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Diet and Psoriasis: Part 2. Celiac Disease and Role of a Gluten-Free Diet

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Abstract

Psoriasis patients have been shown to have a higher prevalence of other autoimmune diseases including celiac disease, a condition marked by sensitivity to dietary gluten. A number of studies suggest that psoriasis and celiac disease share common genetic and inflammatory pathways. Here we review the epidemiologic association between psoriasis and celiac disease and perform a meta-analysis to determine whether psoriasis patients more frequently harbor serologic markers of celiac disease. We also examine whether a gluten-free diet can improve psoriatic skin disease.

Introduction

Psoriasis is a chronic inflammatory disease affecting about 2% of the population characterized by well-demarcated, erythematous, scaly plaques.[1] The pathogenesis of psoriasis involves the interplay between multiple gene susceptibility loci, the immune system, and various environmental factors. Psoriasis is most commonly understood as a T-cell-mediated disease involving IFN-γ and TNF-α as key pro-inflammatory players. More recently, T cells expressing cytokine IL-17 have been found to play a major role in psoriasis.[2]

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Patients with psoriasis are more likely to have autoimmune diseases than the general population. In a recent study conducted by Wu et al. examining the medical records of 25,341 psoriasis patients from the Southern California Kaiser database, psoriasis was found to be significantly associated with 14 other autoimmune diseases.[3] The link between psoriasis and other autoimmune diseases may result from the shared abnormalities in cytokine pathways[4, 5] and genetic susceptibility loci.[6]

The association between psoriasis and celiac disease has been of recent interest, and a number of studies have evaluated a possible therapeutic effect of a gluten-free diet on psoriasis. Celiac disease is defined as a disease of the small intestine characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia upon exposure to dietary gluten, which is mainly composed of two groups of proteins called glutenins and gliadins. Serum antibody levels including IgA tissue transglutaminase antibody (IgA tTG), IgA endomysial antibody (IgA EMA), IgA antigliadin antibody (IgA AGA), and IgG antigliadin antibody (IgG AGA) are most commonly used as diagnostic markers for celiac disease, with IgA tTG and IgA EMA being the most sensitive and specific markers.[7-9] A large meta-analysis found that IgA tTG has a 96% sensitivity and 95% specificity for the diagnosis of celiac disease in adults, and that IgA EMA has an even higher 97% sensitivity and 100% specificity in adults.[10]

Here, we examine the evidence that psoriasis patients are at increased risk for celiac disease and review studies evaluating the impact of a gluten-free diet on psoriasis improvement.

Methods

We searched the electronic MEDLINE database via PubMed using search terms “psoriasis” combined with “celiac disease”, “celiac sprue”, and “gluten”, respectively. We limited our search to articles available in English and those published between 1960 and 2012. Manual searches of bibliographies of the articles were also performed to identify additional studies to be included. We focused on population-based studies examining the co-occurrence of psoriasis and celiac disease, investigations of celiac disease antibody markers in psoriatic cohorts, and clinical trials examining the therapeutic benefit of a gluten-free diet in psoriasis patients. Twenty-eight articles met our inclusion criteria. For data analysis, we synthesized studies that reported on the number of patients that had positive IgA AGA in psoriasis patients and controls (n=9 studies). In addition, we synthesized studies (n=5) that reported on mean IgA levels in cases of psoriasis compared to controls. Meta-analysis was performed using a random effects model in Stata.

Results

Population Studies

Several studies have found that psoriasis patients are at increased risk for celiac disease. A retrospective cohort study comparing 25,341 psoriasis patients to over 125,000 matched controls in the U.S. Southern California Kaiser Permanente database showed an odds ratio of 2.2 for the association of psoriasis with celiac disease.[3] Similarly, a case-control study comparing 12,502 psoriasis patients to 24,285 age- and sex-matched controls using an

Israeli medical database found the prevalence of celiac disease to be 0.29% in psoriasis patients versus 0.11% in controls ($p<0.001$), corresponding to an odds ratio of 2.73.[11] The converse question, whether patients with celiac disease have increased risk of psoriasis, has also been examined. A cohort of 28,958 biopsy-confirmed celiac disease patients from Sweden was evaluated for risk of future psoriasis compared to 143,910 age and sex-matched controls.[12] The authors found that individuals with celiac disease had a hazard ratio of 1.72 for development of future psoriasis.

