

Clinical *nutrition* R O U N D S™

AS PRESENTED IN THE
GRAND ROUNDS OF
PARTICIPATING HOSPITALS
ACROSS CANADA

An update on celiac disease and the gluten-free diet

BY HARMINDER SINGH, MD; SHELLEY CASE, BSC, RD; DONALD R DUERKSEN, MD

Celiac disease (CD), also known as celiac sprue or gluten-sensitive enteropathy, is a chronic malabsorptive disorder of the small intestine caused by dietary exposure to gluten in genetically-predisposed individuals.¹ CD is now recognized as a common autoimmune condition. This review will focus on the recent advances in epidemiology, diagnosis, and management of this disease.

History

Aretaeus the Cappadocian made the first reference to CD in the first century A.D., describing it as an illness associated with diarrhea and general debility.² In the 18th century, the term “sprue” – derived from the Dutch word *spruw*, meaning aphthous disease – was used because of the high prevalence of aphthous mouth ulcers associated with this condition. In 1888, Samuel Gee provided the first modern description of the classical clinical presentation.³ However, it was not until the middle of last century that the link between celiac disease and the ingestion of certain cereals was established. During World War II when there was a shortage of flour in Netherlands, a Dutch pediatrician named Dicke observed that patients with celiac sprue improved, only to have worsening symptoms when the supply of cereals was restored after the war.⁴ Subsequent studies by Dicke and co-workers revealed that the toxic agent was present in the water-insoluble portion, or the gluten moiety, of wheat. In 1954, Paulley provided the first accurate description of the characteristic histological features of the intestinal lesions in celiac disease.^{2,4} The last two decades have seen a rapid expansion in the knowledge of the genetic, immune, and molecular mechanisms underlying the pathogenesis of CD, including a determination of the association with specific HLA haplotypes and identification of dominant epitopes of gliadin.

Epidemiology

Celiac disease has been traditionally considered a disorder of Caucasians of northern European ancestry. Until very recently, CD was considered an uncommon diagnosis in North America, with an estimated prevalence of 1 per 3000 population.⁵ One of the largest epidemiological studies in the United States, published earlier this year, suggests that CD is as common in North America as it is in Europe.⁶ In this study, over 13,000 subjects residing in 32 states were screened serologically for CD. CD was diagnosed when anti-endomysial antibodies (EMA) were detected with either an intestinal biopsy consistent with CD or HLA haplotypes compatible with CD. The prevalence was 1:133 among the 9000 asymptomatic individuals who did not have a 1st- or 2nd-degree relative with CD. The prevalence was 1:22 in the 4500 1st-degree relatives, 1:39 in the 1200 2nd-degree relatives, and 1:56 in the over 3000 symptomatic individuals enrolled in the study. In addition to the high prevalence of celiac disease in northern Europe and Scandinavia, recent epidemiological studies have demonstrated a high prevalence in populations of eastern Europe, Asia, South America and northern Africa.⁷⁻⁹ Celiac disease is rare among people from a purely Afro-Caribbean, Chinese, or Japanese backgrounds.¹⁰

Etiopathogenesis

CD is considered to be an autoimmune disorder triggered by the environmental agent gluten in genetically-susceptible individuals.

Gluten

Cereal proteins (discussed in more detail later) exist in a number of storage forms. Based on their solubility characteristics, they are categorized into 4 general groups:

- prolamins
- globulins
- glutenins
- minor albumins.²



In association with the
Department of Gastroenterology
at the University of Toronto



Editorial Board

Johane P. Allard, MD,
President CSCN, Editor
University of Toronto

Anne Childs, RN, CNSN
Hamilton Health
Sciences Corporation

Donald R. Duerksen, MD
University of Manitoba

Dominique Garrel, MD
Université de Montréal

Leah M. Gramlich, MD
University of Alberta

Khursheed Jeejeebhoy, MD
University of Toronto

Peter J.H. Jones, PhD
McGill University

Brian Jurewitsch, BScPhm, BCNSP
University of Toronto

Janice Siemens, RD
University of Manitoba

**Canadian Society
for Clinical Nutrition**
University Health Network
200 Elizabeth Street, Eaton 9-217A,
Toronto, Ontario, Canada
M5G 2C4
Tel: 416-340-4104
Fax: 416-348-0065
Website: www.cscn-scnc.ca
E-mail: info@cscn-scnc.ca

The editorial content of
Clinical Nutrition Rounds
is determined solely by
the Canadian Society
for Clinical Nutrition.

