

# Are Non-Celiac Autoimmune Diseases Responsive to Gluten-Free Diet?

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**Abstract** Genetic risk factors for autoimmune diseases are constantly discovered, however, environmental factors are lagging behind and the precipitating events leading to development of autoimmune diseases remain enigmatic. Gluten is a well-established inducing nutrient in celiac disease and gluten withdrawal is the only current effective therapy. More and more studies have shown that non-celiac autoimmune diseases can partially respond to gluten free diet. The present editorial reviews those conditions and suggest multiple potential mechanisms that might operate in clinical amelioration of non-celiac autoimmune diseases.

**Keywords:** *gluten free diet, autoimmune disease, gluten, nutrition, mechanisms, autoimmunity*

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## 1. Introduction

It is well known that autoimmune diseases (ADs) have two major causative background: genetic and environmental [1,2,3]. Due to the fact that ADs incidence is markedly increased in the Western countries in the last decades [4,5], it is logical to assume that the surge is due to changing environment, much more than genetic modifications or adaptations. Taking into account that the worldwide wheat consumption and gluten intake are likewise increasing, in the last decades [6], it is tempting to speculate that a positive association exist between the two and the surge of ADs. There is no doubt that, at least for celiac disease (CD), the increase in prevalence is tightly relayed to the increased wheat consumption around the world [4,7]. Since CD is associated with multiple ADs, a question arises does gluten consumption contribute to the surge in the non-CD autoimmune conditions and if so, does gluten withdrawal might as well benefit the autoimmune affected populations.

In this regard, the case reported by the Iranian group on the positive effect of gluten-free diet (GFD) in refractory inflammatory bowel disease is very interesting [8] and brings up the topic of GFD in non-CD autoimmune condition. Rostami-Nejad et al. described a young male with refractory left-sided ulcerative colitis with normal bulbar and duodenal biopsies and CD associated serology. Upon GFD, his symptoms disappeared and the colonic pathology improved. It should be noted that other recent reports on Crohn's disease patients reported that GFD might be beneficial in reducing gastrointestinal symptoms, disease activity index and drug responsiveness [9,10,11]. The present editorial will review the non-CD ADs that under certain

circumstances responded to GFD, and the potential mechanism relaying gluten withdrawal to the improvement of autoimmune diseases and their responsiveness.

## 2. GFD in none Classical Gluten Dependent Autoimmune Conditions

The subject of GFD in other peripheral, non-enteric ADs was reviewed in the past [12,13] and most recently extensively described [14]. Interestingly, in a most recent editorial on the subject of indications for GFD, those non-CD, systemic ADs were not mentioned [15].

## 3. Potential Mechanisms of Gluten Free Nutritional Therapy in Non-Enteric Autoimmune Diseases

The list of all diseases in Table 1 is associated with CD and GFD [39] and multiple autoantibodies that are circulating in the patient's blood circulation [40]. Suspicions about the benefit of GFD as a complementary treatment, either as a causal factor in the pathogenesis, or improvement of symptoms, was raised and reviewed lately [41,42]. The fact that GFD have protective effects on the cumulative prevalence of additional autoimmune diseases in CD patients [43,44], opens a window of opportunities to explore the topic of gluten as a driver of autoimmunity and the place of GFD in ADs dietary therapy.

Not less interesting are the potential pathways by which gluten withdrawal might impact the initiation and the progression of autoimmunity. Following are some of those potential mechanisms.

a. *Shared genes.* CD shares HLA and various non-HLA genes with associated ADs [45,46,47,48].

b. *Increases intestinal permeability and leaky gut induction.* Various processed food ingredients and additives were proved or suspected to breach tight junction functional integrity [6,39]. Gluten is one of them [6,49,50]. Will GFD attenuate the leaky gut process?

c. *Microbiome/dysbiome imbalance.* The dysbiotic repertoire related to animal models of specific ADs was recently summarized [3], and multiple publications exist on the dysbiosis in CD and other human ADs [39,51]. Gluten affects microbiome composition and diversity as shown in animal models and on humans [14,39]. Can gluten drive systemic autoimmunity through its effects on the human microbiome?

d. *Pro-inflammatory and potentially auto immunogenic effects.* Gluten is immunogenic, cytotoxic, pro-inflammatory and activates several immune pathways (including IL-17). It increases apoptosis, suppresses cell viability and differentiation, induces oxidative stress and affects epigenetic behavior [14].

e. *Increased amount, toxicity and immunogenicity.* Contemporary gluten has evolved tremendously since its discovery in the Fertile Crescent around 15000 years ago [2]. The wheat gluten content increased about 8 folds, its worldwide consumption expanded, its toxicity and immunogenicity rose and created a geoepidemiology. This

dynamics paralleled the increased incidence of CD and other ADs [2,4,5,52,53]

f. *Intestinal post translational modification of protein (PTMP)* represents a key regulator in autoimmunity, by transforming naïve/self or non-self-peptides to auto immunogenic ones. [3,39,54]. Gluten is an ideal substrate for enzymatic PTMP, tissue and microbial transglutaminases being typical examples [3,54,55,56].

g. *Tissue and microbial transglutaminases* are extensively distributed in the human body and intestinal lumen, respectively [39,54,57]. Human transglutaminase plays a role in end organ affected ADs. Autoimmune thyroiditis, rheumatoid arthritis, IgA nephropathy, dermatitis herpetiformis and gluten ataxia are some of the examples [58-63]. On the other hand, gluten/gliadin peptides are internalized systemically and are secreted in the human urine [64,65], or appear in the mice pancreas following oral administration [66]. One wonders if in the absence of gluten, no immunogenic or neo-epitopes' complexes will be available to drive autoimmunity.

h. *HLA-DQ2/8-restricted gluten specific T cells* have been observed to migrate from the intestinal lamina propria into peripheral blood upon gluten challenge, representing an additional mechanism for extraintestinal manifestations in CD, or potentially reaching peripheral organs in other ADs and thus, ameliorated on GFD [67].

**Table 1. Summarizes the peripheral/systemic AD that were described to partially respond to GFD**

| Disease type             | Improved Parameter  | Reference                    |
|--------------------------|---|------------------------------|
| Rheumatoid arthritis     | Clinical and joint ultrasound improvement<br>Atheroprotective and anti-inflammatory                 | [16,17]<br>[18]              |
| Type 1 diabetes mellitus | Preserve beta cell function<br>Improve insulin secretion<br>Lower HbA1c<br>Improved quality of life | [19]<br>[20]<br>[21]<br>[22] |
| Autoimmune thyroiditis   | Normalization of subclinical hypothyroidism<br>Decrease in anti-thyroid autoantibodies              | [23]<br>[24]                 |
| Autoimmune hepatitis     | Treatment-free sustained remission  | [25,26,27]                   |
| Multiple sclerosis       | Clinical improvement  | [28,29,30]                   |
| Psoriasis                | Clinical and severity index improvement,<br>Decrease the expression of CD associated antibodies     | [31-35]<br>[36,37]           |
| IBD                      | Clinical, pathological and disease activity improvement   | [8,9,10,11]                  |
| Vitiligo                 | Re-pigmentation   | [38]                         |

Non-celiac autoimmune diseases that partially respond to GFD. Adapted from ref [12,13,14].

## 4. Conclusions

We are far away from unraveling the mechanisms by which GFD can alleviate non-celiac ADs initiation or progression and there are more questions than answers on this very challenging topic.

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