high priority by the majority of the dietitians, with patients being seen within 1–2 weeks of referral in both the United States and Canada, many patients are not always referred to a dietitian for MNT. Another major concern in the United States is the limited or lack of reimbursement for MNT by insurance companies. Most patients must pay for the service, which can range from \$60–\$295/hour with an average rate of \$92/hour. Some patients are unwilling or unable to afford the counseling and are seeking alternative sources of information and education.

Resources

There are numerous resources available to patients and health professionals from a wide variety of sources such as celiac support groups (Celiac Disease Foundation, Gluten Intolerance

Group, Celiac Sprue Association, Canadian Celiac Association); self-help books (Danna Korn, Shelley Case, Tricia Thompson, Nancy Patin Falini, Bonnie Kruszka, LynnRae Ries); cookbooks (Bette Hagman, Carol Fenster, Connie Sarros, Karen Robertson, Donna Washburn, Rebecca Reilly, Roben Ryberg, Sheri Sanderson); and magazines (*Gluten-Free Living*, *Living Without*).

Recommendations

Additional training on CD and its dietary treatment at the undergraduate, internship/residency, and practicing levels for dietitians, physicians, nurses, and other allied health professionals is essential. Dietetic and medical associations need to establish specific MNT protocols for CD and offer CPE programs at national and regional conferences, as well as practical online and print resources. It is important that dietitian consultations providing MNT for CD be covered by insurance for initial and followup nutrition management. Enhanced and more comprehensive food labeling regulations are necessary so that patients can make informed decisions when purchasing foods. Greater cooperation and collaboration among celiac support groups is required to ensure that consistent, evidence-based information is being disseminated to patients, health professionals, the media, and others, as well as a strong, unified voice when lobbying Government for enhanced labeling regulations and MNT coverage for CD management. The food industry needs further education and training for staff about CD and the GFD.

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The Followup of Patients With Celiac Disease— Achieving Compliance With Treatment

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Once an individual has been diagnosed with celiac disease (CD) and received appropriate counseling about the gluten-free diet (GFD), how can the physician measure compliance? Prior to the advent of serology, the diagnosis of CD was based upon criteria published in 1970 by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition.⁽¹⁾ This confirmed CD by histology showing intestinal healing after being on a GFD, with biopsy documented recurrence of damage after a gluten challenge. Revised criteria were published in 1990, which stated that the diagnosis was definitive in those over the age of 2 years who had initial characteristic histologic findings and clinical resolution of symptoms following the institution of a GFD. Repeat biopsy was not necessary.⁽²⁾ Despite these recommendations in pediatric patients, recent studies have shown utility of repeat biopsies in adults. Intestinal damage has been significantly associated with poor dietary compliance, presence of serum anti-endomysial IgA antibodies (EMA), and low plasma albumin.⁽³⁾ Despite a good clinical response to a GFD, abnormal endoscopic and histopathologic appearances persisted in 77 percent of adult CD patients in New York—even in those reporting compliance. Abnormalities included reduced and scalloped folds, mucosal nodularity and fissures, and partial or total villous atrophy.⁽⁴⁾ The American Gastroenterological Association medical position statement recommended a repeat biopsy as early as 4 to 6 months after starting the GFD to assess improvement.⁽⁵⁾

The EMA titer was originally proposed to be indirectly related to mucosal recovery.⁽⁶⁾ However, there is not agreement in the literature that EMA is a reliable marker in monitoring compliance or histologic response to treatment. EMA+ in CD patients on a GFD has been reported to vary from 0 to 68 percent.⁽⁷⁾ Of 53 initially EMA+ patients in Belfast, EMA was undetectable in 58 percent after 3 months, in 75 percent after 6 months, and in 87 percent after 12 months on the GFD.⁽⁸⁾ However, only 40 percent of all seronegatives had complete villous recovery by 12 months, and only 33 percent with subtotal or total villous atrophy remained EMA+. Several researchers believe that EMA negativity reflects the absence of gluten in the diet in those who were initially positive, but is not a predictor of mucosal damage, and that biopsy remains the best tool to measure villous injury.^(9–11)

The reliability of tissue transglutaminase IgA antibodies (tTG) as a predictor of compliance in CD has also been examined. In Switzerland and Sweden, TTG levels correlated with the duration of the GFD, and tTG normalized for most patients after 1 year GF. Furthermore, elevated tTG and EMA could be detected 3–12 months after a gluten challenge.⁽¹²⁾ TTG values were strongly related to compliance in one Italian study,⁽¹³⁾ and tTG better correlated with reported compliance than with intestinal biopsy morphology, suggesting that an accurate dietary interview with tTG testing be done before a repeat biopsy.

