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IgA and IgG Antitransglutaminase 2 Antibodies in the Diagnosis of Celiac Disease

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Abstract Screening for celiac disease (CD) dramatically improved when techniques able to measure blood autoantibodies against tissue transglutaminase 2 (TTG) were developed. Although typically increased in CD, these antibodies are not pathognomonic since they are also detected in several other autoimmune processes. IgA deficiency among celiac patients is more frequent than in general population (up to 25% vs 1-3%). This led to develop kits able to measure IgG-TTG, which until today represent a helpful diagnostic tool during diagnosis of CD in IgA deficient individuals. Today, commercial kits measuring IgG- TTG (and other) antibodies are widely available, are frequently used and create confusion in diagnosing CD in IgA-sufficient individuals. This is attributed to the fact that sensitivity and specificity of IgG-TTG is lower when applied to IgA-sufficient persons, and also because IgG-TTG is detected in several autoimmune disorders, with variable frequency and isotypes depending on the condition. Evidence analyzed indicate that to date available data: i) is insufficient to understand the difference of classes and subclasses detected in CD and other autoimmune conditions; ii) does not support the use of IgG-TTG for diagnosing CD in IgA-sufficient individuals and therefore iii) IgG should not be used in the routine diagnostic process of CD.

Keywords: *celiac disease, transglutaminase 2, autoimmunity, IgA deficiency, IgG-TTG*

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1. Introduction

Celiac disease (CD) is a systemic immune mediated disorder triggered by gluten and prolamines present in wheat, barley and rye in genetically susceptible individuals. Characterized by variable degrees of inflammatory enteropathy, it may present a wide range of digestive and extra digestive symptoms and the presence of specific but not pathognomonic blood autoantibodies [1,2]. Both the extra digestive symptoms and blood autoantibodies are also detected in other autoimmune disorders with variable frequencies (see below). The number of people diagnosed with CD has increased in the last decades due to availability of better diagnostic tools and also to improved awareness among professionals and the general population. There is evidence that suggest that the real frequency of CD has also increased [3]. The only efficacious treatment of CD is maintaining a strict, permanent gluten-free diet for life. Surveillance of this diet during follow up is difficult because there is no objective way to measure actual gluten ingestion; this is especially so during the transition period of adolescence [4]. None of the existing techniques are completely reliable, including measurements of blood autoantibodies, interviews, questionnaires or the more recently described measurement of 33-mer peptide in feces/urine [5,6] or alkylresorcinols in urine [7], which await validation. At present and both for diagnosis and gluten-free diet control during follow up, measuring blood autoantibodies mainly against transglutaminase 2 (TTG) is the most recommended test worldwide. The routine technique consists of measuring IgA-TTG, but because IgA deficiency is more frequent among celiac patients than in general population, kits that measure IgG type TTG have also been developed. Since appearance of these latter, determination of blood IgG-TTG rapidly became the best choice for assessing CD in IgA deficient individuals [8].

Numerous companies currently commercialize kits that measure IgG versions of CD related autoantibodies; unfortunately, widespread use of these kits has led to confusion when interpreting results in IgA-sufficient individuals assessed for CD. This led us to review the available data on TTG, types and isotypes of antibodies clinically used, the relation between TTG and autoimmunity and between IgA deficiency and CD, to finally conclude on the usefulness of measuring IgG-TTG during the diagnostic process of CD. As the information available is scant and does not allow analysis or comparison between the different types and isotypes of the different antibodies (including anti gliadin, anti endomysial, anti deamidated gliadin peptides), this review includes only IgA and IgG antibodies against TTG. The

web search used the words related to “digestive” and “celiac disease”.

Literature search combined the terms IgA- and IgG- “antitransglutaminase (TTG), antigliadin (AGA), antiendomysial (EMA), deamidated gliadin peptides” (DGP) with specific terms, including “celiac disease”, “autoimmunity” and specific autoimmune disorders using accessible databases including PubMed, Medline, Cochrane Library and BioSciences Information.