Celiac Disease Markers in Psoriasis

Seven studies have reported a positive association between psoriasis and celiac disease markers (Table I). All of these studies compared a group of psoriasis patients to a non-psoriatic control group, with the number of psoriasis patients ranging from 37 to 302. Ojetti *et al*.[13] evaluated 92 consecutive psoriasis patients seen in an Italian dermatology department for the presence of celiac disease antibodies compared to 90 healthy controls. Four of the 92 psoriasis patients (4.3%) were diagnosed with celiac disease based on positivity for IgA EMA antibodies and confirmatory small bowel biopsies showing villous atrophy, compared to none of 90 controls ($p<0.0001$). A Swedish study of 302 patients with psoriasis and 99 reference subjects found that psoriasis patients had elevated IgA AGA levels compared to the reference group, but that IgG AGA did not differ.[14] Four additional studies in Turkey[15], Egypt,[16] Poland,[17] and India[18] also found elevated IgA AGA levels in psoriasis patients compared to controls, and also elevated IgA tTG levels in the latter two studies. Beyond serological testing, a case-control study found that malabsorption was present in 60% (33/55) of psoriatic patients and only 3% (2/65) of controls.[19]

On the other hand, several studies did not find evidence of association between psoriasis and celiac disease (Table II). However, these studies were of smaller size and some did not employ control groups.[20-24] A case-control study of 120 patients with psoriasis tested for both IgA and IgG antigliadin antibodies demonstrated no significant difference in prevalence of antigliadin antibodies between the psoriasis and control groups.[21] Another case-control study of 100 patients with psoriasis, 100 patients with psoriatic arthritis and psoriasis, and 100 age-matched controls in the United States showed no difference in prevalence of abnormal antigliadin antibodies among the 3 groups, suggesting no increased prevalence of abnormal antigliadin antibodies in psoriasis patients.[23] In a case-only study, only 3 of 328 psoriatic patients showed elevated IgA endomysial antibody (EMA) or IgA tissue transglutaminase (tTG) antibodies, and only 1 of the 3 was diagnosed with celiac disease.[22]

To summarize the evidence for celiac disease antibody positivity in psoriasis, we performed a meta-analysis of nine studies which reported the frequency of IgA AGA positivity in psoriasis cases and controls. We found a statistically significant relative risk of having positive IgA AGA in patients with psoriasis compared to controls: summary OR=2.36, 95% CI 1.15-4.83 (Figure 1). Heterogeneity was moderate for this meta-analysis I-squared 59%, suggesting conservative random effects meta-analysis was appropriate. In addition, we synthesized studies (n=5) that reported on mean IgA levels in cases of psoriasis compared to controls. We found a statistically significant standardized mean difference (SMD) in cases

of psoriasis compared to controls: pooled SMD=0.66, 95% CI 0.19-1.13 (Figure 2). Overall, these meta-analyses support the conclusion that psoriasis patients have an increased risk of positivity for serological markers of celiac disease.

Psoriatic Disease Severity and Celiac Disease Antibodies

If psoriasis severity were found to correlate with levels of circulating celiac disease antibodies, this would provide stronger evidence that these antibodies were pathogenically related to psoriasis. Two studies suggested that levels of celiac disease antibodies correlate with psoriasis or psoriatic arthritis severity.[25, 26] In a case-only study of 130 psoriasis patients, a significantly higher proportion of patients with elevated celiac disease markers required systemic immunosuppressants or PUVA phototherapy, indicating that elevated celiac disease markers correlated with increased psoriasis disease severity.[25] Of the nine antibody-positive patients who consented to endoscopy and biopsy, however, only one was diagnosed with celiac disease. In another case-only study of comparable size, psoriatic arthritis patients with higher IgA AGA levels had significantly higher ESR and CRP values and longer durations of morning stiffness as compared to patients with lower IgA AGA levels.[26] In addition, while another case-control study did not show any significant correlation between celiac disease antibody positivity and psoriasis severity, they did find that celiac disease patients had the highest IgA AGA levels, followed by psoriasis patients who had moderate levels, followed by healthy controls who had only weak positive IgA AGA levels.[27]

