



# Allergologia et immunopathologia

www.elsevier.es/ai



## EDITORIAL

### Vitamin C as a supplementary therapy for celiac disease?

Celiac disease is one of the most common food-related enteropathies in Western countries, affecting up to 1–2% of the European population.<sup>1–3</sup> The disease occurs in a subgroup of genetically predisposed individuals who are positive for either human leukocyte antigen DQ2 or DQ8. The disease is triggered by consumption of dietary wheat-, rye- and barley-derived gluten and it often manifests with intestinal symptoms such as diarrhoea and malabsorption. The intestinal symptoms correlate with findings of small-bowel mucosal damage characterised by villous atrophy with crypt hyperplasia. Celiac disease is also hallmarked by the presence of antibodies against gluten-derived gliadin peptides as well as autoantibodies against transglutaminase 2.<sup>4</sup>

The small-bowel mucosal injury in celiac disease develops gradually from initial infiltration of intraepithelial lymphocytes to shortening of the villus structure together with enlargement of crypts, finally into overt villous atrophy and crypt hyperplasia in response to activation of the small-intestinal innate and adaptive immune responses. Gluten-derived gliadin contains high amounts of repetitive glutamine- and proline-rich sequences, this rendering them highly resistant to proteolytic degradation by human gastric, pancreatic and brush-border enzymes, even in healthy individuals.<sup>5,6</sup> Thus even fairly long peptides persist, some of which have been identified as toxic, inducing early effects on the small-bowel mucosal epithelium.<sup>7,8</sup> Of the innate immune components these peptides induce, interleukin (IL)-15 has been shown to play a central role in the pathogenesis of celiac disease, as it contributes to intestinal epithelial cell destruction.<sup>9</sup> On the other hand, another subset of the gliadin peptides are immunogenic and responsible for activation of T cell-mediated adaptive immunity in the mucosal *lamina propria* coupled with release of proinflammatory cytokines such as interferon (IFN)- $\gamma$ , IL-6 and tumour necrosis factor (TNF)- $\alpha$ .<sup>10,11</sup>

Currently, the above-described pathogenic process leading to small-bowel mucosal deterioration can only be prevented by complete removal of all gluten-containing food products from the diet. Although effective and harmless, such a life-long gluten-free diet is nevertheless restrictive and burdensome. Given the lifelong necessity of dieting, occasional dietary transgressions are common even in patients with good compliance, or occasionally trace

amounts of gluten contamination in gluten-free products cannot be avoided.<sup>12</sup> For all the above reasons a diet completely devoid of gluten is probably impossible to maintain and a search for alternative treatment options or dietary supplements is thus called for.

In the current issue of *Allergologia et Immunopathologia*, Bernardo and coworkers<sup>13</sup> present an interesting study addressing the question as to whether vitamin C (ascorbate) could be beneficial as a dietary supplement for celiac patients. The authors used the celiac patient small-bowel mucosal biopsy organ culture system to investigate whether vitamin C is able to prevent the gliadin-induced inflammatory response by measuring the amounts of secreted nitrites, IFN- $\gamma$ , TNF- $\alpha$ , IFN- $\alpha$ , IL-17, IL-13 and IL-6, as well as the total quantity of IL-15 in the cultured biopsies. They found that co-administration of vitamin C prevented the augmented secretion of nitrites, IFN- $\gamma$ , TNF- $\alpha$ , IFN- $\alpha$  and IL-6 and increased the expression of IL-15 triggered by gliadin, suggesting that vitamin C supplementation might be beneficial for celiac patients.

Vitamin C is a micronutrient whose health-promoting effects can be attributed to its biological functions as a cofactor for a number of important enzymes and as a water-soluble antioxidant. As we humans are not able to synthesize vitamin C ourselves, we depend on our diet as a source of vitamin C to maintain general health. Vitamin C is known to be able to modulate immune responses in several ways, for instance by stimulating leukocyte function.<sup>14</sup> Moreover, vitamin C enhances lymphocyte proliferation in response to infection<sup>15</sup> and it may also play a significant role in the regulation of the inflammatory response.<sup>16</sup> It has also been suggested to be useful for the induction of tolerance to autoantigens.<sup>17</sup> The implication of vitamin C in tolerance induction makes the findings of Bernardo et al.<sup>13</sup> extremely interesting. Although to our knowledge this is the first study addressing the efficacy of vitamin C as a diet supplement for celiac patients, there are studies demonstrating the beneficial effect of oral vitamin C supplementation in other disorders. For instance, in a randomised controlled trial vitamin C administered together with vitamin E has been reported to reduce oxidative stress in patients suffering from Crohn's disease, another enteropathy distinct from celiac disease.<sup>18</sup> Although during the 4-week vitamin

supplementation disease activity remained stable, one cannot draw conclusions as to any long-term clinical benefits in Crohn's disease.

