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Deamidated Gliadin Peptide Antibodies in Celiac Disease: A Diagnostic Driver or just along for the Ride?

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Abstract Anti deamidated gliadin peptides antibodies are considered as celiac disease associated diagnostic antibodies. They are in clinical use for almost the last two decades. In the first decade they were preferentially used in early childhood, in face of IgA deficiency and occasionally recommended as the prime serological marker, outperforming the anti-tissue transglutaminase autoantibody. Notably, they were recommended in combination with the tissue transglutaminase as enhancer of the diagnostic performances. No more, the circle turned over. In the second decade (2012-2019), most of the studies limited and criticized their past published advantages. They suggested that deamidated gliadin peptides antibodies do not have any advantage over anti-tissue transglutaminase autoantibodies in terms of early childhood, IgA deficiency, diagnostic performances and when both antibodies are combined. It seems that the deamidated gliadin peptide are losing their place in the celiac disease algorithmic diagnostic flow chart.

Keywords: *celiac disease, deamidated gliadin peptide, tissue transglutaminase, diagnosis, serology, serological marker, antibodies*

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1. Introduction

1.1. Celiac Disease

Celiac disease (CD) is an autoimmune food intolerance entity affecting genetically predisposed individuals who consume gluten-containing grains or ingredients of them, originated from wheat, rye, barely and to a lesser extent in oats. CD affects approximately 1-2% of well-developed countries populations. Its prevalence and incidence is increasing constantly, in the last decades, comparably to multiple other autoimmune diseases [1,2]. Co-emergence of increased immunogenic gluten and its world-wide consumption, on the same genetic background, and the surge in CD incidence reinforce the environmental over genetic influence in the contemporary CD spreading.

CD has multiple clinical presentations, many of them being extra-intestinal manifestations, affecting peripheral organs and remote, non-enteric, tissues [3,4,5]. It can be present with obesity [6], in the elderly [7], have even an acute presentation [8] or be a part of a polyautoimmunity syndrome [9]. Interestingly, the epidemiology of the disease is constantly changing, complicating the enigma of the disease and the diagnostic burden of the medical teams. In the recent 3-5 decades, an epidemiological shift toward a more advanced age, increased frequency of latent, hypo-symptomatic or asymptomatic behavior presentation with non-enteric classical manifestations, is occurring [3-8,10]. This multifaceted display make the reliance on symptomatology more remote, thus partially explaining the delay in its diagnosis, as summarized recently [11,12].

1.2. The Importance of Serology in Celiac Disease Diagnosis

A correct diagnosis of CD and life-long gluten withdrawal is the ultimate goal of the medical teams. Years ago, small bowel pathology was the gold standard, but along the years, positive and negative pitfalls appeared [13,14,15] and a need for reliable, sensitive, specific and cost effective bio-markers became a necessity.

In parallel, following the growing knowledge on CD pathophysiology starting with the ingested gluten, gliadin peptides epithelial transport, the posttranslational modifications induced by the endogenous transglutaminase, the processing and presentation to the reactive and innate immune systems, the selection of the CD CD4 T cells and the mucosal destructive inflammation, several autoantigens were selected and the corresponding antibodies were developed, for routine clinical use [11,12,16,17]. Major conceptual and technical advances in the serological diagnostic industries put serology as

a prime candidate for CD screening, diagnosis and follow-up [11,12,16,17].

Nowadays, multiple antibodies tests are available on the market: IgA anti-endomysial antibody (EMA), IgA and/or IgG tissue transglutaminase (tTg), IgA and/or IgG deamidated gliadin peptide (DGP), IgA-tTg being the most frequently used and ESPGHAN's recommended one [12,16,18]. Since the topic of the present review is not CD associated serology as a whole, we will focus on DGP in CD diagnosis.

1.3. DGP Antibodies

When gliadin peptides reach the intestinal sub-epithelial area, they represent an ideal substrate for the tTg that can deamidate or cross-link them. The resulting products are deamidated gliadin peptides and the neo-epitope tTg-gliadin cross linked complexes, respectively [19,20]. The tTg induced deamidation, turns the gliadin peptides negatively charged, more adapted to be presented by the HLA-DQ 2/8 groove and to select the CD specific CD4 T cell clones [21,22]. The loss of tolerance to gliadin peptide, by the tTg action, is a crucial step in CD autoimmunogenesis. Being an autoantigen, the DGP induces specific antibodies that were launched for clinical use in the early 2000 [23]. Analyzing the annual number of publications on deamidated gliadin peptide celiac disease on PubMed, a gradual increase is seen between 1999-2013, plateauing during 2013-2015 and then decreasing (Figure 1). A corresponding trend in the manuscript content can also be detected. The more recent publications, later than 2012, are more critical and question DGP antibodies' (DGPa) place in CD screening and diagnosis. The main advantages of DGPa, published in the past were four: 1. Better performance below the age of 2 years [24]. 2. The DGP-G antibodies are good to detect CD in face of IgA deficiency [24,25]. 3. Comparable diagnostic performance with tTg-A [24,25,26,27]. 4. Combined with tTg-A, it upgrades its diagnostic performances [28-31]. The following will critically review those topics, as presented since 2012.

2. DGP Antibodies Lack Diagnosis Performance in Celiac Disease

In parallel to the decrease in the number of publication on DGPa in CD in the latest years (Figure 1), it seems that the initial diagnostic capacity's enthusiasm of DGPa has decreased in all the above mentioned aspects.