The highest rates of compliance are reported for patients diagnosed with CD at a very young age. In Sweden, while 80 percent of adults who had been diagnosed with CD prior to 4 years of age were compliant, only 36 percent were complaint of those who were older than 4 years at diagnosis.⁽¹⁴⁾ In France and Belgium less than half of the adults with CD strictly

adhered to the GFD after more than 1 year.⁽¹⁵⁾ Reasons for transgressions included poor palatability of GF foods, absence of symptoms after “cheating,” high cost of the GFD, and the nonspecified presence of gluten or erroneous affirmation of gluten absence in foods and medications. Only 56–83 percent of teenagers with CD are considered to be on a strict GFD,^(16–18) while the reported adult compliance has varied between 17 percent and 45 percent.^(19,20) Patients diagnosed with CD via serologic mass screening in Italy showed more EMA+ and lower compliance in comparison to age-matched patients diagnosed with “classic” symptoms during childhood.⁽²¹⁾ Less than one-fourth of these patients followed a strict GFD, while 23 percent had returned to a normal diet after 5 years.

Women with CD perceive a greater burden of illness, and express less satisfaction with the outcome of treatment. Women are also more concerned about needing more knowledge about CD, interference with socializing, and the possibility that their children could get CD. Both sexes express bitterness over not being diagnosed earlier, believing that this could have led to better outcomes.⁽²²⁾ For many persons with CD, the major complaints are general poor health, fatigue, and a feeling of decreased well-being.⁽²³⁾ These symptoms may improve once the patient starts a GFD.⁽²⁴⁾ Corrao et al. published that the overall mortality in adult CD patients was double that of the general population, and that a delay in diagnosis, poor adherence to treatment, and severity of symptoms at presentation unfavorably affected patients’ outlook.⁽²⁵⁾ The GFD has been shown to improve the quality of life even in patients with symptomless CD.⁽²⁶⁾ Patients at the time of CD diagnosis express fear, anger, anxiety, and sadness. Anger can worsen the patient–clinician relationship and has been inversely correlated with dietary compliance.⁽²⁷⁾

In the United States, food labeling does not clearly state whether gluten is present in a product. The American Celiac Task Force made its debut in March 2003 (<http://capwiz.com/ceeliac/home/>) to advocate for changing the food labeling law. In March 2004, the Senate passed the “Food Allergen Labeling and Consumer Protection Act.” Similar legislation was introduced into the House in December 2003. These bills require food manufacturers to clearly state if a product contains the top eight food allergens (including wheat) and calls for the Food and Drug Administration to issue rules defining and permitting the term “gluten-free” on food labeling.

The management of CD primarily consists of monitoring for compliance and complications. The patient should follow up with the gastroenterologist who performed the biopsy once the results confirm CD, and be referred to a dietitian knowledgeable about the GFD (figure 1). Patients should be encouraged to join local chapters of national support organizations, which can aid in finding local resources such as supermarkets, food manufacturers, literature, and restaurants that are familiar with the GFD. Patients should be screened for nutritional deficiencies that can accompany this malabsorptive disorder and monitored for complications, including osteoporosis, neurologic complaints, other autoimmune diseases, refractory sprue, ulcerative enteritis, T-cell lymphoma, and other GI cancers. Numerous studies have documented low bone density in children and adults at the time of initial diagnosis of CD, which improves with the GFD.^(28–31) Children should be examined for protein–calorie malnutrition, linear growth failure, and delayed puberty. First- and second-degree relatives should be offered screening for CD with serum antibodies.

