Type 1 Diabetes and Celiac Disease: Overview and Medical Nutrition Therapy

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In patients with celiac disease (gluten-sensitive enteropathy, or GSE), ingestion of the gliadin fraction of wheat gluten and similar molecules (prolamins) from barley, rye, and possibly oats causes damage to the intestinal epithelium. The injury results from an abnormal T-cell response against gliadin. Thus, GSE is a disease in which host susceptibility must be combined with a specific environmental trigger to affect injury.[1]

Typically, patients with GSE have chronic diarrhea and failure to thrive. However, some patients present with short stature, flatulence, or recurrent abdominal pain. Dermatitis herpetiformis, a pruritic papular rash, is directly related to GSE.[2] Other atypical presentations are increasingly recognized, among them iron-deficiency anemia, osteopenia/osteoporosis, short stature, dental enamel hypoplasia, arthritis and arthralgia, chronic hepatitis/hypertransaminasemia, and neurological problems. GSE has also been found in asymptomatic individuals who nonetheless have evidence of intestinal mucosal injury on biopsy.[1]

Celiac Disease and Type 1 Diabetes

An association of diabetes with GSE has been observed since the late 1960s. In recent years, it has become clear that the incidence of GSE in patients with type 1 diabetes is substantial. A prevalence rate of 4–6% in type 1 diabetes has been reported.[3–5] Some of the variation in prevalence can be attributed to the different diagnostic criteria used in the studies.

The majority of patients with GSE are asymptomatic[4] or are not aware of symptoms. Some patients present with problems recognized only retrospectively as resulting from celiac disease; it is common for "asymptomatic" patients to report improved health or sense of well-being when following a gluten-free diet. Up to one-third of patients may have unexplained failure to thrive, abdominal pain, or short stature.[3,6]

More controversial is the question of whether GSE affects blood glucose control. A study by Acerini et al.[7] in a type 1 diabetic population found no difference between the celiac and non-celiac subpopulation in terms of hemoglobin A_{1c} or total insulin needs. Some celiac patients had morning hypoglycemia after starting a gluten-free diet, but no statistically significant change in insulin needs was found. Another study[8] of adults with type 1 diabetes and GSE found no difference in metabolic control of diabetes with treatment of GSE.

It has been observed that patients with GSE have hypoglycemic episodes and reduced insulin needs before diagnosis, presumably because of malabsorption.[9] In a detailed study of growth parameters, blood glucose control, and dietary intake in a group of children and adolescents with GSE and type 1 diabetes, Westman et al.[10] found no differences between GSE and non-GSE patients. This population was screened annually for GSE and so were diagnosed at an asymptomatic point of the illness. In a case-controlled study of the incidence of hypoglycemia in patients with untreated GSE, Mohn et al.[11] found that there were significantly more episodes of hypoglycemia in the GSE patients than in controls. Institution of a gluten-free diet reduced hypoglycemia, but only several months after initiation.

It seems likely that a malabsorptive disease could create opportunity for hypoglycemia in diabetes, particularly in patients under tight control. Serological testing for GSE in patients with type 1 diabetes, with early diagnosis of GSE, may reduce this risk by allowing patients to be diagnosed in a pre-symptomatic state. It also seems prudent to closely monitor insulin needs and blood glucose control during the early phase of instituting a gluten-free diet.

Testing People With Diabetes for GSE

Serological testing is an important screening tool for patients with atypical or silent celiac disease or family members of patients with GSE. While the evolving nature of serological testing for GSE makes any recommendation difficult, most investigators would advocate a profile consisting of three antibody assays: *1*) anti-gliadin IgG, *2*) anti-gliadin IgA, and *3*) either an anti-endomysial or an anti-tissue transglutaminase assay. Serum IgA must be quantitated in all patients because the most specific antibodies are IgA, and GSE is more common in patients with IgA deficiency.[12–14]