Available on the Internet
www.clinicalnutritionrounds.ca

The term “gluten” encompasses the prolamins and glutelins and toxicity studies demonstrate that both damage the intestinal mucosa of individuals with celiac disease.¹¹ The prolamins of wheat are referred to as “gliadins.” Prolamins from other cereals including rye and barley are also considered gluten and should to be avoided.

CD results from an inappropriate T-cell-mediated immune response against ingested gluten. Recent studies suggest that the generation of immunogenic short peptide antigens (epitopes) for recognition by CD4+ T cells requires deamidation of this protein by tissue transglutaminase.¹² In 2002, a 33-amino acid peptide containing all 3 previously-described T-cell epitopes was characterized as the putative candidate that may trigger CD.¹³ This peptide is susceptible to breakdown by a bacterial enzyme, suggesting possible future strategies for generating non-toxic varieties of gluten and an alternative to a gluten-free diet.¹⁴

Genetic factors

The importance of genetic factors in the pathogenesis of CD is suggested by family studies. CD occurs in about 10% of the 1st-degree relatives of affected persons.¹⁵ The concordance rate is as high as 70% in monozygotic twins.¹⁶ There is also a close association between CD and certain HLA class II haplotypes; HLA-DQ2 is found in 90%–95% of cases and the related HLA-DQ8 is found in most of the remaining cases.¹⁷ HLA-DQ2 is also present in 25%–30% of Europeans and because CD develops in only a minority of these individuals, it is not a useful screening test. The HLA contribution to the development of CD among siblings has been estimated to be about 36%.¹⁸ Therefore, other non-HLA genes may be stronger determinants of disease susceptibility.

Clinical manifestations

The classic presentation of celiac disease with steatorrhea and weight loss is now uncommon in the western world and represents only the tip of the “celiac iceberg.” Typically, CD was considered a disease of infants who presented with a gradual onset of symptoms after cereals were introduced in the diet. The availability of serological testing and active case-seeking has resulted in the diagnosis of celiac disease with presentations that are different from the classic symptoms of steatorrhea and weight loss.¹⁹

Atypical CD refers to the presentation without the overt features of malabsorption or persistent diarrhea, but includes short stature, anemia, iron deficiency, folate deficiency, infertility, psychiatric syndromes, and various neurological conditions (eg, peripheral neuropathy, ataxia, and seizures). Serological and small bowel findings suggestive of celiac disease may be found in up to 9% of patients with isolated elevation of serum transaminases.²⁰ *Silent* CD refers to the detection of asymptomatic patients with serological screening.

Some clinical features correlate with the length of the small intestine that is involved. Although CD is a disorder of the proximal small bowel, it can involve the entire small bowel in some patients. Proximal involvement leads to malabsorption of iron, calcium, and folic acid, while more extensive involvement can lead to diarrhea due to malabsorption of fat and carbohydrates.

Associated conditions

Dermatitis herpetiformis (DH) is a skin disease characterized by an intensely pruritic papulovesicular rash that occurs mainly on the extensor surfaces of the extremities, neck, and scalp. At least 80% of patients with DH have the characteristic features of CD on small intestinal biopsy.²⁰ A gluten-free diet for

6 to 12 months reverses the skin rash and intestinal lesions, and reduces the risk of lymphoma.^{21,22}

Several autoimmune diseases occur more frequently in patients with CD, especially autoimmune thyroiditis and type I diabetes.^{23–25} Three to 8% of patients with type I diabetes may have CD.^{23,24} Unexplained diarrhea or hypoglycemic episodes should raise the possibility of CD in patients with type I diabetes.¹⁰ The duration of gluten exposure correlates with the prevalence of associated autoimmune diseases.²⁶

Diagnosis

The laboratory findings in celiac disease vary with the extent and severity of intestinal involvement. In symptomatic cases, serum hematologic and biochemical tests, stool studies, and radiologic studies show abnormalities similar to those seen in other intestinal malabsorption disorders. The diagnosis is established based on serological tests and small intestinal biopsy.

Small intestinal biopsy

The gold standard diagnostic test for CD has been the small intestinal biopsy. Guidelines and diagnostic criteria, including those from the American Gastroenterology Association (AGA) and European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) recommend small intestinal biopsy as mandatory for establishing the diagnosis.^{1,27} The characteristic findings on the biopsy include villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes. An adequate number of biopsies need to be taken because the disease can be patchy and some of the biopsy specimens may not be properly oriented. The biopsies should be obtained from the second or third part of the duodenum to avoid the distortions produced by Brunner’s glands and peptic duodenitis in the first part. In infants, cow’s milk or soy protein intolerance may result in identical biopsy findings and documentation of morphological improvement on gluten withdrawal, with worsening on gluten rechallenge may be necessary to establish the diagnosis.² There are other conditions that mimic celiac disease histologically including tropical sprue, giardiasis, acute viral gastroenteritis, small intestinal bacterial overgrowth, and Zollinger-Ellison syndrome.

