



Safe gluten threshold for patients with celiac disease: some patients are more tolerant than others

Markku Mäki
Katri Kaukinen

Dear Sir:

The long-expected first randomized controlled study of a micro-gluten challenge in patients with celiac disease has been published by Catassi et al (1). The authors stated that 50 mg gluten/d is harmful in celiac disease patients, whereas 10 mg/d is not. The results are based on a small but significant change in the small-intestinal mucosal villous height crypt depth ratio, even though the biopsy specimens did not show mucosal cell infiltrativity or accumulation of inflammatory cells—the known first effects of the disease on gluten ingestion. The question of what happens at doses between 10 and 50 mg/d (eg, a dose of 25 mg/d) remains.

A diet entirely free of gluten contamination would of course be ideal, but today it seems to be unrealistic; even naturally gluten-free products may contain significant amounts of gluten (2). Furthermore, too strict limits might lead to the poor availability of gluten-free products, which again would hamper overall dietary compliance. The study by Catassi et al also implies that minor gluten contamination was not harmful to most of the patients.

In Finland, the current Codex standard of 200 ppm (mg/kg) seems to not be too high; at this dose, mucosal recovery is complete and the quality of life of celiac disease patients is not different from that of the general population (3). In fact, the mean ratio of villous height to crypt depth was higher than in the study by Catassi et al, ≈ 3.2 and 2.5, respectively (4). Because most of our gluten-free products contained < 200 ppm, we concluded that 100 ppm would be a safe limit (2). The daily ingestion of gluten might also then remain well below 50 mg, at least in Finland.

Clearly, more studies are needed to settle on a safe limit of gluten contamination in gluten-free products. In the meantime, what are the clinical implications of the current studies? It appears that even occasional dietary lapses may slow down or prevent mucosal recovery (3, 4). Whether the safe limit of gluten contamination should be 0, 20, 50, or 100 ppm remains to be seen. As the study by Catassi et al (1) showed, celiac disease patients respond individually to small amounts of gluten. The individual variability denotes that the treatment should be individual too. Here, we emphasize the role of a control biopsy sample taken from adult celiac disease patients consuming a gluten-free diet. Although a biopsy is not usually required to establish a diagnosis, it is important to confirm mucosal integrity. A clear improvement in mucosal integrity after 1 y of a diet indicates that the diet is gluten-free enough to render mucosal recovery. In conclusion, the results of this interesting pilot study need confirmation before firm conclusions can be drawn about the safe limit of gluten ingestion.

The authors had no conflicts of interest to declare.

Pekka Collin

Departments of Gastroenterology and Alimentary Tract
Surgery and Pediatrics
Tampere University Hospital
PO Box 2000
FIN-33521 Tampere
Finland
E-mail: pekka.collin@uta.fi

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Reply to P Collin et al

Dear Sir:

We sincerely appreciate the comments from Collin et al and agree with most of the issues raised. Indeed, ours was the first randomized controlled double-blind study that was aimed at settling a long discussion among experts in the field on a safe threshold of traces of gluten allowable for celiac disease patients (1). Given the complexity of the study design, we had to limit our microchallenge doses to 10 and 50 mg gluten/d. Therefore, we surely agree that information regarding intermediate amounts of gluten are lacking. Nevertheless, the fact that 10 mg gluten/d appeared safe for most of the subjects studied, whereas 50 mg/d induced histologic changes after 3 mo of exposure, allowed us to conclude that 20 ppm would be the safest and most conservative threshold to recommend for gluten-free products. Given the regional differences in daily wheat substitute intakes, this threshold would be applicable worldwide rather than being customized to local lifestyle realities. The fact that the circulation of gluten-free products is now beyond national boundaries requires guidelines as widely applicable as possible. We agree that too strict limits, as advocated by some celiac support leaders (2), may lead to the limited availability of gluten-free products and an increase in production

costs. However, it is our understanding that the current costs, availability, and palatability of wheat substitutes in countries where 20 ppm is the accepted threshold are not different from those of products sold in northern Europe, where 200 ppm is the recommended daily gluten intake. Therefore, we see no advantage to embracing gluten limits that may harm those populations that consume higher amounts of wheat substitutes than the Finnish population (3). The fact that the Food and Drug Administration recently defined gluten-free products as those products that contain <20 ppm gluten (4) is testimony to the validity and feasibility of this threshold. This has been a noteworthy accomplishment, as testified by national newspaper editorials, including the *Wall Street Journal* (2). To conclude, although we agree that the findings of our pilot study should be confirmed by clinical trials in a larger number of subjects, the findings of our study will contribute to the improvement in the quality of life of celiac disease patients and their families.

