

# Can dietary enzyme supplements aid people with coeliac disease?

Many enzyme supplements, sold through pharmacies, health food shops and via the internet, purport to aid the digestion of gluten. Some of these products even suggest they may allow coeliac patients to digest gluten safely, despite having no scientific evidence or basis to support these claims. However, this does not mean that the concept of dietary enzyme therapy for coeliac disease (CD) is scientifically invalid.

Indeed, clinical study results recently published in the *International Journal of Celiac Disease*<sup>1</sup> show evidence for the use of a new dietary enzyme supplement (GluteGuard®) to provide some therapeutic benefit for people with CD on a gluten free diet who may accidentally ingest small amounts of gluten.

## An historical perspective

Coeliac disease has a long history<sup>2</sup>, but it was not until the early 1950s that CD was formally discovered and the link between CD and grass cereals, particularly the gluten proteins commonly found in wheat, emerged<sup>3,4</sup>. At this time, a lifelong gluten free diet became the therapeutic management tool for CD.

A wheat industry burgeoning due to rapidly expanding availability of new, high-yield varieties<sup>5</sup>, improved methods for diagnosing CD, and a rise in CD prevalence set the scene in the 1970s for Australia to become a global epicentre of CD research, as it remains today. It was here that the chemistry of gluten and the mechanisms of CD began to emerge. In 1973, led by the late Dr Rudge Townley, the team from the Royal Children's Hospital, Melbourne, first described the most toxic component of gluten to the CD patient's mucosa, Fraction 9 of A-gliadin<sup>6,7</sup>, and confirmed its toxicity<sup>8,9</sup>.

As scientific technology advanced through the 1980s, a new understanding of the small parts (peptides) of gluten that are reactive in people with CD became possible. Our research group at the RMIT University identified two types of reactive peptides within Fraction 9 that initiated different types of action in those with CD: cytotoxic (directly causing gut damage) and immunogenic (allowing the body's immune system to react to gluten, thereby damaging the gut)<sup>11-14</sup>. Further research determined common amino acid structures within these toxic peptides, fundamentally describing what makes them so dangerous for those with CD<sup>10-15</sup>. Understanding the composition of these small, CD-inducing peptides provided what is essentially a roadmap for developing potential therapies for CD, including vaccine and enzyme therapy.

## The enzyme deficiency hypothesis of CD

Generally, our research has been focussed on two main theories as to the cause of CD:

1. Enzyme deficiency – insufficient enzymes in the gut to break down the cytotoxic peptides of gluten into harmless smaller pieces<sup>15,16</sup>, leading to the enzyme therapy research, and
2. Abnormal immune responses – some people may develop an immune response to certain immunogenic peptides of gluten and this localised immune response in the gut causes duodenal damage<sup>17,18</sup>, leading to the CD vaccine research.

These theories are not mutually exclusive, as described by Cornell and Stelmasiak in the unified hypothesis of CD<sup>19</sup>. Clearly, to develop abnormal immune responses to gluten, the immunogenic peptides of gluten, to which the immune system reacts, would have to be present in the gut. However, if enzymes in the gut had digested these immunogenic peptides into small fragments, development of such an

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immune response, and the associated symptoms, would be averted.

For the enzyme deficiency theory, it is important that specific enzymes are present to break down both cytotoxic and immunogenic peptides into harmless smaller fragments so they can be used by the body.

Enzyme deficiency in CD was formally demonstrated in the early 1970s when a mucosal enzyme deficiency was found in the duodenum of children with CD<sup>4</sup>, and later confirmed using synthetic peptides of A-gliadin<sup>20</sup>. The deficient enzyme was thought to be one that would digest the toxic gluten peptides into harmless fragments<sup>15</sup>. Based on this initial research, we searched for an enzyme that would attack the relevant peptides and identified various possible candidates.

## From theory to therapy

The scientific work conducted to identify the toxic peptides of gluten that cause CD and demonstrate that the natural enzymes that digest these peptides were deficient in CD patients, led to the simple theory that restoring appropriate enzyme activity in the gut of CD patients should alleviate gluten-induced symptoms. An obvious method for achieving this would involve patients taking an enzyme-containing supplement when consuming foods that may contain small amounts of gluten.

There are a number of caveats with the above theory, the main ones being that the enzyme must be specifically capable of digesting the toxic peptides of gluten, and that the enzyme should be administered in such a way that it will be active where it is required, i.e. in the small intestine.





In the search for an appropriate enzyme, we evaluated many over a number of years, and identified the best candidate for CD therapy<sup>21</sup>.

With a targeted enzyme identified, the next step was to establish a mode of delivering the enzyme through the hostile, acidic stomach environment to the small intestine. With the support of Glutagen, the technology was patented to produce GluteGuard®, an enzyme supplement specifically coated to be able to deliver the gliadin-digesting enzyme action to the small intestine.

