

Mechanisms of Pathogenesis in Celiac Disease and Non-Celiac Gluten Sensitivity

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Abstract Celiac disease (CD) has in recent years become understood as a disease in which the importance of complete digestion of gliadin is essential for safe management of patients. Lately, the use of enzyme therapy for treatment of CD has gained wider acceptance as an adjunct to the gluten-free diet. A closer examination of Non-Celiac Gluten Sensitivity (NCGS) is warranted to determine if enzyme supplementation could be beneficial for individuals with this condition. Incomplete digestion of gluten produces toxic and/or immunologically active peptides which are implicated in both CD and in NCGS. These peptides are from a region close to the N-terminus of A-gliadin and contain serine or tyrosine residues. NCGS is caused by certain serine-containing peptides in A-gliadin and particularly those near the N-terminus. Peptide 11-19 is the most active of these peptides *in vitro* but may not be involved in cell-mediated immune reactions in CD. These reactions are related to tyrosine-containing peptides. Further along the chain is peptide 75-86, the most tissue damaging of the A-gliadin peptides in CD patients. This peptide is a tyrosine-containing peptide where damage caused to mucosal tissue is greater in CD than in NCGS. Hence, although CD and NCGS are both caused by gluten, the pathogenesis of the diseases has different mechanisms. However, both serine-containing and tyrosine-containing peptides are attacked by caricain, the protective enzyme in GluteGuard, thus rendering both types of toxic peptides harmless to the intestinal mucosa of susceptible individuals. Just as has been seen with Dermatitis Herpetiformis (DH), gluten is becoming a focus for several conditions when the neurological effects of gluten need to be considered.

Keywords: celiac disease, enzyme therapy, non-celiac gluten sensitivity, caricain, dermatitis herpetiformis

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1. Introduction

Celiac disease (CD) is one in which the lining of the small intestine is damaged by ingestion of cereals such as wheat, barley, triticale and certain varieties of oats containing gluten-like proteins [1]. Criteria for damage to the finger-like villi need to be met [2] and confirmed by further histology after a period of months on a diet free from gluten [3]. Credit for discovery of the disease goes back to 1950 when Professor Dicke [4] discovered that children in the post-war Netherlands were in relatively better health on potatoes rather than hard-to-get cereals such as wheat.

Symptoms of CD range from gastrointestinal complaints such as abdominal pains, bloating and diarrhea, to severe malabsorption of nutrients caused by reduction of the absorptive surface area of the small bowel [5]. It affects about 1% of Caucasian people globally.

Another form of this disease is Non-Celiac Gluten Sensitivity (NCGS) where tissue damage is not as severe and yet another called Dermatitis Herpetiformis (DH) where

blisters on the skin are caused by consumption of gluten.

Mucosal digestion experiments indicate that serine-containing peptides like 11-19 of A-gliadin, while active in the fetal chick assay, are incompletely digested by remission celiac mucosa [6,7]. The smaller peptides such as 11-18 and 77-84 are still toxic which suggests that the aetiology of CD has to do with defective mucosal digestion. Moreover, it seems that the pathogenesis of CD could be due to the action of the undigested peptides on the mucosa. In the case of peptide 11-19 it is the octapeptide sequence 11QNPSQQPQ19 and for peptide 75-86 it is the octapeptide sequence 77QQPYPQPQ84 corresponding to undigested residues 77-84 of A-gliadin.

The activity of peptide 75-86 on peripheral blood lymphocytes was detected by its ability to increase the production of gamma-interferon which could initiate tissue damage. This peptide has the amino acid sequence 75RPQQPYPQPQ86. This is a typical example of a cell-mediated immune reaction and seems to indicate that there are different mechanisms causing damage to the mucosa. One is direct toxicity and the other involves immune system reactions.