Serological tests

There are 4 serological studies commonly used in clinical practice to screen for CD:

- IgG antigliadin antibody (AGA)
- IgA AGA
- IgA endomysial antibody (EMA)
- IgA tissue transglutaminase antibody (tTG).

EMA binds to connective tissue surrounding smooth muscle cells; tissue transglutaminase has been recently identified as the target antigen. EMA is detected using an immunofluorescent assay, while tTG is detected using an ELISA assay. The sensitivities and specificities of these tests vary depending on the laboratory and the severity of disease. For example, in one study involving 5 laboratories in the US, the sensitivity of endomysial (EMA) IgA ranged from 57% to 90%.²⁸ In another study of 101 patients with biopsy-proven CD, the sensitivity of EMA in patients with total villous atrophy was 100% compared to 31% in those with partial villous atrophy.²⁹ The approximate reported sensitivities and specificities are shown in Table 1.³⁰

IgA EMA and IgA tTG, using human recombinant tissue transglutaminase, are the most specific tests. The latter is not yet widely available, but in labs where it is used, it has become the test of choice. The high specificities of serologic testing have led to a debate about the necessity of obtaining a confirmatory

Table 1: Serologic testing for celiac disease

Serological test	Sensitivity (%)	Specificity (%)
AGA		
IgG AGA	69-85	73-90
IgA AGA	75-90	82-95
IgA EMA	85-98	97-100
IgA tTG		
Using guinea pig substrate	95-98	94-95
Using human substrate	93-96	99-100

intestinal biopsy, especially when the pretest probability of CD is high. In a recent study, serial testing with transglutaminase antibodies (tTG) and anti-endomysial antibodies (EMA) provided a post-test probability of >99% in groups of patients with an estimated prevalence of CD >75%, suggesting that serial testing may avoid the need to biopsy in some cases.³¹ However, at present, small bowel biopsies are recommended in all patients to confirm the diagnosis.^{1,10,27}

The positive predictive value of anti-gliadin antibodies in the general population is poor and they probably should not be used except in special clinical circumstances. For example, IgA anti-gliadin is the most useful serological marker in children <2 years old, a group in which the false-negative rate of EMA and tTG testing is high. It may also be helpful for monitoring dietary compliance since its levels are easiest to quantify and they gradually become undetectable 3-6 months after gluten withdrawal.

There is an increased prevalence of IGA deficiency in patients with celiac disease and false-negative EMA and tTG testing may also occur in individuals with IGA deficiency and celiac disease.

Complications associated with CD

Recently, a number of complications including an increased risk of malignancy, osteoporosis, and autoimmune disorders have been associated with CD.

Malignancy

Malignant diseases seen more frequently in patients with CD include small bowel adenocarcinoma, esophageal and oropharyngeal squamous cell carcinoma, melanoma, and non-Hodgkin's lymphoma.³² Small intestinal lymphomas account for more than half of these malignancies. The risk of gut lymphomas is increased 17-fold compared with healthy controls (OR 16.9).³³ The risk of small bowel adenocarcinoma is 80-fold greater than in the general population.²² Since both of these malignant disorders are rare, the absolute risk is still small. There is evidence that adherence to a gluten-free diet decreases this risk.³⁴

Bone disease

Osteoporosis is more common in patients with untreated CD than the general population. Among newly diagnosed patients, the prevalence of osteoporosis is 15%-28%. At the time of diagnosis, children and adults have similarly low bone mineral density (BMD); however, children are more likely than adults to fully restore their bone mass after a gluten-free diet.³⁵ In a recent population-based cohort study, a small increase in the fracture rate (an overall hazard ratio for any fracture: 1.3) was found in patients with CD.³⁶

Autoimmune disease

As discussed previously, several autoimmune diseases occur more frequently in patients with CD. The prevalence of autoimmune disorders in celiac disease appears to be related to the duration of exposure to gluten.²⁶ Gluten withdrawal may prevent the development of these disorders and can help in their management.³⁷

Refractory celiac disease

The most common reason for individuals failing to respond to a gluten-free diet is continued gluten ingestion, which may be inadvertent.¹¹ Alternative diagnoses such as irritable bowel syndrome (IBS), chronic infections, pancreatic insufficiency, and bacterial overgrowth should be considered. Rarely, celiac disease may be complicated by collagenous sprue, ulcerative jejunitis, or lymphoma that may present with symptoms that are refractory to a gluten-free diet.²

