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5

Gluten-free diet—what is toxic?

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The cornerstone of treatment of coeliac disease is a gluten-free diet devoid of proteins from wheat, rye, barley and related cereals. Oats are tolerated by most patients with coeliac disease but are not totally innocent. There are considerable differences between individual patients with respect to clinical and mucosal responses to gluten challenge. In vitro and in vivo testing has identified synthetic peptides that are toxic to the coeliac small intestinal mucosa. This toxicity overlaps at least partly to the known epitopes that are recognised by small intestinal T-cells. However, the clinical significance of several of these epitopes is unclear, as is the maximum level of gluten intake that can be recommended to be safe for patients with coeliac disease. Future efforts may lead to better understanding of the disease processes as well as possible new therapeutic options.

Key words: gluten; coeliac disease; toxic effects; wheat; oats.

WHAT IS MEANT BY TOXICITY?

Coeliac disease (CD) is defined as an inflammatory response in the small intestinal mucosa exacerbated by gluten. The demonstration of villous atrophy, blunting or at least an epithelial infiltrate of T-cells is the generally held view that is required to

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diagnose CD. Any discussion on toxicity should involve aspects of small intestinal inflammatory responses. However, not everyone agrees with this view, for example, a number of extraintestinal manifestations may be considered to constitute signs of toxicity, for example, the rash of dermatitis herpetiformis. This gluten dependent skin disorder is a sensitive marker of gluten intake but we will here restrict our discussion to the effects on the small intestinal mucosa.

Another very important aspect relating to the gluten toxicity to patients with CD is the well-known fact that compliance is a major problem. It is clear that lack of compliance is the single most important threat to disease remission in this group of patients, and compliance rates of 50–80% are frequent. Non-compliant patients usually continue their normal gluten-containing diet due to lack of motivation, lack of information or a combination of the two. Continuous follow-up, especially by experienced dieticians, may be a good way to improve compliance rates.[1] The importance of following a gluten-free diet by patients with CD is protection against the increased risk of developing gastrointestinal malignancy,[2] other autoimmune disorders, including diabetes mellitus[3] and osteoporosis.[4]

THE EXPERIMENTAL BACKGROUND FOR TOXICITY CONSIDERATIONS

The pathogenesis of CD is described in detail elsewhere in this book. Considerable progress has been made during the last decade. It is clear that patients with CD but not healthy individuals express a small intestinal T-cell response to gluten.[5] This T-cell response is restricted by either HLA-DQ2 or -DQ8, the two disease associated HLA variants. It is also clear that this T-cell response is directed against gluten peptide epitopes that are resistant to enzymatic digestion in the gastrointestinal tract and typically have a high content of proline and glutamine residues.[6,7,8] The T-cell response is focused on certain regions of the gluten proteins and immunodominant epitopes have been defined.[9,10] A typical feature of several, if not most, of these epitopes is that the glutamine residues are converted to glutamic acid in a process of deamidation by the small intestinal enzyme tissue transglutaminase.[11] As a result, the peptides bind better to HLA-DQ2 and -DQ8 and are much more efficiently presented. Both adaptive, T-cell-mediated, immune mechanims and the innate immune system are involved and the relative contributions of the two systems to the total immunopathogenesis are the subject of much interest.[12,13,14]

It is also clear from a number of studies that biochemical separation of gliadin and gluten proteins is difficult and often incomplete. Thus, several previous studies on toxicity must be interpreted with caution.

CLASSIFICATION OF CEREAL PROTEINS

Wheat grains have three major constituents that are separated by milling: the outer husk or bran, the germ and the endosperm or white flour, which constitutes 70–72% of the whole grain by weight and which contains the toxic components. The storage proteins of cereals fall into two major groups; the ethanol-soluble fraction termed prolamins and the polymeric glutenins.[15] Prolamins from different cereals are termed