Patients with positive serological tests and those who have symptoms compatible with GSE and negative serology should be referred to a gastroenterologist for further diagnostic studies. In the past, the diagnosis of GSE required three small-bowel biopsies generally performed endoscopically. The first, done while the patient was symptomatic, would show mucosal injury. A second biopsy would be performed after a minimum

of 1 year on a gluten-free diet. If those results were normal, the patient then would be challenged carefully with gluten, and a third biopsy, which would again show abnormalities, would be performed either when the patient was symptomatic or after 1 year on gluten.[15] The evolution of serological testing has allowed modification of this protocol, although individual patients may still require multiple biopsies to distinguish GSE from diseases that produce a similar histopathological injury.[16]

There are limitations to serological testing. First, a positive serological test is not diagnostic of GSE. Small-bowel biopsy is required to confirm the diagnosis. Second, patients under the age of 2 years may have false-negative results on serology. When celiac disease is strongly suspected in patients within this age-group, they should have a small-bowel biopsy despite negative antibody testing. If they are asymptomatic, they should be re-tested at an older age. Third, it is clear that a single serological test with negative results does not preclude the later development of celiac disease. Although clear recommendations are not available, many centers test yearly for the first 3 years of diagnosed diabetes, every 3–5 years thereafter, and whenever symptoms develop.

Treatment of GSE

Current U.S. and Canadian recommendations for the treatment of GSE include a strict gluten-free diet to be maintained for life. For many patients with diabetes, this may seem unreasonable given the changes they have no doubt already made to their diet after their diabetes diagnosis. However, the stringency of this recommendation is based on sound reasoning.

First, strict elimination of gluten has been shown to lower the risk of small-bowel lymphoma associated with GSE.[17] Although there are no reliable incidence figures for lymphoma in GSE, a recent survey by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition[18] reported five cases of small-bowel lymphoma with responses from about half their membership. All five patients were eating gluten. It should be noted that this reflects only the lymphoma diagnoses in children in this region; the risk may rise in adults, particularly if the diet is not maintained. This constitutes the most compelling reason to advocate strict adherence to the diet.

Many GSE patients, despite their resistance to the diet, find they feel better and have more energy when their diets are gluten-free. Frequently, both children and adults have more energy, feel less irritable and cranky, display better skin color, and report better overall health following treatment of GSE. Some people with diabetes and GSE report that blood glucose control is easier to maintain when they follow the gluten-free diet. While these are not universal benefits, they should be noted in discussions with patients.

Finally, patients with untreated celiac disease are at risk of multiple deficiencies of micronutrients and vitamins because of the malabsorption of these nutrients by the injured small intestine. Among the reported problems are iron and vitamin B_{12} deficiency. At diagnosis, many celiac patients have osteopenia, which resolves on a gluten-free diet. Clearly, the risk of malnutrition is another important reason to advocate a strict gluten-free diet.

Celiac disease is a lifelong condition; thus, the diet is a permanent change for these patients. Many patients become exquisitely sensitive to the ingestion of even small amounts of gluten after a gluten-free period. Violent vomiting, severe diarrhea, abdominal cramping, and even shock may occur in these patients.

In some patients, ingestion of small amounts of gluten will not produce overt symptoms. Some patients experience a reduction in response to gluten during their teens—the so-called "honeymoon period." Unfortunately, despite the lack of perceived symptoms, biopsies of the small intestine in these patients demonstrate ongoing mucosal injury associated with gluten ingestion. It is believed that this persistent recurrent injury to the intestine is the factor that predisposes these patients to lymphoma. Thus, absence of symptomatic response to gluten ingestion should not be construed as indicating that gluten intake is safe.

To aid patients in maintaining the diet, they should be tested regularly for ingestion of gluten (at least yearly and perhaps more often for those who have difficulty following the diet). Antigliadin antibodies rise within weeks of gluten ingestion in patients with GSE and constitute a useful marker of dietary management. Patients may inadvertently ingest gluten because of its abundant use in many prepared foods. Contamination of gluten-free foods in a family toaster full of wheat crumbs, for example, may be discovered by interviewing the family after a positive antigliadin antibody test.

Most studies suggest that osteopenia and vitamin and mineral deficiencies associated with GSE resolve on the gluten-free diet. Thus, in patients adhering to the diet, little long-term screening for these deficiencies is warranted.