1.1. Celiac Disease (CD) – Mechanisms Initiated from Mucosal Digestion

Early work by Cornell and Townley [8] using a peptic-tryptic-pancreatic digest of wheat gliadin showed that it contained a fraction (Fraction 9) that was poorly digested by mucosal homogenates from children with CD in remission. All the other fractions were well digested by remission mucosa. All fractions including Fraction 9 were well digested by mucosal homogenates from normal children. The fact that serum antibodies against Fraction 9 were also detected in children with CD was further evidence that there could be an enzyme deficiency in CD that was allowing levels of toxic gliadin peptides to build up in the small intestine.

Further work focused on obtaining the amino acid sequence of those peptides showed that the main active fraction had the amino acid sequence corresponding to positions 75-86 of A-gliadin. The residual peptides left after digestion of this peptide with remission celiac mucosa have the sequence corresponding to 77-84 of A-gliadin [9].

These results support the work of Professor Frazer (10), who showed by feeding tests on people with CD that a gluten digest was well tolerated after treatment with hog intestinal mucosa, suggesting that enzymes in the hog mucosa degraded the peptides and caused the loss of their toxicity. This was put forward as the enzymopathic hypothesis of the cause of celiac disease.

The other major hypothesis of the etiology of CD involves immunological mechanisms and was put forward by Falchuk and Strober in 1974 [11].

Later, Maki and Collin [12] proposed that T-lymphocytes respond by releasing cytokines which are involved in cell damage. The T-cell mediated response occurs because specific peptides are recognised by individuals with HLA - DQ2 and HLA- DQ8 genetic markers.

1.2. Amino Acid Sequences in Non-Celiac Gluten Sensitivity (NCGS) Toxic Peptides

It was indicated that peptides involved in CD and NCGS have different molecular shapes, hence different modes of action. Peptides corresponding to those near the N-terminus represent the α -helical shape featuring serine (11-19) while those further along the chain (75-86) are of random coil type, featuring tyrosine.

Sturgess et al. [13] found that peptide 31- 49 was toxic *in vivo* to patients with CD. It has the tyrosine-containing motif PYPQ also found in the toxic A- gliadin peptide 75-86.

Both types of action are possible if there is defective digestion creating the active peptides, as mucosal digestion studies indicate. In the case of the serine-containing peptides, the activity is linked to the presence of amino acid sequences such as PSQQ and QQP. With the tyrosine group, motifs such as QQPY, PYPQ and/or QPYP are thought to be involved. All tyrosine motifs which are present in the peptide of Sturgess et al. [13] have been shown to be toxic *in vivo* to those with CD.

Serine-containing peptides in gluten are involved in the direct cytotoxic reactions with the enterocytes of people

with CD, which is even seen in some of their first-degree relatives. On the other hand, the tyrosine containing peptides are operating through both direct and cell-mediated reactions which are related to its random coil conformation. These reactions cause more extensive tissue damage than serine-based peptides. This is evidenced by the ability of peptide 75-86 of A-Gliadin to produce -interferon in cultures of blood from people with CD [14].

2. Hypotheses of Celiac Disease (CD)

Since the early work of Cornell and Townley [8], which produced evidence of an enzyme deficiency in CD, further studies produced a unified hypothesis of CD [15]. This hypothesis combines direct toxicity and immunological mechanisms related to the genetic pre-disposition to CD due to presence of HLA-DQ2 and HLA-DQ8 genes in susceptible individuals. This has been further supported by work on NCGS where we suggest that the serine containing peptides of gliadin are responsible for some of the symptoms and the mild damage seen in NCGS. Furthermore, the additional immunological reactions causing more severe damage seen in CD is now known to be due to the observed response that produces Interferon. These reactions seem to be generated by other gliadin peptides which involve tyrosine located between positions 75 and 86 of A-gliadin.

Our later work has confirmed an enzyme deficiency in CD with an inference that this is also the case with NCGS. It was followed by the development of the dietary enzyme supplement GluteGuard [15,16].

A third hypothesis for the mechanisms of CD was suggested by Bjarnason and Peters [17] who proposed that there was a defect in the permeability of the intestinal mucosa. Drago et al [18] suggested that increase in permeability is caused by gliadin stimulation of zonulin release. Yet another proposal was that auto-immune mechanisms add to the pathogenesis of CD [19].