As for the general performances in CD diagnosis, DPG-G+A increases neither the sensitivity nor the specificity of EMA and tTg-A [32]. DGP-G should not be a part of initial screening for CD in children as it does not differentiate effectively between the patients and controls [33]. Accuracy of detection of CD by DGP-G is not increased compared to tTg-A [34]. Sensitivity of DGP-A and G tests are less than for tTg-A [35]. Adding DGP A/G to the pre-biopsy test in pediatric CD affects the sensitivity and specificity negatively [36]. DGP-A shows inferior accuracy and DGP-G may help in excluding more than diagnosing CD [37]. Finally, a most recent study suggested that in face of moderately increased tTg-A, screening by DGP-A+G lacks specificity, does not help and does not provide any beneficial information whether to perform or postpone duodenal biopsies [38].

As to the better performance in early childhood, several recent studies show the opposite. Studying serological performances below 3 years of age, an Israeli group concluded that use of DGP A+G is insufficient for definite diagnosis of CD [39]. In the same year, Swedish researchers deducted that tTg-A is superior to DGP-A/G in CD diagnosis, even below 2 years of age. Even the cost effectiveness was lower for DGP usage [40]. tTg-A performs better below 2 years of life and above 6 month of age. No need to perform DGP activity in the young [41,42].

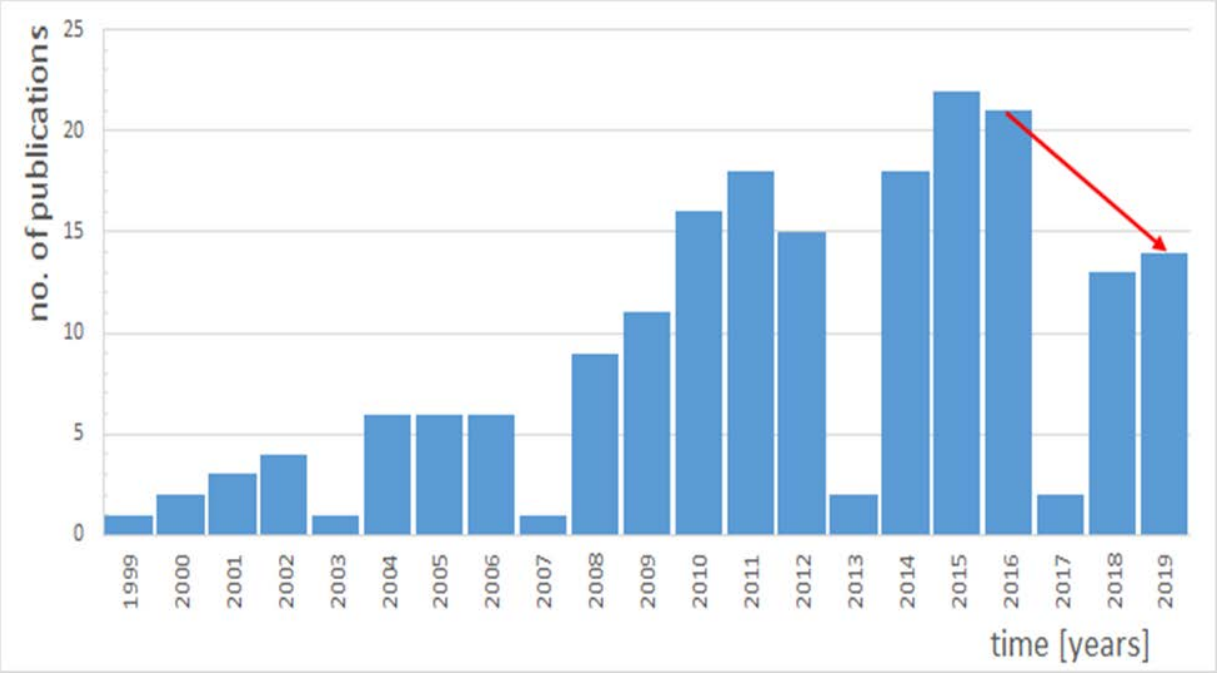

Figure 1. The number of publications on deamidated gliadin peptides plotted against the yeas 1999-2019

Even in CD with IgA deficiency, DGP-G levels appears to be less efficient, as compared to tTg-G [43]. In an expert review update of the AGA society from 2019, the recommended work-up in face of CD IgA deficient patient was total IgA , DGP+G and tTg-G and not only DGP-G [44]. Further on, when CD screening was performed on pediatric type 1 diabetes population, tTg-A was more accurate than DGP-A [45]. The last aspect is the combined serological test, combining two isotype of the same or two different antibodies. Combining tTg and DGP does not decrease the number of missed cases of CD, the number of unnecessary intestinal biopsies nor increase the cost effectiveness of the procedure [40]. Adding DGP-G to tTg-A does not improve the diagnostic yield in pediatric CD population [46]. A more definitive message came from Dahlbom et al. They stated that in CD "the inclusion of DGP antigens in the IgA/IgG combination assays seems to affect the sensitivity and specificity negatively" [36]. Finally, analyzing the place of DGPa in CD algorithmic diagnosis, Zucchini et al, concluded that "anti-DGP antibodies may not have the diagnosis value required as an additional screening test to anti TG2 antibodies for identifying CD patients in medical centers where anti endomysium detection is available [47].

In summary, it seems that the trend that recommended DGP usage for CD screening and diagnosis, during the first decade of the current millennium (2000-2012) changed direction. Following multiple studies and reviews the DGPa cannot compete with tTg-A, as a prime serological marker in CD. DGPa are no longer recommended during infancy and early childhood, its G isotype is not advantageous in IgA deficiency, tTg-A outperforms the DGPa diagnostic capacities and the combination of DGP-A/G with tTg-A is not beneficial and not cost effective in CD detection.

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