It should be noted that immediately after diagnosis, some supplements and dietary modifications may be necessary that will be unnecessary after the intestinal mucosa is healed. Patients are frequently lactose-intolerant at diagnosis because of injury to the disaccharidases in the small intestine. Patients should be screened at diagnosis for iron, zinc, B_{12}, folate, calcium, magnesium, and fat-soluble vitamin deficiencies and treated if abnormalities are found. Most specific supplements can be stopped 6–12 months into therapy.

Because gluten-free foods may be lower in B vitamins, folate, iron, and fiber, careful planning is necessary to ensure adequate intake of these nutrients.[19,20] A daily multivitamin may be recommended for patients with GSE.

The Diet

Ideally, a gluten-free diet would eliminate any prolamin or similar protein capable of stimulating an adverse T-cell response. (See Tables 1 and 2.) Unfortunately, there is no way to directly determine the capacity of individual grains to elicit a response, and current recommendations rely on in vivo testing. As a result, there is controversy regarding the most appropriate diet for patients with GSE. For example, moderate consumption of oats has been shown in several short-term studies to be safe;[21–24] however,

Table 1. Starches, Grains, and Other Foods Appropriate on a Gluten-Free Diet

- Amaranth,* arrowroot, whole-bean flour, buckwheat,* corn, cornstarch, cornmeal, flax, millet,* nut flours, oats,* oat bran,* oat gum,* pea flour, potato, sweet potato and yam, potato flour, potato starch, quinoa,* rice and wild rice, rice bran, rice flour, sago, sorghum, soy, tapioca, teff*
- Fresh, frozen, or canned unprocessed fruits and vegetables
- Fresh meats, poultry, seafood, fish, game, eggs, some processed meats with gluten-free ingredients, tofu, dried peas, beans, and lentils
- Milk, yogurt, and cheese made with gluten-free ingredients
- Oils, tree nuts, seeds, natural peanut butter, and salad dressings and spreads with gluten-free ingredients
- Honey, sugar, pure maple syrup, corn syrup, jams, jellies, candy, and ice cream with gluten-free ingredients
- Pure spices and herbs, salt, wheat-free soy sauce, vinegar with gluten-free ingredients
- Coffee ground from whole beans, brewed tea, carbonated beverages, some root beer

This is only a partial listing. Patients are encouraged to read all labels and to seek comprehensive food and additive lists from celiac organizations and the American Dietetic Association.

*Recommendations about acceptability are inconsistent. Many physicians restrict these grains for the first 6 months after diagnosis or until patients are in full remission.

many celiac organizations and the American Dietetic Association are not yet recommending oats as safe for consumption. It is also unclear whether several other grains, such as buckwheat and amaranth, are acceptable on a gluten-free diet.[25] A consensus is needed among the various organizations to minimize confusion for practitioners and patients.[26]

Codex Standards

The Codex Alimentarius Commission of the World Health Organization and the Food and Agriculture Organization of the United Nations provides the only *international* gluten-free food standards for manufacturers. The standards for gluten-free foods as defined by the commission allow small amounts of prolamin in foods that are designated gluten-free.[27] In Europe, the United Kingdom, and Scandinavia, ingestion of wheat starch that has been rendered gluten-free is permitted. European Codex Alimentarius-quality wheat starch has been used in some European countries for several decades and is considered safe.[28] However, the United States and Canada have adopted a strict gluten-free regimen and do not recommend the use of wheat starch that contains small amounts of toxic prolamins until further studies can confirm its safety.[29]

It is important to inform patients traveling to countries adhering to Codex standards of this labeling discrepancy. In addition, individuals in the United States and Canada should be aware that the term "gluten-free" on imported foods purchased through direct mail order may not have the same implication it would if the food were produced locally.

Other Hidden Sources of Gluten

Complete removal of gluten-containing grains is challenging. Hidden sources of gluten/prolamins may be found in the ingredients of many processed foods in the form of additives, stabilizers, thickeners, flavorings, extracts, emulsifiers, hydrolyzed textured vegetable proteins, and certain ground spices. Other sources of prolamins include grain alcohol, some prescription and over-the-counter medications, certain multivitamins, toothpastes, lip balms, mouthwash, and adhesive on stamps and envelopes. Ingredient reference lists are extensive and must be available to all patients and health care providers. Patients with dermatitis herpetiformis need to check labels and/or manufacturers for prolamins in lotions, creams, and cosmetics. Patients must become lifelong label readers because ingredients in food and non-food items may change over time.