In CD, two types of mechanisms of tissue damage operate. An outline of these mechanisms is essential for designing efficient enzyme therapy. The first mechanism involves the toxic action of peptides like 5-20 of A-gliadin [14] which have activity in the fetal chick assay of Mothes et al [20]. This contrasts with the immunogenic mechanisms which are present in CD and apply to A-gliadin peptide 75-86 [21].

The latter peptide contains two of the three motifs associated with the celiac toxic cereals – wheat, rye and barley, namely QQPYP, at positions 78-82. It is noted that this motif is also present at positions 40-44 of A-gliadin. The motif PQQPY is also present in A-gliadin fraction 75-86 at positions 76-80, again indicating that tyrosine-containing peptides are involved in CD [22].

The main active fraction from the digestion of A-gliadin was a peptide corresponding to A-gliadin 75-86 which has not only high activity in the fetal chick assay but is also able to induce the production of γ -interferon in blood from people with CD [21]. Thus, we can conclude that the toxicity of the first group of gliadin peptides, which contain the motifs PSQQ and QQP are important in direct toxicity mechanisms [23].

The toxicity of the other group of A-gliadin peptides

seems to be associated with motifs like PYPQ which we shall refer to as tyrosine containing motifs. It is also important to note that the residual peptide from mucosal digestion of Fraction 9 corresponds to the octapeptide 77-84 of A-gliadin with sequence 77QQPYPQPQ84. This octapeptide still has activity in the fetal chick assay [9].

Studies of the toxicity of A-gliadin and CD have shown that the serine containing peptides appear to be cytotoxic in animal models of CD such as the fetal chick and fetal rat assays, while the tyrosine containing group have the capacity to initiate more damaging reactions [9]. It is expected that there is a link between toxicity and cell mediated immune response in CD because the predominant toxic peptide in Fraction 9 produced γ -interferon in cultures of whole blood. Fraction 9 of the A-gliadin digest and synthetic peptides based on the A-gliadin structure gave negative results with blood from controls and the other synthetic gliadin peptides tested.

These results provide evidence of a link between toxicity and cell-mediated immune response in CD and confirm that peptide 75-86 of A-gliadin, a tyrosine-containing peptide in Fraction 9 of a peptic-tryptic-pancreatic digest of wheat gliadin identifies one of the most toxic peptides that people with CD must contend with. Fortunately, they can do this successfully as this peptide was one that was employed in the development of GluteGuard, the supplement used with a gluten free diet for management of CD, NCGS and DH.

2.1. Lysosomes and Celiac Disease (CD)

The direct action of gliadin peptides on lysosomes could be one of the mechanisms of pathogenesis. Evidence for this has come from Riecken et al [24] who pointed out the disruption caused by gluten *in vivo*. Later, Dolly and Fottrell [25] showed the same effects could be seen *in vitro* with peptide fractions of gliadin using rat liver lysosomes. Cornell and Townley [8] were able to confirm the toxicity of Fraction 9 of their peptic-tryptic-pancreatic digest of gliadin using this assay.

3. Non-Celiac Gluten Sensitivity (NCGS)

Non-celiac gluten sensitivity (NCGS) was originally described by Cooper et al [26] in the 1980s and more recently reviewed by Catassi et al [27].

Comparisons of CD with NCGS is of prime importance, especially when it was observed that damage to tissue in NCGS was caused by different peptides in gliadin than those which cause damage in CD. In NCGS, damage appears to be caused mainly by peptides containing serine. This contrasts with toxic peptides responsible for the more severe pathogenetic mechanisms associated with CD, which are caused by tyrosine-containing peptides of gliadin and involve cell-mediated immunological reactions which lead to more extensive damage to intestinal tissue [9].

NCGS can be looked upon as a milder form of CD or as a condition in which extra-intestinal symptoms related to the ingestion of gluten-containing food are observed. At the present time, it also appears that gluten has been implicated in several neuropsychiatric disorders

particularly autism and schizophrenia [27].