Gluten-free Diet for the Treatment of Psoriasis

A number of studies have examined the effect of a gluten-free diet (GFD) on psoriasis severity. In one study, the impact of a 3 month GFD was evaluated in 33 psoriasis patients with elevated antigliadin antibodies (AGA) compared to 6 psoriasis patients without elevated AGA. All subjects received a duodenal biopsy prior to start of the GFD. Seventy-three percent of the AGA-positive psoriasis patients showed an improvement in their psoriasis area and severity index (PASI) compared to none of AGA-negative psoriasis patients.[28] After the GFD, AGA values were lower in 82% of the psoriasis patients who improved. Interestingly, 16 of the AGA-positive patients whose psoriasis improved had a pre-GFD duodenal biopsy showing normal histology, suggesting that a gluten-free diet may be beneficial in psoriasis patients with gluten sensitivity (marked by AGA positivity) but not necessarily biopsy-confirmed celiac disease. Limitations of this study include a lack of randomization, small control group, and the possible impact of the placebo effect in producing the study's results.[29] In another clinical trial of 28 patients, a gluten-free diet was shown to decrease the expression of tissue transglutaminase in psoriasis patients with AGA positivity.[30] A case series of 6 psoriasis patients and one patient with palmoplantar pustulosis all of whom had gluten intolerance reported clearance of the skin after a gluten-free diet. There have also been 3 case reports in which psoriasis patients experienced rapid lesion resolution following a gluten-free diet.[31-33]

Another author, however, presented 3 patients who experienced no improvement after 6 months of the same dietary restrictions. Of the 328 psoriasis patients screened in the study,

these 3 showed elevated IgA EMA or IgA tTG antibodies, and 1 was diagnosed with celiac disease.[22]

Based on the above studies, a gluten-free diet may potentially be beneficial in celiac antibody positive psoriasis patients, but additional more well-powered studies are needed to confirm this.

Discussion

It is well established that psoriasis patients are more likely to have concurrent autoimmune diseases, particularly those affecting the gastrointestinal tract such as Crohn's disease and ulcerative colitis.[3, 4] Here we document that another such autoimmune disease is celiac disease, with a recent large study showing that psoriasis patients have 2.2 fold risk of being diagnosed with celiac disease compared to matched controls.[3] We perform a meta-analysis to show that psoriatic populations have an approximately 2.4-fold increased risk of elevated levels of antigliadin antibodies compared to controls. Overall, IgA AGA antibodies were positive in about 14% of psoriasis patients versus 5% of healthy controls. Moreover, in two studies there was a positive correlation between celiac disease antibody positivity and severity of psoriasis or psoriatic arthritis. Interestingly, in these psoriasis patients elevated celiac disease antibodies did not necessarily correspond to a biopsy-confirmed diagnosis of celiac disease, suggesting that psoriasis may be associated with gluten sensitivity (marked by antibody positivity) but not necessarily gluten enteropathy.

Regarding the benefit of a gluten-free diet (GFD) in psoriasis patients, two small clinical trials showed a decrease in serological markers of celiac disease after GFD and one showed a significant reduction in the PASI (Psoriasis Area Severity Index). Three case reports also documented resolution of psoriasis after GFD.

Based on the available evidence, we recommend that providers verbally screen their psoriasis patients for symptoms of gluten sensitivity such as diarrhea, flatulence, fatigue, and history of iron-deficiency anemia. Positive symptoms should be followed up with antibody testing, with IgA EMA or IgA tTG recommended as the most sensitive and specific tests. In patients with positive antibody tests, a trial of a gluten-free diet may be considered.

The pathogenesis of psoriasis and celiac disease may involve shared biological mechanisms. Genome-wide association studies of psoriasis and celiac disease have revealed that these two diseases share genetic susceptibility loci at eight genes, including at *TNFAIP3*, *RUNX3*, *ELMO1*, *ZMIZ1*, *ETS1*, *SH2B3*, *SOCS1*, and *UBE2L3*.[34-36] These genes regulate innate and adaptive immune responses. Although celiac disease is associated with autoantibody formation typical of the Th2 axis, immunologic studies of celiac disease indicate that Th1 cells[37, 38], Th17 cells[39], gamma-delta T cells, and NK-like cells play an important role in disease pathogenesis[40]. Psoriasis has been similarly linked to Th1 cells, Th17 cells, gamma-delta T cells. Additional hypotheses linking psoriasis to celiac disease include increased intestinal permeability present in both conditions[41, 42] and the idea that psoriasis in celiac disease patients can be induced by vitamin D deficiency.[31, 41-46]