Increased mortality

Large epidemiologic studies have demonstrated that patients with CD have a 1.4- to 2.0-fold increase in mortality.³⁸ Mortality rates are higher when diagnosis is delayed and in patients who are non-compliant with a gluten-free diet.³⁹ On the other hand, in patients who strictly adhere to a gluten-free diet, documented survival rates are similar to the general population.⁴⁰

Management

A life-long adherence to a strict gluten-free diet is the cornerstone of treatment for CD. Removing gluten from the diet usually results in symptomatic and histologic resolution of the disease. Response to a gluten-free diet may take several weeks to several months or even years and varies greatly from one patient to another depending on a number of factors.⁴¹⁻⁴⁶ These include the length of time between the onset of symptoms and diagnosis and the degree of villous atrophy, associated nutritional problems (ie, secondary lactose intolerance), anemia or other vitamin and mineral deficiencies, patient age, and the ability of the patient to completely eliminate all sources of gluten from the diet. Patients who continue to have symptoms despite strict adherence to a gluten-free diet need a thorough work-up for infectious and noninfectious conditions for the conditions listed under refractory CD (above).

It is critical that patients are referred to a registered dietitian with experience in celiac disease at the time of diagnosis. The dietitian will complete a nutritional assessment and, if necessary, recommend appropriate supplements in consultation with the physician. The dietitian can also provide in-depth education about celiac disease including the toxicity of gluten-containing grains; foods and ingredients that may be consumed, those to avoid, and those to question; label reading; shopping and meal planning guidelines; prevention of cross-contamination at home and when eating out; sources of gluten-free specialty foods; and recipes. Family members and/or caregivers, especially those involved in food preparation, should also attend in order to understand the importance of the diet and offer support. Follow-up visits with the dietitian are essential since the gluten-free diet is complex and cannot be taught in one session. Patients will have questions and concerns once they initiate the diet and discover how widespread gluten is in the food supply and the enormous changes that are required in their eating habits. Some will find it difficult to eliminate their favourite gluten-containing foods and will need considerable encouragement. It is highly recommended that patients join the

Table 2: Gluten-containing ingredients that should be avoided

Barley	Malt Syrup**
Bulgur	Malt Vinegar**
Cereal Binding	Oat Bran***
Couscous	Oats***
Durum	Oat Syrup***
Einkorn*	Rye
Emmer*	Semolina
Farro*	Spelt (Dinkel)
Filler	Triticale
Graham Flour	Wheat
Kamut*	Wheat Bran
Malt**	Wheat Germ
Malt Extract**	Wheat Starch
Malt Flavoring**	

* Types of wheat

** Derived from barley

*** Cross contamination of oats with wheat and/or barley remains a concern in North America, therefore oats are not recommended by celiac organizations in Canada or the US at this time.

Adapted from *Gluten-Free Diet: A Comprehensive Resource Guide*, 2003 edition, by Shelley Case

national celiac association and their local chapter for ongoing support and resources (see Appendix).

Basis of the gluten-free diet

In order to gain a better understanding of the gluten-free diet, it is important to clarify the term “gluten.” To the baker, gluten is the ingredient in wheat that plays a role in leavening, forming the dough structure, and holding baked products together. To the cereal scientist and health professional, gluten is the general name for storage proteins called prolamins in various cereal grains. Specific peptide sequences in the alcohol-soluble prolamins fractions of gliadin in wheat, secalin in rye, and hordein in barley cause the toxic reaction in celiac disease. These grains share a common taxonomy and belong to a tribe of grasses called “triticeae”. All forms of wheat, rye, and barley must be strictly avoided by the person with CD (Table 2). As noted in a previous section, glutenins – the partially soluble protein fraction of these grains – should also be avoided. Other grasses not in the triticeae tribe (eg, corn, sorghum, rice, millet, ragi, teff, Job’s tears, and wild rice) are safe. Dicotyledenous plants that are very distantly related to the grass family (eg, amaranth, buckwheat, flax, and quinoa) are also allowed in a gluten-free diet.

