Mini Review

Antibodies against deamidated gliadin peptides in the diagnosis of celiac disease

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Abstract

Celiac disease (CD), a.k.a. gluten enteropathy is a global health problem due to its prevalence of up to 1% in the general population and the high risk of multiorgan complications. Along with confirmed anti-gliadin antibodies, anti-tissue transglutaminase antibodies, anti-endomysium antibodies, etc., in the diagnosis of CD, results on antibodies to deamidated gliadin peptides (anti-DGP antibodies) have been accumulated in the past ten years. Anti-DGP antibodies have shown comparable and even better characteristics in terms of diagnostic specificity and sensitivity for the identification of patients with CD, especially in those with IgA deficiency, as well as in other diseases associated with sensitivity to gluten, monitoring the effect of the gluten-free diet. The combined determination of a panel of autoantibodies related to CD, including the anti-DGP antibodies, improves the diagnose process and follow-up of these patients.

Keywords: antibodies, celiac disease, gliadin, gluten enteropathy, gluten-free diet, serology

Introduction

Gluten enteropathy also called celiac disease (CD) or non-tropical sprue, is a complex inflammatory disease with autoimmune characteristics that affects the small intestines of genetically predisposed children and adults. CD is caused by immunological hypersensitivity to ingested gluten [1]. The disease prevalence varies between 1:100 and 1:300 in different regions of the world, with a slight predominance in women [1,2]. According to Celiac Disease Foundation, one out of every 133 persons can be affected by the disease, but only 3% of patients are diagnosed, causing CD to be described as a hidden epidemic [3]. Although CD is defined as a childhood illness, more and more patients are diagnosed with the disease as adults [4]. A rare presentation of CD with typical symptoms in adults compared to children leads to a significant delay in diagnosis in the population resulting in increased mortality in adult patients with the disease. Only 50 years ago 4% of the diagnosed patients were over 60 years of age, whereas this group now represents 19-34% [5]. Considering the frequent occurrence of this disease in the population, CD is suggested to be the most common cause of steatorrhea in people over the age of 50 and the second most common cause in adults over 65 [5]. In line with this, reliable screening tests are needed to help diagnose CD in each age group.
Historically, the serological tests for gluten enteropathy have evolved, including anti-gliadin antibodies (AGA), anti-reticulin antibodies, antibodies against endomysium (EMA), antibodies against tissue transglutaminase-τTG (anti-τTG), and anti-actin antibodies (AAA). More and more data are being accumulated for relatively “young” antibodies against deamidated gliadin peptides.

Antibodies to deamidated gliadin peptides (anti-DGP antibodies) have been described by Schwertz et al. for the first time in 2004 [6]. In the lumen of the small intestines, the gliadin is digested by the enzymes to peptides and amino acids. In the case of increased permeability of the intestinal membrane, gliadin peptides may enter lamina propria of the mucosa, where they encounter the intestinal τTG. τTG is a calcium-dependent protein that catalyzes hydrolysis (deamidation of the amino acid glutamine into glutamate) of peptide-binding glutamine residues. Since gliadin is rich in glutamine, it is a specific substrate of τTG [7]. Deamidated gliadin peptides are probably the trigger for initiating the immune response to gluten in genetically susceptible individuals [6]. According to Molberg et al. the complex of gliadin associated with τTG forms a neoantigen, which is most commonly presented by the class II molecules (HLA-DQ2) of the main histocompatibility complex and recognized by the gliadin-specific T lymphocytes in the intestinal mucosa [8]. Gluten-sensitive CD4+ T lymphocytes are then activated, and a Th1 immune response develops, associated with activation of transcriptional factor T-bet and the expression of large amounts of IFNγ [4] leading to inflammation and damage to the mucous membrane [9]. This process is not executed in healthy individuals [6]. Autoantibodies that are formed in the immune process are mainly against gliadin, tissue transglutaminase, and deamidated gliadin peptides.

Furthermore, the deamination of the gliadin molecule increases the formation of complexes between AGA and gliadin in CD patients [6]. There is a hypothesis about the formation of anti-DGP antibodies and their high concentration in patients with CD. One explanation is linked to a preferred activation of these B lymphocytes, which present epitopes of deamidated peptides to existing specific T lymphocytes in the intestinal mucosa. Another possible reason is associated with a higher concentration of modified peptides in patients with CD compared to healthy individuals as a result of the higher activity of the enzyme τTG in the mucosa of CD patients [7]. This leads to an increase in the formation of anti-DGP antibodies which, in addition to the local mucosa, are also found in the peripheral circulation [7]. Precisely, selective deamination of conformational intact B-cell epitopes increases their antigenicity, and this is at the basis of the development of anti-DGP antibodies in the serum of patients with gluten enteropathy [7,10].