#### Clinical studies

The enzyme therapy study published in the *International Journal of Celiac Disease*<sup>1</sup>, was led by Australian gastroenterologist and scientist, Professor Finlay Macrae, and was a relatively small randomised study of 20 CD patients in clinical remission on a gluten free diet. All patients ingested 1 gram of gluten (equivalent to approximately 2 biscuits) each day for 42 days, with 14 of them taking GluteGuard at the same time and 6 taking a placebo tablet. Patients recorded their CD symptoms and wellbeing each day, and intestinal tissue was examined before and after the study.

Thirteen of 14 CD patients taking GluteGuard (93%) demonstrated no detrimental changes in clinical symptoms, biopsy results or wellbeing throughout 42 days of gluten challenge. Conversely, 4 of 6 (67%) taking placebo developed severe CD symptoms and withdrew from further gluten challenge after

14 days. Comparing the therapy and placebo groups across the first 14 days of gluten challenge, those taking GluteGuard reported fewer CD symptoms and averaged higher wellbeing scores.

The results indicated that GluteGuard supplementation offered some protection from CD-related symptoms and enabled sustained wellbeing despite daily gluten challenge. Tissue damage was also less in the treatment group.

Another study investigating the effectiveness of GluteGuard was conducted in patients with dermatitis herpetiformis (DH)<sup>22</sup>, a skin condition associated with CD. Like CD, a strict lifelong gluten free diet is essential for managing DH and preventing long-term intestinal inflammation and complications.

In this randomised study of DH patients in clinical remission, all 20 patients consumed approximately 6 grams of gluten (e.g. 9 Vita-wheat biscuits) daily for 7 days, with 10 concurrently taking GluteGuard tablets and 10 placebo. GluteGuard seemed to offer protection from increasing area of skin lesions, a substantial reduction in the appearance of skin lesions, and a large reduction in emergence of troublesome itch. Of 7 DH patients that withdrew from the study due to gluten challenge-related symptoms, 6 were taking placebo.

Overall, the results from these two published studies indicate that for CD and DH patients on a gluten free diet, GluteGuard supplementation may provide benefit when inadvertent gluten ingestion occurs by both alleviating gluten-induced symptoms and minimising tissue damage.

#### Current opinion on enzyme supplementation

The above information and clinical studies demonstrate that an enzyme supplement developed on the basis of clinical trials, may provide benefits to CD patients, although at the present time there is insufficient evidence to define their therapeutic role and further research is required.

Many of the enzyme supplements currently available claiming to aid gluten digestion are not based on science applicable to CD patients and are causing confusion for those medically required to follow a gluten free diet.

To effectively digest gluten, a supplement needs to contain the right enzyme and employ a mechanism to deliver the right amount of that enzyme to the right place (small intestine) at the right time (e.g. same time as gluten exposure).

It is also important to note that the scientific literature in no way supports enzyme supplements replacing a gluten free diet; thus, GluteGuard is not intended to replace a gluten free diet. Instead, it is intended as an adjunct to support those on a gluten free diet who may inadvertently ingest gluten from time to time, e.g. to minimise the effects of possible cross contamination of a gluten free meal when dining out.

#### Unifying approaches for CD therapy

As the research articles in recent issues of this magazine highlight, current concepts in CD research have gone past the theoretical to become the basis of several promising treatments. Dr Tye-Din has described several potential CD therapies in the later stages of clinical development by various groups around the world. With regard to those therapies, enzyme therapies, such as GluteGuard, may play a complementary role.

Just where each of these therapies will fit into the history of the science of CD is yet to be written. In the meantime, it is important to pass the knowledge on to the next generation of scientists and clinicians in the area of CD, who can enhance our current knowledge in the future and translate the science into meaningful strategies and effective therapies. Continued investment in CD research of all types, whether the focus is on the genetics, immunology or a complementary medicine, vaccine or drug treatment, is critical to ensure we have as many avenues as possible leading to improved health and wellbeing for those living with CD and DH.

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Figure 1 A Timeline of enzyme therapy development for coeliac disease

1970's	Fractionation of gluten into components with differing toxicities In vitro assays of toxicity for fractions
1980's	Development of proteomics technology
1990's	Chemical analysis and differentiation of fractions of gliadin digests Confirmation of chemical composition and structure by the use of synthetic peptides Confirmation of toxicity by in vivo methods
2000's	Further studies on the mechanism of toxicity Studies of immunological mechanisms of CD pathogenesis
2010's	Clinical trials of therapeutic products for CD Launch of GluteGuard enzyme therapy
2020's	Development of new assays and therapies for CD and gluten-related sensitivities

Overall, the results from these two published studies indicate that for CD and DH patients on a gluten free diet, GluteGuard supplementation may provide benefit when inadvertent gluten ingestion occurs by both alleviating gluten-induced symptoms and minimising tissue damage.