Until 1995, the avenin prolamins in oats was also thought to damage the small intestine; however, studies in both children and adults with CD have revealed that consumption of pure oats in moderate amounts is safe.⁵⁸⁻⁶⁶ Unfortunately, oats can be contaminated with wheat or barley. The extent of the contamination in commercial oat products in North America is unknown; therefore celiac organizations in both Canada and the US do not recommend oats at this time.¹⁵

The challenge of a gluten-free diet

Following a gluten-free diet can be a major challenge for several reasons. Gluten is not only found in breads and other baked products, cereals, cookies, crackers and pastas,

but also in a wide variety of other foods, such as sauces, seasonings, salad dressings, soups, bouillon cubes, prepared meats (eg, hot dogs, deli meats, hamburger patties), snack foods, flavoured coffees and teas, dairy-free soy or rice beverages, candy, baking powder, and some nutritional supplements and medications (Table 3). Gluten is often a “hidden ingredient” in many foods and is disguised as modified food starch, seasonings, flavourings, hydrolyzed vegetables, or plant proteins. Current labeling regulations in Canada and the US do not require companies to completely disclose all the ingredients or components of ingredients on the food label, making it difficult for persons with CD or other food allergies/intolerances to determine their safety. Health Canada (HC) and the Canadian Food Inspection Agency (CFIA) have developed proposed labeling regulations entitled “Schedule of Amendments 1220: Enhanced Labeling of Food Ingredients” that would require manufacturers to list the top 8 allergens (peanuts, tree nuts, eggs, milk, soy, fish, shellfish, and wheat) and other cereal grains containing gluten, sulphites, and sesame seeds on the food label. Although these regulations are not yet official, HC/CFIA strongly encourages companies to voluntarily label the major ingredients known to cause allergies and sensitivities. The US Food and Drug Administration (FDA) is currently reviewing its labeling regulations for allergenic ingredients and considering whether rule-making is necessary. The newly formed American Celiac Task Force, comprised of celiac organizations, health professionals specializing in CD, gluten-free companies, and others are lobbying Congress to improve food labeling regulations.

For a large segment of the population including those with CD, hectic lifestyles have resulted in an increased frequency of eating out and dependence on the use of convenience or “fast” foods, the majority of which contain gluten. This poses a further challenge for people trying to follow a gluten-free diet.

Gluten-free foods

Many foods are naturally gluten-free including plain meats, fish, poultry, nuts, seeds, eggs, legumes, milk, yogurt, cheese, fruits, vegetables and alternative grains and their flours. With increasing numbers of people diagnosed with CD, there is a rapidly growing gluten-free specialty food market in North America and Europe that offers a wide variety of products such as pizza, pastas, cereal, crackers, soups, sauces, entrées, snack foods, and ready-to-eat baked goods and mixes for breads, bagels, buns, muffins, cakes, cookies, pastries. These foods are available in healthfood and grocery stores, pharmacies, and directly from gluten-free vendors. Some of these products are made in dedicated facilities that manufacture only gluten-free products. Other companies produce both gluten-free and gluten-containing products so there is a greater risk of cross-contamination, especially in bakeries.

Patients need to be cautioned about the difference between products labeled “wheat-free” and “gluten-free.” Wheat-free products often contain spelt, kamut, or barley, which are *not* gluten-free. In Canada, there is a specific regulation for the term “gluten-free” and Health Canada randomly monitors products with a gluten-free claim by testing for gluten. If the product exceeds 20 parts per million (ppm), it is recalled. The US does not have a definition for the term “gluten-free” and does not test products

Table 3: Sources of hidden gluten

Rice or corn cereals	May contain barley malt flavouring or extract
Baked beans	Some are thickened with wheat flour
Imitation seafood	May contain fillers made from wheat starch
Dry roasted or flavored nuts	May contain wheat or seasonings with wheat flour or wheat starch
Hot dogs, luncheon meats, hamburger patties	May contain fillers made from wheat May contain hydrolyzed wheat protein
Canned soups, dried soup mixes, soup bases, bouillon cubes	May contain noodles or barley, hydrolyzed plant, or vegetable protein from wheat. Cream soups are often thickened with wheat flour Seasonings may contain wheat flour, wheat starch, or hydrolyzed wheat protein
Salad dressings	Seasonings may contain wheat flour or wheat starch
Herbal teas, instant teas, flavoured coffees, coffee substitutes	Some may contain barley malt flavouring or grain additives
Soy, rice or nut beverages	May contain barley malt flavouring or extract
Potato or tortilla chips	Some potato chips contain wheat. Seasonings/flavouring may contain wheat flour, wheat starch, or hydrolyzed wheat protein
Baking powder	Contains starch, which may be from wheat
Seasonings	May contain wheat flour, wheat starch, or hydrolyzed wheat protein
Candy	Licorice and Smarties contain wheat
Soy sauce	Many brands are a combination of wheat and soy
Sauces and gravies	Often thickened with wheat flour
Worcestershire sauce	May contain malt vinegar which is not gluten-free
Communion wafers	Made from wheat
Modified food starch	Often made from corn, but may be derived from wheat
Maltodextrin	Usually from corn, potato, or rice, but can also be made from wheat
Dextrin	Usually from corn, but sometimes derived from wheat