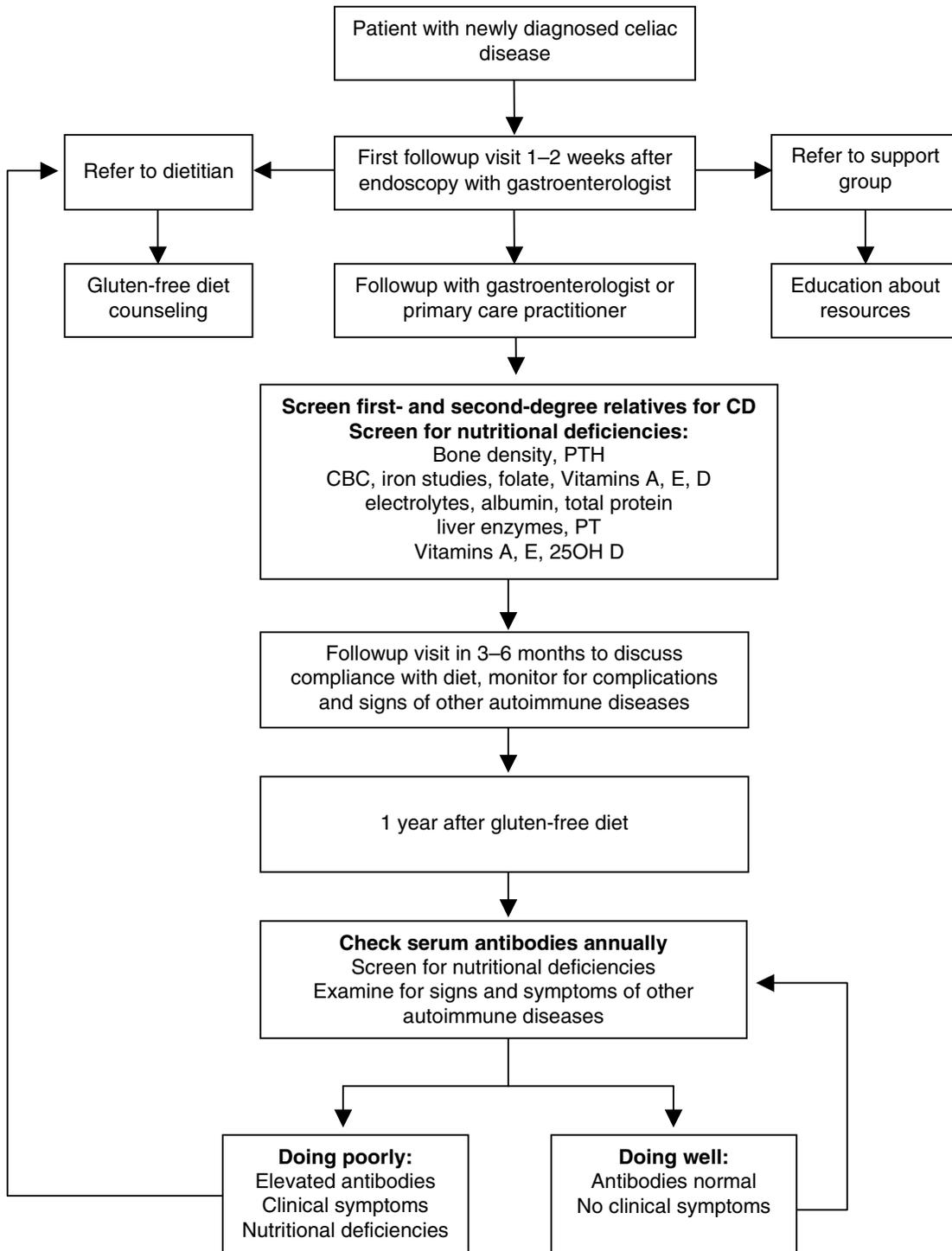


Figure 1. An Approach to the Management of a Patient With Newly Diagnosed Celiac Disease

Patient education, close supervision by an interested physician, and regular dietary counseling by a dietitian are the most important factors in achieving dietary compliance.⁽³²⁾ Compliance is improved, even in adolescents, who are seen by a physician on regular basis.^(33,34) Dietary compliance assessed by a trained interviewer is the best marker of CD control due to low cost, noninvasivity, and a strong correlation to intestinal damage. It will also reinforce the need for strict adherence to a GFD and educate the subjects in the avoidance of gluten-containing foods.

Future research must be directed at finding alternatives to the GFD, which will in turn increase compliance with treatment. These future potential treatments may include the development of genetically detoxified grains, an oral or intranasal “celiac vaccine” to induce tolerance, inhibitors of the effects of zonulin on intestinal permeability,⁽³⁵⁾ or detoxification of immunogenic gliadin peptides via oral peptidase supplement therapy.⁽³⁶⁾

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