A pilot study by Skavland et al. sought to determine whether wheat antigens could serve as an immunologic trigger in psoriasis patients. The study exposed peripheral blood mononuclear cells from 37 psoriasis patients and 37 controls to various wheat proteins/peptides in vitro and measured proliferation responses. They found that the p62-75 peptide induced a significant response more frequently in the psoriasis patients compared to controls ($p<0.05$). Several wheat antigens were able to induce expression of the skin homing marker cutaneous lymphocyte antigen (CLA). The authors concluded that certain wheat protein antigens may be important to a subgroup of psoriasis patients, who could benefit from a gluten-free diet.[47]

Conclusion

Epidemiological and clinical studies suggest there is an association between psoriasis, celiac disease, and celiac disease markers. There is early evidence to suggest that a gluten-free diet may benefit some psoriasis patients, but further trials in defined populations are needed. Still, clinicians may want to question their psoriasis patients about symptoms of celiac disease including diarrhea, flatulence, fatigue, and history of iron-deficiency anemia. Positive symptoms should prompt clinicians to test for IgA EMA or IgA tTG antibodies, with positive antibody results suggesting the potential benefit of a gluten-free diet.

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Abbreviations and Acronyms

IgA EMA	IgA endomysial antibody
IgA tTG	IgA tissue transglutaminase antibody

IgA AGA	IgA antigliadin antibody
IgG AGA	IgG antigliadin antibody
GFD	gluten-free diet
IL	interleukin
TNF	tumor necrosis factor
IFN	interferon

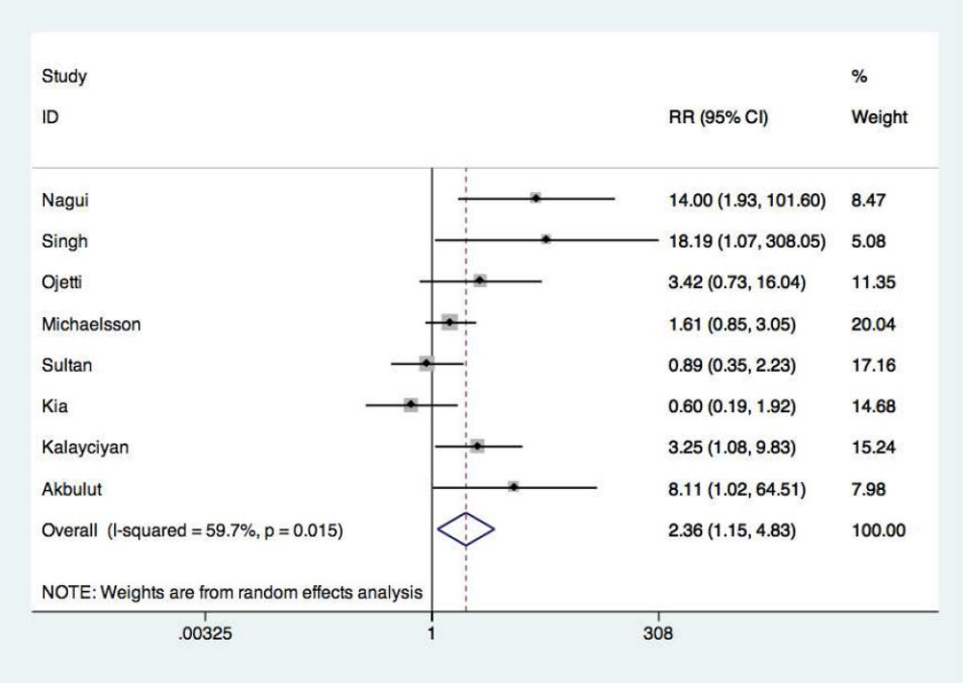

Figure 1.

Forest plot comparing odds ratio of testing positive for celiac IgA antigliadin antibodies in psoriasis patients versus controls.