1.1. Transglutaminases

These are a family of enzymes related by structure and function that catalyze posttranslational modifications in eukaryotic proteins of plants and mammals [9]. TTG is ubiquitously expressed and has multiple functions supplemental to its protein crosslinking ability [10]. It is recognized as the most important autoantigen detected in blood of celiac patients [11]. However, it may be also increased in processes like fibrosis, atherosclerotic plaques formation, metastatic cells and several autoimmune disorders [9]. Anti-transglutaminase antibodies would be locally induced in the small intestinal mucosa by IgA-producing plasma cells [12]. Epitope-mapping studies identify relevant regions both in the enzyme core [13,14] and amino terminus [14]. TTG has a relevant role in the pathogenesis of CD deamidating the gliadin peptides that will subsequently bind HLA- restricted groves in HLA-DQ2 and DQ8 (Figure 1). Proinflammatory signals originated from the various mucosal cells will contribute to increase TTG production. IgA-TTG are most studied in CD, but other isotypes can also be found in the condition, like IgG-TTG, which has been described, but insufficiently characterized [8].

1.2. TTG and ELISA Kits

Antitransglutaminase antibodies are usually measured by ELISA technique; it was first developed in guinea pigs and later human recombinant protein was used. Both have high sensitivity and specificity, over 90% in children and adults [11]. Sensitivity and specificity are lower for measurements of IgG-TTG; Comerford et al described IgG-TTG positivity was 22% among pediatric patients and 47% in adults [15]. Despite these figures, it is interesting that IgG-TTG values were always higher in patients with untreated CD and both in children and adults results were higher in patients than in controls.

At present, kits measuring different antibodies (like IgA-TTG plus IgG-TTG or TTG plus deamidated gliadin peptides) have been developed. Those in favor of measuring IgA- and IgG- TTG at the same time argue that this will help diagnosing CD in all persons, independent of their IgA status [16]. However, studies assessing IgG are so scarce and sensitivity and specificity yielded by these kits lower than those obtained for IgA-TTG that recommendations and clinical Guidelines currently advice the use of IgA-TTG as the first, cost- effective and more reliable method to detect celiac individuals [1,2].