Clinical applications of autoantibodies found in CD have been investigated in many studies, in CD patients, and other diseases. Antibodies directed against deamidated gliadin peptides were compared with other validated serological tests for gluten enteropathy. Most authors found that antibodies against short gliadin deamidated peptides, homologs of gliadin, were more specific to CD than antibodies to the entire gliadin molecule. Moreover, AGA can also be seen in ulcerative colitis, Crohn’s disease, IgA nephropathy, HIV infection, some neurological and liver disorders [6,11]. Various studies also detect diagnostic sensitivity of antibodies to multiple epitopes of deamidated peptides between 86.5-94.2% and diagnostic specificity between 90.8-94.3%.

Furthermore, the diagnostic accuracy of anti-DGP antibodies is increased 7 to 11.8 times than the AGA in CD patients [6,12]. Sugai et al. also received similar results in 2006 investigating antibodies against deamidated gliadin peptides for monitoring the effect of a gluten-free diet (GFD) at the 6th month and in the first year. The results convincingly show that anti-DGP antibodies decrease in a large percentage of CD after the diet. They also found that a large portion of patients was positive for anti-DGP antibodies when they had more severe histological damage in the villous apparatus [12]. Other authors documenting decreasing the number of positive for anti-DGP antibodies patients from 91% to 18% after a GFD, whereas 67% of the patients with refractory CD and testing the anti-DGP antibodies could be a useful method for early detection of them [13]. Thus, serological markers can be used to monitor the effect of GFD [14]. We also have results regarding the follow-up of CD patients on GFD. Moreover, we found that patients with elevated IL-17 at baseline were more prone to not reduce the levels of CD-related autoantibodies after GFD [15,16].

Our experience with antibodies to deamidated gliadin peptides in patients with CD, children, and adults, dates back to 2011. Our results showed a diagnostic sensitivity of 95% and a specificity of 98%. A positive predictive value of 99% is highly encouraging that almost all of the CD patients will be diagnosed serologically. The negative predictive value of 97% indicates that only 3% of patients with CD cannot be excluded [17]. We have also demonstrated a strong correlation between the testing of three antibodies, AGA, anti-τTG, and anti-DGP antibodies (p < 0.05). These results have also been confirmed by some research teams [11,14,18,19]. The meta-analysis of Lewis and Scott, covering eleven studies for the period up to 2008, showing that the specificity of anti-DGP antibodies is comparable to the “gold standard” in serologic diagnostics, anti-τTG antibodies testing [20]. Moreover, the simultaneous positivity of both anti-τTG IgA and anti-DGP IgA/IgG antibodies strongly suggests the diagnosis of CD, and it is recommended to undertake an endoscopic biopsy study for histological analysis [20]. The combined study of AGA, anti-τTG, and anti-DGP antibodies can be very likely to confirm or rule out the CD diagnose, to reduce the cost of diagnosing, and the number of endoscopic studies, which in turn leads to a better acceptance diagnostic procedure for patients [21].
Another useful feature was observed for anti-DGP antibodies. Unlike anti-tTG antibodies that are the most specific and sensitive for CD when of class IgA, the anti-DGP antibodies from both classes of IgA and IgG may be useful in the diagnosis CD. The specific IgG immune response to deamidated peptides was observed even at low concentrations of IgA in the serum [7]. Moreover, the use of commercial kits with combined testing for antibodies of both IgA + IgG class could help to diagnose CD in patients with IgA deficiency [11,12]. Studies of the clinical significance of antibodies against deamidated gliadin peptides have also revealed their ability to be used in the serology testing for several gluten-associated diseases, such as gastrointestinal-related dermatitis herpetiformis [22], reproductive failure [23], and ataxia [24,25].

**Pearls for the clinical practice:**
- Measurement of anti-DGP antibodies in serum is an excellent predictive marker with high diagnostic accuracy for CD.
- Determination of anti-DGP antibodies is a valuable addition to existing serology panels for the diagnosis of CD, especially when the results of AGA and/or anti-tTG are negative but the clinical picture is typical.
- The existence of several reliable diagnostic parameters makes it possible to create algorithms for the diagnosis of CD in children and adults.
- Anti-DGP antibodies can be used successfully to monitor the effect of gluten-free diet in patients with CD.
- Anti-DGP antibodies (both class IgA and IgG), are equally relevant in CD, making the combination a screening-friendly test even in the study of IgA deficient patients.
- Anti-DGP antibodies are also found in a high percentage of dermatitis herpetiform patients, women with reproductive failure, gluten-sensitive neurological disorders as ataxia, and others.

**Concluding remarks**
CD is a global health problem due to its relatively high incidence and high risk of complications without GFD, which requires a multidisciplinary approach. The combined testing of celiac-related antibodies improves the diagnosis, quality of life, and survival of these patients.

**Conflict of interest**
All authors declare that they have no conflict of interest.

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**References**