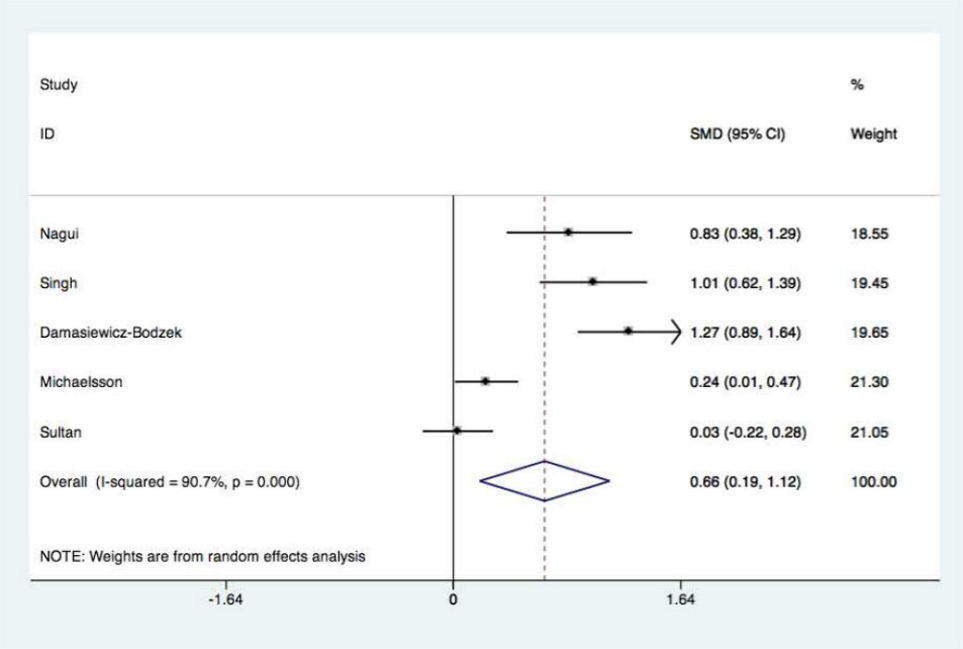

Figure 2.

Forest plot comparing the standardized mean difference of celiac IgA antigliadin antibody levels in psoriasis patients versus controls.

Table I

Studies showing a positive association between psoriasis and celiac disease or celiac disease markers

Study	Study Design	Region	Size/Population	Celiac Disease Markers	Key Results
Michaelsson et al. 2003	Clinical Trial	Sweden	28 AGA-positive Pso patients put on 3-month GFD	IgA tTG	Decrease in IgA tTG (p=0.0079) following GFD
Michaelsson et al. 2000	Clinical Trial	Sweden	30 AGA-positive and 4 AGA-negative Pso patients put on 3-month GFD	IgA AGA IgG AGA ECP PASI	Following GFD: Decrease in PASI in AGA-positive Pso patients after 3-month GFD; No SS PASI change in AGA-negative patients; Overall decrease in IgG AGA (p=0.041); no IgA SS AGA change in either group
Wu etal. 2012	Retrospective Cohort Study	USA	25,341 Pso patients	CD prevalence from hospital system database	2.2 odds ratio for Pso patients to development CD
Ludvigsson 2011	Retrospective Cohort Study	Sweden	28,958 CD patients 143,910 controls	ICD diagnosis of Pso	1.72 hazard factor and 57/100,000 excess risk of developing Pso in CD patients
Nagui etal. 2011	Case-Control	Egypt	41 Pso patients 41 controls	IgA AGA IgA tTG IgA EMA	Higher overall prevalence of IgA AGA, tTG, EMA in Pso group but only IgA AGA was SS (p<0.001)
Singh etal. 2010	Case-Control	India	56 Pso patients 60 controls	IgA AGA IgG AGA IgA tTG HLA Cw6	Elevated IgA AGA (p<0.05), IgG AGA (p<0.05), IgA tTG (p<0.05), HLA Cw6 (p<0.05) in Pso vs. control group
Birkenfeld et al. 2009	Case-Control	Israel	12,502 Pso patients 24,285 controls	CD prevalence from disease registry	CD in 0.29% of Pso patients vs. 0.11% of controls (p<0.001)
Damasiewicz-Bodzek and Wielkoszynski 2008	Case-Control	Poland	67 Pso patients 30-85 controls	Guinea pig tTG Human tTG IgA AGA IgG AGA IgA EMA	Elevated pig IgA tTG, IgG tTG, human IgA tTG, and IgA AGA in Pso group (p<0.05)
Ojetti etal. 2006	Case-Control	Rome	55 Pso patients 65 controls	D-xylose absorption (marker for malabsorption)	SS D-xylose absorption difference (p<0.001) between Pso and control group
Ojetti etal. 2003	Case-Control	Italy	92 Pso patients 90 controls	IgA AGA IgG AGA IgA EMA IgA tTG	Elevated IgA AGA, EMA, tTG CD markers in Pso (p<0.0001) vs. control group
Michaelsson etal. 1993	Case-Control	Sweden	302 Pso patients 99 controls	IgA AGA IgG AGA IgG IgA IgM ARA EMA	Elevated IgA AGA in males only (p=0.03), but not overall for Pso vs. control group (p=0.09)
Woo et al. 2004	Case-Only	Ireland	130 Pso patients	IgA AGA IgG AGA IgA tTG IgA EMA	SS correlation between IgG AGA + PUVA therapy (p=0.03); between elevated CD antibodies + need for immuno-suppressant therapy (p=0.04); elevated CD antibodies correlated with increased Pso severity
Lindqvist et al. 2002	Case-Only	Sweden	109 psoriatic arthritis patients	IgA AGA IgG AGA IgA EMA IgM IgA CRP ESR	Elevated IgA AGA (p<0.0005), IgA (p<0.0001); Elevated CRP and ESR (P=0.037) if elevated IgA AGA (P=0.049); Decreased IgM (p<0.0001) Higher IgA AGA correlated with higher ESR and CRP and longer duration of morning stiffness