Excerpts from *Gluten-Free Diet: A Comprehensive Resource Guide*, 2003 edition by Shelley Case

that are labeled “gluten-free.” European countries have different definitions for the term “gluten-free.” Some products labeled gluten-free are made with wheat starch, which contains varying amounts of gliadin; however, wheat starch is not permitted in gluten-free foods in Canada. The use of wheat starch in the gluten-free diet is controversial.⁶⁷⁻⁷⁰

Physicians and dietitians need to have a positive approach when working with patients with CD. They must emphasize the importance of strictly following a gluten-free diet for life, not only to improve their quality of life, but to prevent complications such as lymphoma and the development of other autoimmune conditions and osteoporosis. Health professionals and the Celiac Association can provide valuable support and education to patients. For more information about CD and resources see the Appendix.

Conclusion

Celiac disease is a common autoimmune disease that is unique in that it can be controlled with diet therapy alone. Increased education is needed for healthcare professionals to recognize this common underdiagnosed condition. Gluten-free food labeling in North America needs to be improved to assist individuals with celiac disease in adopting a life-long gluten-free diet.

Dr. Harminder Singh is a GI Fellow in the Department of Medicine, University of Manitoba.

Dr. Donald Duerksen is a physician in the Division of Gastroenterology of St. Boniface Hospital, Winnipeg, Manitoba, and an Associate Professor in the Department of Medicine, University of Manitoba.

Shelley Case, B.Sc., R.D., is a consulting dietician specializing in celiac disease. She is also a speaker, author, and member of the Professional Advisory Board of the Canadian Celiac Association. She is on the Medical Advisory Boards of the Celiac Disease Foundation and Gluten Intolerance Group in the U.S.

References

- Ciclitira PJ, King AL, Fraser JS. AGA technical review on celiac sprue. American Gastroenterological Association. *Gastroenterology* 2001;120(6):1526-1540.
- Farrell RJ, Kelly CP. Celiac sprue and refractory sprue. In: Feldman M, Friedman LS, Sleisenger MH, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 7th ed. Philadelphia PA: Saunders;2002:1817-1841.
- Ciclitira PJ, Moodie SJ. Coeliac disease. *Best Pract Res Clin Gastroenterol* 2003; 17(2):181-195.
- Cronin CC, Shanahan F. Exploring the iceberg – the spectrum of celiac disease. *Am J Gastroenterol* 2003;98(3):518-520.
- Talley NJ, Valdovinos M, Petterson TM, Carpenter HA, Melton LJ III. Epidemiology of celiac sprue: a community-based study. *Am J Gastroenterol* 1994;89(6):843-846.
- Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;163(3):286-292.
- Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001;120(3):636-651.
- Volta U, Bellentani S, Bianchi FB, Brandi G, De Franceschi L, Miglioli L, et al. High prevalence of celiac disease in Italian general population. *Dig Dis Sci* 2001;46(7):1500-1505.
- Dobru D, Pascu O, Tanta M, Gheorghe C, Goldis A, Balan G, et al. The prevalence of coeliac disease at endoscopy units in Romania: routine biopsies during gastroscopy are mandatory (a multicentre study). *Rom J Gastroenterol* 2003;12(2):97-100.
- Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346(3):180-188.
- De Vincenzi M, Luchetti R, Peruffo AD, Curioni A, Pogna NE, Gasbarrini G. In vitro assessment of acetic-acid-soluble proteins (glutenin) toxicity in celiac disease. *J Biochem Toxicol* 1996;11(4):205-210.
- Mowat AM. Coeliac disease—a meeting point for genetics, immunology, and protein chemistry. *Lancet* 2003;361(9365):1290-1292.