In this paper we shall concentrate on the close relationship of NCGS and CD that has been demonstrated because of studies of digestibility of wheat gliadin in CD, NCGS and related disorders such as dermatitis herpetiformis, a blister-causing form of CD. The reason for this is because we also want to present a relatively new product for management of these disorders called GluteGuard which is a supplement based on the principle of enzyme therapy used to detoxify small amounts of contaminating gluten in the gluten-free diet for those with CD and NCGS [16].

3.1. Laboratory Diagnosis of Non-Celiac Gluten Sensitivity (NCGS)

So far, no specific biomarker for NCGS has been found. In studies by Volta et al [28] the prevalence of Ig anti-gliadin antibodies detected in patients with NCGS was 56.4%, compared with 81.2% for those with CD. The prevalence of IGA anti-gliadin antibodies was only 7.7%.

Because of the overlap of clinical, biological, genetic and histological data, diagnosis of NCGS presents a challenge in separating it from CD and other gluten-related conditions. The need for use of an algorithm and a gluten free diet with a safeguard supplement is strongly recommended in both diagnosis and management.

In Australia, approximately 1 in 80 individuals are diagnosed with CD; however, NCGS is likely to be more prevalent than this estimate. The symptoms of NCGS have broadened significantly, including several that were previously associated with neurological conditions. Therefore, it is crucial to gain a better understanding of NCGS, the Autism Spectrum, and Schizophrenia, among others.

In NCGS, small intestinal damage must be evaluated by endoscopy or biopsy. The Marsh criteria are used to grade the damage and determine the need for a gluten-free diet. Accurate diagnosis is crucial for the patient's well-being. Significant tissue damage should be discussed with a gastroenterologist for appropriate treatment like in CD.

There is a need for the developments in the diagnosis of NCGS, particularly in the discovery of biochemical markers for this special condition. These could include specific enzyme assays, but other markers in the blood would be a better alternative, thus eliminating the need for a biopsy as a source of intestinal enzymes [28,29].

It appears as if the incidence of NCGS in the general population is higher than CD. The range of frequency reported for NCGS varies from 0.5% to 6% but there is doubt as to the validity of some studies and its prevalence in children is not known to date. The incidence of CD is better understood at the level of 1% in Caucasian populations.

The CD predisposing phenotypes HLA-DQ2 and HLA-DQ8, found in 95% of patients with CD are only found in 50% of NCGS patients. This compares with 30% for the general population [30].

Patients with NCGS reveal normal to mildly inflamed duodenal mucosa (Marsh 0-1) compared with CD patients who show partial or sub-total villous atrophy with crypt hyperplasia (Marsh 3-4).

3.2. Diagnosis of Non-Celiac Gluten Sensitivity (NCGS)

There is a need for new developments in the diagnosis of NCGS such as those based upon novel biochemical markers of the disease. These markers could include analysis of digestive enzymes, but in these cases a biopsy would be likely to be needed. In the meantime, we probably must rely on blood tests together with the use of a gluten challenge of about 3g/day for 14 days together with blood tests for tissue Transglutaminase (TTG) antibodies. Results of less than 20 U/ml indicate compliance to the gluten-free diet.

The current anti-gliadin antibodies test is not as sensitive and specific as the TTG test which is related better to the detection of auto antigen in celiac disease [31].

3.3. Fetal Chick and Fetal Rat Assays

Early studies of the toxicity of A-gliadin peptides showed that in the peptides with very high activity (11QNPSQQQPQ19) toxicity is attributed to the motifs PSQQ and QQQP [23]. This nano-peptide has very high activity in the fetal chick assay of Mothes et al [20].

The toxic peptides in A-gliadin which are of most interest in CD and NCGS are believed to be of two different types – those which contain serine, such as the 11-19 of A-gliadin and those which contain tyrosine, such as the peptide 75-86 of A-gliadin (see 5.1). The molecular shapes of these groups of peptides have been shown to be different as would be expected from their different modes of action. In animal models of CD (fetal rat and fetal chick), the serine-containing group demonstrates significant cytotoxicity. Conversely, the tyrosine-containing group exhibits the potential to trigger harmful immunological reactions in patients with CD and, possibly, NCGS. Our later computer modelling studies show serine-containing toxic peptides have an α -helical shape [32], while tyrosine-containing peptides, like peptide 75-86, are random coils with β -turns.