AF has economic interests in Alba Therapeutics, a company that conducts research on the treatment of autoimmune diseases, including type 1 diabetes and celiac disease. CC serves as a consultant for Biaglut and Schär, companies that produce gluten-free products.

Carlo Catassi
Alessio Fasano

Center for Celiac Research
20 Penn Street
University of Maryland School of Medicine
Baltimore, MD 21201
E-mail: afasano@mbrc.umaryland.edu

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Evidence-based medicine and vitamin E supplementation

Dear Sir:

In a recent editorial in the *Journal*, Traber (1) recommended vitamin E supplementation for most adults in the United States. The logic behind her recommendation was as follows. First, Wright et al (2) reported in the same issue of the *Journal* that the lowest overall risk for mortality in the 19-y follow-up of the Alpha-Tocopherol Beta-Carotene (ATBC) Study occurred at serum vitamin E concentrations of 13–14 mg/L, and Traber labels that as an optimal concentration for reducing the risk of chronic disease. Second, 75% of men in the United States have serum vitamin E concentrations of <14.6 mg/L, which suggests widespread vitamin E deficiency in her

opinion. Third, “given the dietary habits of most Americans,” “optimal” concentrations of serum vitamin E are achievable only with vitamin E supplements (1).

We believe that Traber’s recommendation for vitamin E supplementation in the general population is unjustified. Inferring cause and effect and making such broad public health recommendations for supplements on the basis of observational data violate the established principles of evidence-based medicine. In fact, her recommendations are not aligned with those based on systematic reviews of large clinical trials of vitamin E supplementation, which do not recommend vitamin E supplement use (3) and discourage the use of high-dose vitamin E supplements (4).

The risks of recommending dietary supplements on the basis of observational studies are well documented. The classic example is the divergence between the finding of an inverse association between serum concentrations of β -carotene and lung cancer risk and the finding of increased risk of lung cancer in subjects assigned β -carotene supplements in controlled clinical trials (as reviewed in reference 5). The lesson of the β -carotene example is that the unreliability of drawing strong cause-and-effect conclusions from correlation data has evolved into an important teaching example for students of epidemiology.

Recommendations for vitamin E supplementation are not supported by findings from the trial period of the ATBC Study. In subjects in the lowest quintile of plasma α -tocopherol concentration, the similar mortality in the groups with supplement intakes of 50 and 0 mg α -tocopherol ($n = 1628$ and 1610 , respectively; see Table 3 in reference 2) refutes the notions that a low α -tocopherol intake—ie, 9.4 mg/d—is the specific cause of high mortality and that correction of this “deficiency” with 50 mg α -tocopherol/d would affect mortality in this high-risk quintile.

Other clinical outcomes reported from the ATBC Study show that supplementation with 50 mg vitamin E/d has divergent relations with the incidence of pneumonia and the common cold. Although vitamin E showed no overall benefit against pneumonia, the age at smoking initiation significantly modified the effect of vitamin E, so that it was harmful or beneficial, depending on this characteristic in each participant (6). The effect of vitamin E on common cold incidence was significantly modified by smoking level at baseline, age, and residential neighborhood (7). It is worth noting that, in both of these cases, smoking-related variables modified the effect of vitamin E. Although it is not reasonable to assume that the factors that modify the effect of vitamin E on respiratory infections identically modify the effect of vitamin E on cancer, coronary heart disease, or total mortality, the possibility that the effect on these latter outcomes is also modified by various factors should not be ignored. Because of this heterogeneity in the effects of vitamin E, it is possible that supplementation of a wide population may cause harm to some restricted population groups, as indicated by a recent meta-analysis (4).

These results highlight the misconception that supplementing to correct “deficiencies” of a single micronutrient is an inaccurate interpretation of the relation between nutritional markers and the risk of chronic disease in epidemiologic studies. Most blood concentrations of micronutrients, including antioxidants, are collinear. High concentrations of antioxidants reflect an antiatherogenic diet (lower in fat and saturated fat and higher in fruit, vegetables, nuts, whole grains, and low-fat dairy), which also has beneficial effects on traditional cardiovascular disease risk factors, including blood pressure, lipid concentrations, and glucose metabolism. Supplementing with vitamin E has no effect on traditional cardiovascular disease risk factors and does not lower the risk of chronic disease by other proposed mechanisms, such as by reducing oxidative stress.