13. Shan L, Molberg O, Parrot I, et al. Structural basis for gluten intolerance in celiac sprue. *Science* 2002;297(5590):2275-2279.
14. McManus R, Kelleher D. Celiac disease – the villain unmasked? *N Engl J Med* 2003; 348(25):2573-2574.
15. Bevan S, Popat S, Braegger CP, et al. Contribution of the MHC region to the familial risk of coeliac disease. *J Med Genet* 1999;36(9):687-690.
16. Greco L, Romino R, Coto I, et al. The first large population based twin study of coeliac disease. *Gut* 2002;50(5):624-628.
17. Fasano A. Celiac disease—how to handle a clinical chameleon. *N Engl J Med* 2003; 348(25):2568-2570.
18. Petronzelli F, Bonamico M, Ferrante P, et al. Genetic contribution of the HLA region to the familial clustering of coeliac disease. *Ann Hum Genet* 1997;61(Pt 4):307-317.
19. Collin P, Reunala T, Rasmussen M, et al. High incidence and prevalence of adult coeliac disease. Augmented diagnostic approach. *Scand J Gastroenterol* 1997;32(11): 1129-1133.
20. Abdulkarim AS, Murray JA. Review article: The diagnosis of coeliac disease. *Aliment Pharmacol Ther* 2003;17(8):987-995.
21. Garioch JJ, Lewis HM, Sargent SA, Leonard JN, Fry L. 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. *Br J Dermatol* 1994; 131(4):541-545.
22. Green PH, Jabri B. Coeliac disease. *Lancet* 2003;362(9381):383-391.
23. Cronin CC, Feighery A, Ferriss JB, Liddy C, Shanahan F, Feighery C. High prevalence of celiac disease among patients with insulin-dependent (type I) diabetes mellitus. *Am J Gastroenterol* 1997;92(12):2210-2212.
24. Sjöberg K, Eriksson KF, Bredberg A, Wassmuth R, Eriksson S. Screening for coeliac disease in adult insulin-dependent diabetes mellitus. *J Intern Med* 1998;243(2):133-140.
25. Counsell CE, Taha A, Ruddell WS. Coeliac disease and autoimmune thyroid disease. *Gut* 1994;35(6):844-846.
26. Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. *Gastroenterology* 1999;117(2):297-303.
27. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990; 65(8):909-911.
28. Murray JA, Herlein J, Mitros F, Goeken JA. Serologic testing for celiac disease in the United States: results of a multilaboratory comparison study. *Clin Diagn Lab Immunol* 2000;7(4):584-587.
29. Rostami K, Kerckhaert J, Tiemessen R, von Blomberg BM, Meijer JW, Mulder CJ. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. *Am J Gastroenterol* 1999;94(4):888-894.
30. Farrell RJ, Kelly CP. Diagnosis of celiac sprue. *Am J Gastroenterol* 2001;96(12):3237-3246.
31. Scoglio R, Di Pasquale G, Pagano G, Lucanto MC, Magazzu G, Sferlazzas C. Is intestinal biopsy always needed for diagnosis of celiac disease? *Am J Gastroenterol* 2003;98(6):1325-1331.
32. Green PH, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. *Am J Med* 2003;115(3):191-195.
33. Catassi C, Fabiani E, Corrao G, et al. Risk of non-Hodgkin lymphoma in celiac disease. *JAMA* 2002;287(11):1413-1419.
34. Holmes GK, Prior P, Lane MR, Pope D, Allan RN. Malignancy in celiac disease – effect of a gluten free diet. *Gut* 1989;30(3):333-338.
35. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003;124(3):795-841.
36. West J, Logan RF, Card TR, Smith C, Hubbard R. Fracture risk in people with celiac disease: a population-based cohort study. *Gastroenterology* 2003;125(2):429-436.
37. Sategna-Guidetti C, Volta U, Ciacci C, et al. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. *Am J Gastroenterol* 2001;96(3):751-757.
38. Peters U, Asklung J, Gridley G, Ekblom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Arch Intern Med* 2003;163(13): 1566-1572.
39. Corrao G, Corazza GR, Bagnardi V, et al. Mortality in patients with coeliac disease and their relatives: a cohort study. *Lancet* 2001;358(9279):356-361.
40. Collin P, Reunala T, Pukkala E, Laippala P, Kyriläinen O, Pasternack A. Coeliac disease-associated disorders and survival. *Gut* 1994;35(9):1215-1218.
41. Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. *Gastrointest Endosc* 2003;57: 187-91.
42. Tursi A, Brandimarte G, Giorgetti GM, Gigliobianco A. Endoscopic features of celiac disease in adults and their correlation with age, histologic damage, and clinical form of the disease. *Endoscopy* 2002;34:787-92.
43. Ciacci C, Cirillo M, Cavalloro R, Mazzacca G. Long-term follow-up of celiac adults on a gluten-free diet: prevalence and correlates of intestinal damage. *Digestion* 2002; 66:178-85.
44. Wahab PJ, Meijer JW, Mulder CJ. Histologic follow-up of people with celiac disease on a gluten-free diet: slow and incomplete recovery. *Am J Clin Pathol* 2002;118:459-63.
45. Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of non-responsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002;97:2016-21.
46. Selby WS, Painter D, Collins A, et al. Persistent mucosal abnormalities in celiac disease are not related to the ingestion of trace amounts of gluten. *Scand J Gastroenterol* 1999;34:909-14.
47. Storsrud S, Olsson M, Lenner RA, Nilsson LA, Nilsson O, Kilander A. Adult coeliac patients do tolerate large amounts of oats. *Eur J Clin Nutr* 2003;57:163-69.
48. Janatuinen EK, Kempainen TA, Julkunen RJK, et al. No harm from five-year ingestion of oats in coeliac disease. *Gut* 2002;50:332-35.
49. Hoffenberg E, Haas J, Drescher A, et al. A trial of oats in children with newly diagnosed celiac disease. *J Pediatr* 2000;137:361-66.
50. Janatuinen EK, Kempainen TA, Pikkarainen PH, et al. Lack of cellular and humoral immunological responses to oats in adults with coeliac disease. *Gut* 2000;46:327-31.
51. Reunala T, Collin P, Holm K, et al. Tolerance to oats in patients with dermatitis herpetiformis. *Gut* 1998;43:490-93.
52. Hardman CM, Garioch JJ, Leonard JN, et al. Absence of toxicity of oats in patients with dermatitis herpetiformis. *N Engl J Med* 1997;337:1884-87.
53. Srinivasan U, Leonard N, Jones E, et al. Absence of oats toxicity in adult coeliac disease. *BMJ* 1996;313:1300-01.
54. Janatuinen EK, Pikkarainen PH, Kempainen TA, et al. A comparison of diets with and without oats in adults with celiac disease. *N Engl J Med* 1995;333:1033-37.
55. Thompson T. Oats and the gluten-free diet. *J Am Diet Assoc* 2003;103:376-379.
56. Thompson T. Wheat starch, gliadin and the gluten-free diet. *J Am Diet Assoc* 2001; 101:1456-59.
57. Lohiniemi S, Maki M, Kaukinen K, Laippala P, Collin P. Gastrointestinal symptoms rating scale in celiac disease patients on wheat starch-based gluten-free diets. *Scand J Gastroenterol* 2000;35:947-49.
58. Kaukinen K, Collin P, Holm K, et al. Wheat starch-containing gluten-free flour products in the treatment of coeliac disease and dermatitis herpetiformis. A long-term follow-up study. *Scand J Gastroenterol* 1999;34:163-69.
59. Chartrand LJ, Russo PA, Duhaime AG, Seidman EG. Wheat starch intolerance in patients with celiac disease. *J Am Diet Assoc* 1997;97:612-18.