Studies by De Ritis et al [23] have shown that 4-mer amino acid motifs PSQQ and QQQP were present in toxic peptides from A-gliadin but absent in non-toxic peptides.

Cornell et al [14] characterised gliadin peptides that are biologically active in celiac disease, and the cause of this disease appears to be associated with impaired digestion by the mucosa of the small intestine. The T-cell response is one of the cell-mediated mechanisms considered important. Direct cytotoxic activity also occurs and is believed to be predominant when there is high activity in the fetal chick assay [20] and the fetal rat assay [23].

This review aims to elucidate the differences in the severity of damage to the small intestinal mucosa between NCGS and CD. It further investigates whether these differences can be attributed to variations in the toxic gliadin fractions involved and the mechanisms underlying their toxicity.

There is clear evidence that the peptides remaining after celiac *in vitro* digestion of Fraction 9 of gliadin contain glutamine, proline and serine and others glutamine, proline and tyrosine [7]. Further evidence from the use of different assays, has indicated that the serine-containing peptides are the main peptides responsible for direct

toxicity, not involving the cell-mediated immune system and the tyrosine containing peptides are the main peptides involving the cell-mediated immune system. This means that the serine-containing peptides close to the N-terminus of A-gliadin some of which are very active in the fetal chick assay, are those which may be the main contributors of NCGS symptoms while the tyrosine-containing peptides with their ability to influence the production of γ interferon are the main contributors to the more extensive damage to small intestinal tissue seen in CD.

The significance of key amino acid sequences in the toxicity of gliadin was suggested by De Ritis et al [23]. Their research indicated that the motifs PSQQ and QQQP were associated with toxic peptides near the N-terminus of A-gliadin (5-20) and agrees with the finding that these peptides have direct toxic action on celiac mucosa. This contrasts with the tyrosine-containing peptide 75-86 of A-gliadin which appears to be immunogenic in its action and may be connected to its ability to produce γ -interferon [21].

Why is there a difference between CD and NCGS in the severity of damage to the small intestinal mucosa between these other forms of CD? Can it be explained by differences in the toxic gliadin fractions and the different mechanisms of that toxicity? It appears that in CD, tissue damage is caused by cell-mediated immune responses triggered by tyrosine-containing peptides. In NCGS, cytotoxic reactions triggered by serine-containing peptides cause milder tissue damage.

Although both diseases are caused by gluten, their mechanisms differ. To manage them effectively, a completely gluten-free diet is required, supported by an enzyme supplement such as GluteGuard.

4. Conclusions.

In conclusion, CD and NCGS appear to be caused by the action of certain peptides in gluten, which are the causative agents in both conditions. The gluten peptides are the cause of DH, where GluteGuard showed effective protection levels supported by a clinical trial [33]. For NCGS, data is limited to unblinded reports from self-diagnosed users of GluteGuard, a product accepted among CD patients. Laboratory results demonstrate that tyrosine-containing peptides in gliadin induce γ -interferon in CD patients. In contrast, serine-containing peptides do not trigger immunological reactions but may cause direct toxicity, potentially due to enzyme deficiency in the small intestine, as suggested by studies on siblings of CD patients [34]. One peptide (11-19 of A-gliadin) exhibits high toxicity in fetal chick assays, though it does not show activity in other assays involving immunological reactions.

4.1. The Active Peptide in Non-Celiac Gluten Sensitivity (NCGS)

Peptide 31-43 of A-gliadin, although active in the foetal chick assay, cannot be considered an active fraction in CD, compared with A-gliadin 75-86. However, peptide 31-43 can be implicated in causing the milder NCGS symptoms. It has the sequence 31 LGQQQPYPYPQPY43.