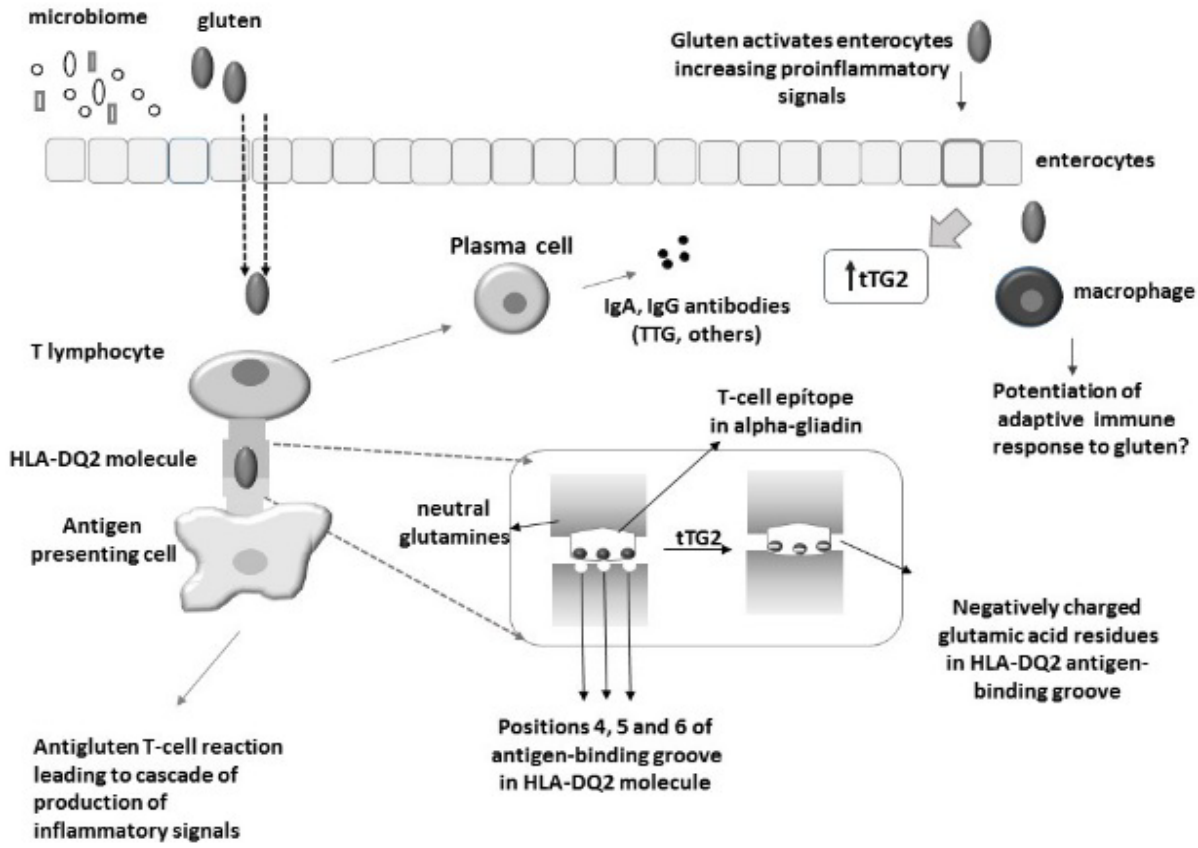

Figure 1. Tissue transglutaminase 2 (TTG2) in the dysregulation of celiac disease. Gluten peptides resist gastrointestinal degradation due to their high proline content. The microbiota may act modifying gluten proteolysis and the net production of immunogenic peptides, which cross the epithelium and reach the lamina propria. TTG2 catalyzes deamidation of these peptides, which results in negatively charged molecules that then are more efficient binding to HLA-DQ2 or -DQ8 molecules on antigen presenting cells. This initiates an anti-gluten T-cell response with release of pro inflammatory signals leading to epithelial damage. Gluten enterocytes and macrophages activation will increase proinflammatory signals that will expand TTG production

When screening for CD age is one of the factors influencing the results obtained. When screening for CD age is one of the factors influencing the results obtained. Using IgA-TTG in celiac patients sensitivity and specificity have been described at 98.1% (95% CI: 90.1% – 99.7%) and 98.0% (95% CI: 95.8 –99.1) in adults [17,18] and 95.7% (CI: 90.3–98.1) and 99.0% (CI: 94.6 –99.8) in children [19,20], respectively.

2. IgA Deficiency and Auto-antibodies in CD

The relation between IgA deficiency and CD is currently well established [21,22]. In Europe, prevalence of CD is 0.5-6% in general population and it increases up to 25% among celiac patients [23]. Estimates are that 2-5% of celiac individuals are IgA deficient [24]. Therefore, it is certainly important to be able to measure IgG-TTG in patients with insufficient IgA levels who are in the diagnostic process of CD. In IgA deficient celiac patients IgG-TTG determination has yielded sensitivity and specificity that vary between 68 and 100%, respectively, but sensitivity is lower in IgA sufficient patients [11]. Also in IgA-deficient patients, specificity of 100% and sensitivity of 90-96% have also been reported [25], however, among patients exhibiting a wide range of small intestinal lesions the negative predictive value decreased. These limitations have always been and continue being relevant in population studies, which often cannot confirm the diagnosis by biopsy. This evidence has led to agree that IgG-TTG antibodies are not satisfactory to search for CD in IgA-sufficient individuals [8,26].

3. Autoimmunity

One of the problems measuring anti transglutaminase autoantibodies for diagnosing CD is that although they are typical of this disease they can also be found in non-celiac conditions, mainly autoimmune disorders [27], AIDS [28] and terminal phases of cardiac insufficiency [29]. In non-celiac patients IgG type antibodies are frequent and there is no direct relation between the antibodies type found, either IgA- or IgG-. For example, IgG-TTG in absence of IgA-TTG has been described in patients with DMT1 [30]. Positive IgA-TTG and negative IgA-EMA were reported in patients with Crohn's disease [31], with unclear results on the presence of IgG-TTG [32]. There are reports in rheumatoid arthritis describing patients positive for IgA-TTG and negative for IgA-EMA [33] or IgG-TTG [34]. Also, IgA- and/or IgG- TTG have been reported in systemic lupus erythematosus [32,35], granulomatosis with polyangiitis [36], ankylosing spondylitis (IgA and IgG) and psoriatic arthritis (IgA and IgG) [37]. Differences observed between epitope specificity and the IgA- or IgG- TTG isotype observed may derive from the different mechanisms acting on the enzyme during the process that leads to autoimmunity

