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The million-dollar question: is ''gluten-free'' food safe for patients with celiac disease?[1,2]

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Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines present in wheat, barley, and rye in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy (1, 2). In the affected intestine of patients, but not in healthy controls, proinflammatory T cells are present that are specific for gluten-derived fragments bound to the disease-associated HLA-DQ2 and HLA-DQ8 molecules (3, 4). A strict and lifelong gluten-free diet is the only, yet very effective, cure because it eliminates the trigger for the T cells. Gluten, however, is widely used in the food industry because it possesses highly desirable properties. It is a cheap protein source, is available in large quantities, and, perhaps most important, is an essential component of high-quality dough because it provides viscosity, elasticity, and the capacity to retain gas released during fermentation, which is required for the production of high-quality bread, cookies, and pizza, just to name a few of our favorites. Because of this widespread use, many food products that are not naturally associated with wheat may contain gluten, sometimes on purpose, often just by accident. The gluten-free diet is thus a challenge, primarily for patients but also for physicians and dietitians.

Fortunately, there are now many companies that provide a range of ''gluten-free'' products that are guaranteed to be ''gluten free'' [ie, contain <20 mg gluten/kg food product (20 ppm)]. ''Gluten free'' is set in quotation marks because 20 mg gluten/kg food product indicates that some gluten may still be present. So, the million-dollar question is whether this is enough to cause concern, and can such an amount still be detrimental for patients. This is an issue that keeps returning because full mucosal healing does not always occur, especially in adult patients, even when they are on a strict gluten-free diet. There can be several reasons for this, but some sort of gluten exposure is the most logical assumption because this exposure would continue to stimulate the gluten-specific T cells in the small intestine and maintain some degree of inflammation.

So where does the gluten come from? In this issue of the Journal, Gibert et al (5) report on a study in which they investigated whether the amounts of gluten present in commercially available gluten-free products could be responsible for the observations. They have collected data on the consumption of gluten-free products by patients in Italy, Spain, Germany, and Norway. They also determined the amounts of gluten in the gluten-free products most commonly used by the patients included in the study. The results confirm that most of such food products are indeed ''gluten free'' according to the currently accepted international regulations. On the basis of this, they could calculate the exposure to gluten in the patient groups. Also, in a previous study, a safe gluten threshold was determined, and the authors combined these data to perform a probabilistic risk assessment to calculate the risk of an adverse event based on the gluten present in commercially available gluten-free foods. Various scenarios were tested, and the bottom line is that the risk is minimal: 0.18% of the patient population in Europe will be affected due to the consumption of gluten-free products. This means that 18 of 10,000 patients are at risk. Of course, this is 18 too many, but the more important conclusion is that exposure to gluten through consumption of commercially available gluten-free foods cannot explain the high number of patients in whom full mucosal healing does not occur. So the message of the article is that the gluten exposure must come from elsewhere, and the authors suggest that voluntary transgressions and foods consumed outside the household may be the cause. In addition, naturally gluten-free foods that are contaminated with gluten may pose a risk.

Now, is this the final verdict? Well, not quite. There are still a few catches. First, all of the food products were tested with the R5 sandwich ELISA method. This method fails to detect relatively small gluten fragments and is specific for gliadins and does not detect glutenins, a second class of gluten proteins that can stimulate T cells, and may thus underestimate the actual gluten content of foods (4, 6). Better methods to determine the actual gluten content of gluten-free foods are thus still needed. Second, it is feasible that a combination of small amounts of gluten in gluten-free foods together with similar amounts of gluten in contaminated foods could lead to unacceptable exposure and

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First published online December 5, 2012; doi: 10.3945/ajcn.112.053777.

cause problems. Third, formal proof that patients indeed ingest hidden gluten in quantities sufficient to sustain mucosal inflammation is still lacking. Having said this, the study indicates that it is unlikely that the consumption of commercial gluten-free foods by itself will cause problems in the large majority of patients. The consequence is that patients, physicians, and dietitians need to better watch the diet and be more suspicious of transgressions and naturally gluten-free foods. Unfortunately, it does not get easier.

The authors had no conflicts of interest.

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