Appendix

Celiac Disease and Gluten-Free Diet Resources

Canadian Celiac Association

L'association Canadienne de la Maladie Coeliaque

Website: www.celiac.ca Email: celiac@look.ca

Fondation Québécoise de la Maladie Coeliaque

Website: www.fqmc.org Email: info@fqmc.org

Gluten-Free Diet: A Comprehensive Resource Guide, 2003 edition

Website: www.glutenfreediet.ca

Email: info@glutenfreediet.ca

Kids With Celiac Disease:

A Family Guide to Raising Happy, Healthy Children

Website: www.woodbinehouse.com

Wheat-Free, Worry-Free:

The Art of Happy, Healthy Gluten-Free Living

Website: www.hayhouse.com

Upcoming meeting

25 October 2003

Western Canada Nutrition Day

Edmonton Alberta

CONTACT: Tel: 780 407-7406 Fax: 780 407-6432

Email: conofrec@cha.ab.ca

Website: www.capitalhealth.ca

Change of address notices and requests for subscriptions to *Clinical Nutrition Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Clinical Nutrition Rounds* in your correspondence. Undeliverable copies are to be sent to the address above.

This publication is made possible by an educational grant from

Ross Products Division, Abbott Laboratories Limited

© 2003 The Canadian Society for Clinical Nutrition, which is solely responsible for the contents. The opinions expressed in this publication do not necessarily reflect those of the publisher or sponsor, but rather are those of the authoring institutions based on the available scientific literature. Publisher: **SNELL Medical Communication Inc.** in cooperation with The Canadian Society for Clinical Nutrition. All rights reserved. The administration of any therapies discussed or referred to in *Clinical Nutrition Rounds* should always be consistent with the recognized prescribing information in Canada. **SNELL Medical Communication Inc.** is committed to the development of superior Continuing Medical Education.