3.1. TTG, IgG-TTG and Antibodies Subclasses

It must be kept in mind that IgG-TTG described in autoimmune disorders are of different isotypes and these may be of a predominant subclass or a mixture of them. In CD the predominant subclass is IgG1 [38]. This subclass is also found in DMT1, but it is infrequent in Crohn's disease and in granulomatosis with polyangiitis [15]. Studies analyzing IgG subclasses are quite scarce. Comerford [15] analyzed IgG-TTG by age and showed that IgG-TTG levels were highest in celiac children 0-4 years of age (which coincides with Agardth study [39]) and significantly higher compared to that of CD patients aged 4-8 years (p= 0.0225), and adults celiacs (p= 0.0009); IgG2 was present in 35% of patients, IgG3 was greater in adults than in children and IgG4 was higher among children. Distribution of IgG subclasses was similar in diabetic patients but different from patients with Crohn's disease, where IgG3 and IgG4 predominated (69%), while in granulomatosis with polyangiitis IgG1 was always negative and positivity was given by IgG2 and IgG3.

IgG4 deserves a special comment. At present there is a novel disease category, associated with IgG4. They may involve different organs and systems, being characterized by increased IgG4 in serum, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, tumefactive lesions with storiform fibrosis, which quickly respond to glucocorticoids [40]. This group includes diseases such as Mikulicz's syndrome, retroperitoneal fibrosis, Küttner's tumor, and Riedel's thyroiditis [41], but not CD.

This review identified only three additional studies, which cannot be compared, assessing antibodies and/or isotypes in celiac patients. Choung et al presented interesting results at the American Gastroenterology Association meeting (AGA 2016) [42]; they evaluated serum 4976 samples from patients that were evaluated for CD. They related the IgG-TTG and IgA-TTG values found and the IgA status. 5.2% were completely IgA deficient, 30.5% had partial IgA deficiency and 64.3% showed IgA sufficient values. Distribution of IgG-TTG and IgA-TTG are summarized in Table 1. Presence of HLA risk alleles did not differentiate patients by their IgA status. Whereas it was interesting that among IgA sufficient patients only 41.2% of those IgG-TTG positive carried risk alleles for CD.

Table 1. Distribution of IgA and IgG positivity in 4976 serum samples from celiac patients*

IgA	At least one tTG (+)	Isotypes (in %) present in positive samples	
Complete deficiency	13.8%	100% IgG isotype	
Partial deficiency	4.9%	85.3% IgG isotype	30.7% TTG-IgA isotype
Normalcy	4.2%	68.1% TTG-IgG	50.4 % TTG-IgA

*= Based on Choung RS report (44).

A second study included measurement of IgG-AGA and IgG-TTG in 126 celiac patients with complete IgA deficiency at the time of study [43]. Both antibodies were negative in 6% of patients. 37/40 who had both antibodies positive accepted a duodenal biopsy and diagnosis was confirmed. In patients with only IgG-AGA positive small intestinal biopsies were all normal and in 11/18 of patients with only IgA-TTG positive patients the biopsy confirmed CD. In all, CD was diagnosed in 11/126 IgA deficient patients (8.7%). Authors conclude that measurement of IgG-TTG is recommended for screening of CD in IgA- deficient persons an also, that IgG-AGA should not be used during the routine CD diagnostic process [43]. This is in agreement with Villalta et al [44], who recommended measuring IgG-DGP in these uncertain patients. It seems indeed reasonable that when antibodies are not clear a small intestinal biopsy should continue being the gold standard for diagnosing CD.

Finally, there is a recent study that evaluated 178 patients that proved IgA-TTG negative and IgG-TTG positive during the diagnostic study [45]. Results were contrasted against histological findings; 1/178 demonstrated to have CD, which means that the test was useful in 3% of patients. In the group assessed, 18% suffered other autoimmune disorders. A total of 3 patients were diagnosed CD, but none was IgA deficient; of those patients with partial IgA deficiency (n=72) none was celiac. Authors conclude that in this series IgG-TTG did not show association with histological findings and did not help predicting CD, even in those patients with partial selective IgA deficiency.

In summary, the evidence reviewed indicate that: i) measuring IgA-TTG is an effective and helpful tool during the diagnostic process of CD; ii) measuring IgG-TTG shows high sensitivity and specificity in IgA deficient patients, representing a helpful tool in the diagnosis of CD in IgA deficient patients; iii) antitransglutaminase autoantibodies reflect the autoimmune processes present and not necessarily CD, representing a potential confusion factor during CD diagnosis; iv) the lower sensitivity and specificity of IgG-TTG makes it not suitable for the routine CD diagnostic process in IgA sufficient individuals.

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