Study	Study Design	Region	Size/Population	Celiac Disease Markers	Key Results
Addolorato et al. 2003	Case Report	Italy	CD patient with concurrent Pso	IgA AGA IgG AGA Total IgA IgA EMA	Increased total IgA in Pso patient; Complete psoriasis lesion resolution following GFD for 1 month
Frikha et al. 2012	Case Report	Tunisia	Pso patient presenting with osteomalacia	AGA	Complete resolution of symptoms after following GFD for 1 month
Akbulut et al. 2013	Case control	Turkey	37 Pso patients 50 controls	IgA AGA IgG AGA IgA tTG IgA EMA	Elevated IgA AGA in psoriasis patients compared to controls and significant difference increase in mean IgA AGA between psoriasis patients and controls ($p<0.05$)

Legend

AGA = Antigliadin Antibodies
ARA = Antireticulin Antibodies
CD = Celiac Disease
EMA = Antiendomysial Antibodies
ECP = Eosinophilic Cationic Protein
GFD = Gluten-free diet
Pso = Psoriasis
tTG = Antitissue Transglutaminase Antibodies

Table II

Studies without evidence for an association between psoriasis and celiac disease markers.

Study	Study Type	Region	Size/Population	Celiac Disease Markers	Key Results
Sultan et al. 2010	Case-Control	Kashmir	120 Pso patients 120 controls	IgA AGA IgG AGA	No SS differences in AGAs between Pso vs. control groups
Montesu et al. 2010	Case-Control	Italy-Sardinia	100 Pso patients 100 controls	IgA tTG	Elevated IgA tTG in Pso group, but not SS
Kiaet al. 2007	Case-Control	USA	100 Pso patients 100 Psoriatic arthritis patients 100 controls	IgA AGA IgG AGA	No SS difference in AGAs among patients with psoriasis (14%), psoriasis and psoriatic arthritis (18%), and controls (19%)
Kalayciyan and Kotogyan 2006	Case-Control	Turkey	127 Pso patients 31 controls 6 CD patients	IgA AGA IgG AGA	Elevated IgA AGA in 16.5% Pso vs. 9.6% controls, but not SS CD group had highest IgA AGA; Pso had moderate IgA AGA; controls had lowest IgA AGA
Cardinali et al. 2002	Case-Control	Mediterr anean	39 Pso patients 39 controls	IgA AGA IgG AGA IgA tTG IgA EMA ECP IgE	No SS difference in AGAs, IgA tTG, or IgA EMA in Pso vs. control group; only elevated ECP and IgE in Pso vs. control group
Zamani et al. 2010	Case-Only	Iran	328 Pso patients	IgA tTG IgA EMA	No IgA tTG or IgA EMA elevation in Pso patients; no improvement following GFD in 3 IgA tTG- or EMA-positive patients, including 1 with CD
de Vos et al. 2009	Case-Only	Netherlands	76 Pso patients	IgA AGA	IgA AGA not elevated in Pso patients

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