There is strong evidence that this peptide forms part of the A-gliadin peptide and could be considered the active

part of the molecule in NCGS. Fraction 9 was shown to contain these toxic peptides as well as the celiac active 75-86 sequence of A-gliadin and one of these sequences was the 9-19 A-gliadin peptide with high activity in the fetal chick assay. It has the sequence QNPSQQQPQ with serine but without tyrosine. Part of this activity was attributed to components corresponding to those in residues of A-gliadin 31-43, which has been shown to damage enterocytes but was unable to stimulate celiac intestinal CD4 helper T cells required for a proliferation of the immune responses and tissue damage [35]. Other peptides in this area such as peptide 31-43 have not only the QQQ motif but also the tyrosine containing motif QQPY which are toxic *in vivo* to celiac patients hence for NCGS toxicity we need to go only so far as residue 43.

5. Gluten Free Diet and Enzyme Therapy

There is currently no cure for celiac disease and related disorders. A strict gluten-free diet must be followed to allow the body to heal. For those with celiac disease exposure to even small amounts of gluten allows intestinal damage to continue, regardless of the absence of symptoms. Avoiding gluten is essential but can be harder than it seems, hence the need for enzyme therapy.

Enzyme therapy is essential due to the failure of nominal gluten-free diets, which are often contaminated with traces of gluten and cereal proteins banned for people with CD, NCGS, and DH.

Patients with these conditions need an early and accurate diagnosis, followed by proper dietary management to ensure their food is entirely gluten-free. Avoiding gluten contamination is challenging, as even a few mg can trigger disease symptoms. Small quantities of gluten can be neutralized using enzyme supplements like GluteGuard. GluteGuard contains caricain, an enzyme that breaks down gluten into small, harmless fragments.

Enzyme supplementation with a suitable enzyme can reduce the risk of gluten exposure while away from home, reduce the severity of symptoms and make the dining experience more pleasurable without the worry of the food being contaminated by gluten.

Individuals diagnosed with NCGS should complement their gluten-free diet with appropriate supplements and undergo further testing under the supervision of a gastroenterologist to confirm whether their condition is CD or NCGS, as these conditions may share similar symptoms but have different mechanisms of action triggered by gluten ingestion. The management of accidental gluten consumption can be effectively supported by incorporating GluteGuard as a supplement to a standard gluten-free diet.

5.1. Removing the Worry of Gluten

GluteGuard thus takes the worry out of deciding whether the food consumed will cause harm and allows one to enjoy every meal and derive the maximum health benefits from it. Users of GluteGuard report a wide range of health benefits, and it follows that by keeping the small intestine in the best possible condition, one will lessen the chance of succumbing to more serious conditions such as

anemia and lymphomas. Diagnosis of CD and NCGS should be made in childhood because of the damage to the small intestine and the resulting malabsorption of vital nutrients causing stunted growth in the teenage years.

Overall, the use of GluteGuard is a positive way of ensuring that the small bowel is protected because GluteGuard quickly digests any gluten down to harmless small fragments thus avoiding damage to the absorptive surface of the small bowel, so essential for the utilization of key nutrients.

5.2. The Need for Safer Digestion of Gluten

The call for safer digestion of gluten by those with CD and NCGS is by placing the enzyme caricain as the foremost ingredient for enzyme therapy. Caricain has been shown to detoxify over 90% of gliadin in a typical breadmaking procedure, as determined by an ELISA assay [36]. Lerner [37] comments that the proper degradation of gluten toxic/immunogenetic peptides is one of the most effective strategies now available for helping to cope with the shortcomings of the gluten-free diet.

5.3. GluteGuard Summary

GluteGuard – this supplement was developed as a safeguard for those with sensitivity to gluten, including those with coeliac disease (CD) and non-coeliac gluten sensitivity (NCGS). It is based on a naturally occurring enzyme (caricain) present in the fruit of the *Carica Papaya* plant. It is approved for use by the Therapeutic Goods Administration of Australia and has won an Australian self-care excellence award in November 2023, based on feedback from users. It is available through leading pharmacies and does not require a prescription.

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