Although the necessity of vitamin C for general health is well known, the study by Bernardo et al.<sup>13</sup> is to our knowledge the first to address the efficacy of vitamin C as a diet supplement for celiac patients. The results of this proof-of-principle study suggest that vitamin C might reduce mucosal inflammation in celiac disease and therefore encourage further studies on the subject.

## References

- Mäki M, Mustalahti K, Kokkonen J, Kulmala P, Haapalahti M, Karttunen T, et al. Prevalence of celiac disease among children in Finland. *N Engl J Med*. 2003;348:2517–24.
- Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, et al. Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther*. 2007;26:1217–25.
- Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med*. 2010;42:587–95.
- Lindfors K, Mäki M, Kaukinen K. Transglutaminase 2-targeted autoantibodies in celiac disease: pathogenetic players in addition to diagnostic tools? *Autoimmun Rev*. 2010;9:744–9.
- Hausch F, Shan L, Santiago NA, Gray GM, Khosla C. Intestinal digestive resistance of immunodominant gliadin peptides. *Am J Physiol Gastrointest Liver Physiol*. 2002;283:G996–1003.
- Shan L, Molberg Ø, Parrot I, Hausch F, Filiz F, Gray GM, et al. Structural basis for gluten intolerance in celiac sprue. *Science*. 2002;297:2275–9.
- Maiuri L, Ciacci C, Auricchio S, Brown V, Quarantino S, Londei M. Interleukin 15 mediates epithelial changes in celiac disease. *Gastroenterology*. 2000;119:996–1006.
- Maiuri L, Ciacci C, Ricciardelli I, Vacca L, Raia V, Auricchio S, et al. Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. *Lancet*. 2003;362:30–7.
- Hüe S, Mention JJ, Monteiro RC, Zhang S, Cellier C, Schmitz J, et al. A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. *Immunity*. 2004;21:367–77.
- Anderson RP, Degano P, Godkin AJ, Jewell DP, Hill AVS. In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope. *Nat Med*. 2000;6:337–42.
- Nilsen EM, Lundin KE, Krajci P, Scott H, Sollid LM, Brandtzaeg P. Gluten specific, HLA-DQ restricted T cells from coeliac mucosa produce cytokines with Th1 or Th0 profile dominated by interferon gamma. *Gut*. 1995;37:766–76.
- Collin P, Thorell L, Kaukinen K, Mäki M. The safe threshold for gluten contamination in gluten-free products. Can trace amounts be accepted in the treatment of coeliac disease? *Aliment Pharmacol Ther*. 2004;19:1277–83.
- Bernardo D, Martínez-Abad B, Vallejo-Diez S, Montalvillo E, Benito V, et al. Ascorbate-dependent decrease of the mucosal immune response to gliadin in celiac disease patients. *Allergol Immunopathol*. 2012;40:3–8.
- Maggini S, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune response. *Br J Nutr*. 2007;98:S29–35.
- Yang KC, Yang CS, Siu WY, Tsai YS, Liao SW, Kuo JS. Supplementation with vitamins C and E enhances cytokine production by peripheral blood mononuclear cells in healthy adults. *Am J Clin Nutr*. 1996;64:960–5.
- Härtel C, Strunk T, Bucsky P, Schultz C. Effects of vitamin C on intracytoplasmic cytokine production in human whole blood monocytes and lymphocytes. *Cytokine*. 2004;27:101–6.
- Tan PH, Sagoo P, Chan C, Yates JB, Campbell J, Beutelspacher SC, et al. Inhibition of NF-kappa B and oxidative pathways in human dendritic cells by antioxidative vitamins generates regulatory T cells. *J Immunol*. 2005;174:7633–44.
- Aghdassi E, Wendland BE, Steinhart AH, Wolman SL, Jeejeebhoy K, Allard JP. Antioxidant vitamin supplementation in Crohn's disease decreases oxidative stress a randomized controlled trial. *Am J Gastroenterol*. 2003;98:348–53.

K. Lindfors\*

*Pediatric Research Center, University of Tampere and Tampere University Hospital, Tampere, Finland*

K. Kaukinen

*School of Medicine, University of Tampere and Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland*

\*Corresponding author.

*E-mail address: katri.lindfors@uta.fi (K. Lindfors).*