The potential for cross-contamination is also of concern. Equipment

Table 2. Grains and Other Foods/Ingredients Not Appropriate on a Gluten-Free Diet

- Barley, bran, bulgur, couscous, durum flour, farina, graham flour, hydrolyzed plant protein (HPP), hydrolyzed vegetable protein (HVP), kamut, malt, malt extract, malt flavoring, malt syrup, semolina, rye, spelt (dinkel), triticale, wheat, wheat bran, wheat germ, wheat starch
- Imported foods that are labeled "gluten-free" but that may contain wheat starch*
- Processed meats and luncheon meats containing HVP or HPP, breaded meats, meats with sauces or gravies, casseroles
- Fruits and vegetables with sauces, breading, or thickeners
- Flavored milk, yogurt, processed cheese, and spreads made with gluten-containing ingredients
- Canned soups, soup mixes, bouillon, miso
- Candy, snack foods, desserts, frozen yogurt, and ice cream with gluten-containing ingredients
- Ground spices, condiments, and soy sauce with gluten-containing ingredients
- Margarine, salad dressing, and dips with gluten-containing ingredients
- Instant coffee, instant tea, instant cocoa mixes, some root beer, grain alcohol

This is only a partial listing. Patients are encouraged to read all labels and to seek comprehensive food and additive lists from celiac organizations and the American Dietetic Association.

*Food produced in the United States or Canada and labeled "gluten-free" does not contain gluten or wheat starch.

used for processing and shipping grains (bins, rail cars, trucks) and grains sold in bulk at natural food sections/stores may be contaminated via cross-use of equipment, bins, and scoops with prohibited grains.

Eating in restaurants poses additional challenges. A gluten-free item may be cooked in a pan or on a grill that is also used to cook problem foods and that may not be cleaned between food orders. Deep-fat fryers are also a source of contamination. Patients must be prepared to ask detailed questions about menu items and preparation.

Cross-contamination in the home may occur from toasters, kitchen counters, and containers of jam, peanut butter, and other spreads. Some patients have separate cooking utensils, toasters, mixers, storage containers, and other kitchen items. Health care institutions, diabetes camps, daycare providers, schools, and other care providers must be knowledgeable about gluten-free diets and the potential for cross-contamination.

Educational Materials

Referring patients to a registered dietitian who has expertise in medical nutrition therapy (MNT) for GSE is imperative. An MNT protocol has been developed and is a valuable tool for ensuring comprehensive education for patients with GSE.[30] Patients also must be strongly encouraged to join national and local support groups (Table 3) for access to the latest information, educational materials, and support.

There is a need for educational materials that combine MNT for celiac disease and MNT for diabetes. Gluten-free foods are not always equivalent in carbohydrates to similar gluten-containing foods. Other diabetes educational materials, such as instructions for treatment of hypoglycemia with specific foods, should also be available in versions for patients with GSE.

Because of the overwhelming number of foods containing gluten, intensive patient training is imperative. Dietitians must be prepared to help patients navigate the conflicting information from various organizations and health care providers.

Table 3. GSE Support Organizations in the United States and Canada

Pamphlets, books, recipes, cookbooks, specialty food companies, reference materials, and local support groups can be accessed through these organizations:

American Celiac Society
59 Crystal Ave.
West Orange, NJ 07052
973-325-8837
E-mail: amerceliacsoc@netscape.net

Celiac Disease Foundation
13251 Ventura Blvd., Suite 3
Studio City, CA 91604
818-990-2354

Gluten Intolerance Group of North America
15110 10th Ave. SW, Suite A
Seattle, WA 98166-1820
206-246-6652
www.gluten.net

Celiac Sprue Association/USA, Inc.
P.O. Box 31700
Omaha, NE 68131-0700
402-558-0600
www.csaceliacs.org

Canadian Celiac Association
190 Britannia Road East, Unit 11
Misissauga, ON L4Z 1W6
Canada
905-507-6208 or 800-363-7296
www.celiac.ca

American Dietetic Association
216 West Jackson Blvd., Suite 800
Chicago, IL 60606-6995
312-899-0040 or 800-366-1655
www.eatright.org

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