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Positivity of celiac disease–specific antibodies and non-celiac hypersensitivity in psoriasis

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Abstract

Introduction: Plaque psoriasis and celiac disease are multisystemic diseases. The association of psoriasis and enteropathy with histological changes similar to celiac disease has already been described, and it has also been found that a gluten-free diet improves psoriatic changes. This study assesses the relationship between celiac disease antibodies and psoriasis.
Methods: The study included 112 participants: 60 with psoriasis in a test group and 52 healthy subjects in a control group. Within the psoriasis group, participants were further divided into two subgroups: one consisting of patients with both psoriasis and psoriatic arthritis ($n = 17$) and another comprising patients with psoriasis alone ($n = 43$). After informed consent was obtained, the Dermatology Life Quality Index (DLQI) score and Psoriasis Area and Severity Index (PASI) score were evaluated. Laboratory tests included assessment of anti-deaminated gliadin peptide antibodies (DGP), anti-gliadin antibodies (AGA), and anti-tissue transglutaminase antibodies (tTG).
Results: Immunoglobulin G (IgG) and immunoglobulin A (IgA) DGP antibodies were detected more frequently and at higher serum concentrations in patients with psoriasis compared to healthy controls ($p = 0.03$, $p = 0.04$, respectively). Similarly, elevated levels of IgG-tTG antibodies ($p = 0.003$) and IgA-DGP antibodies ($p = 0.02$) were observed in the same test group.
Conclusions: A relationship between positivity to celiac disease antibodies and psoriasis, particularly with regard to AGA, has been identified. Further studies are required to elucidate the nature, pathophysiology, and significance of these findings.

Keywords: psoriasis, celiac disease–specific antibodies, non-celiac hypersensitivity, anti-gliadin antibodies

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Introduction

Plaque psoriasis is a chronic immune-mediated inflammatory skin disease that affects approximately 2% to 3% of the global population (1). The pathogenesis of psoriasis involves a complex interaction of systemic pro-inflammatory events as well as environmental and genetic factors. The basic feature of psoriasis is sustained inflammation that leads to uncontrolled proliferation of keratinocytes and their disturbed differentiation (2).

Celiac disease is also a multisystemic disease. It is caused by the intertwining of genetic predisposition, immune response, and gluten. Gluten is the most important factor for the development of celiac disease and subsequent diagnosis, after decades of gluten exposure leading to long-term consequences of malabsorption and complications (3). Proline and glutamine are the most important amino acids in gluten. The high proportion of proline makes gluten resistant to degradation by gastrointestinal enzymes, and large immunogenic gluten peptides are produced, which reach the intestinal mucosa and stimulate the inflammatory response (4). Impaired immune response (i.e., loss of gluten tolerance) is evident in celiac disease, and a constant bowel inflammatory process leads to atrophy of the small intestine mucosa, resulting in impaired absorption.

Over the past 2 decades, the widespread utilization of serological tests has notably contributed to the heightened diagnosis of celiac disease. The initial serological markers, anti-gliadin antibodies (AGA), have since been replaced by considerably more specific antibodies, while still retaining their significance in identifying non-celiac hypersensitivity (5). Today, the serological diagnosis of celiac disease is based on highly predictive tests, including endomysial antibodies (EMA), anti-deaminated gliadin peptide antibodies (DGP), and anti-tissue transglutaminase antibodies (tTG). These antibodies belong to the immunoglobulin A (IgA) and immunoglobulin G (IgG) classes, but only IgA antibodies can be considered highly specific and sensitive for celiac disease. EMA are highly sensitive and specific; however, they typically appear several years after the onset of the disease, explaining their negative findings in childhood. TTG are highly sensitive and specific, making them an excellent choice for initial screening. IgG-DGP antibodies have demonstrated utility in diagnosing celiac disease in early childhood (6). Nevertheless, the central role in diagnosing celiac disease still lies in the morphological changes of the mucosa, which can be detected through histopathological examination.

Certain diseases exhibit an unexpectedly higher prevalence among patients with celiac disease. Those include genetic diseases such as Down syndrome, Turner syndrome, and Williams syndrome; neurological diseases such as cerebellar ataxia, multiple sclerosis, and cerebral atrophy; and autoimmune diseases such as type 1 diabetes, autoimmune thyroid disease, autoimmune hepatitis, dermatitis herpetiformis, Addison's disease, alopecia, psoriasis, and Sjögren's syndrome (7). The diagnosis of these celiac disease–related conditions (e.g., autoimmune thyroiditis, dermatitis herpetiformis, type 1 diabetes mellitus, etc.) is significant due to the possible disappearance of symptoms by introducing a gluten-free diet, which prevents

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complications and improves the clinical course of these diseases (7, 8). Likewise, the association of psoriasis and enteropathy with histological changes similar to celiac disease was first described by Marks and Shuster in 1971 (9). Numerous epidemiological studies have been conducted in recent years, with varying results, primarily due to small samples, different populations, or the lack of a control group (10–13). The presence of AGA, serum eosinophil cations, and duodenal inflammation have been reported in patients with psoriasis (14–16). Furthermore, it has been found that a gluten-free diet improves psoriatic changes (17–20). A study by Woo et al. observed an association between antibodies to celiac disease and the severity of psoriasis (21). In a large cohort study, Ludvigsson et al. demonstrated that celiac patients are at higher risk for developing psoriasis before and after celiac disease is diagnosed (22). Furthermore, Ungprasert et al. published the results of the first systematic review and meta-analysis and showed that psoriasis patients are three times more likely to develop celiac disease (23).

The aim of our research was to determine the prevalence of IgA- and IgG-AGA and IgA- and IgG-tTG in patients with psoriasis, and to determine and clarify the relationship between serum concentrations of these antibodies and the incidence and disease severity of psoriasis.

Methods

The research was designed as a case-control study and conducted at the Department of Dermatology and Venereology, Osijek University Hospital, between December 2017 and June 2019. It received approval from both the Ethics Committee of Osijek University Hospital (R2: 19189-4/2017) and the Ethics Committee of the Faculty of Medicine at Josip Juraj Strossmayer University in Osijek (class 602-04/18-08/07, no. 2158-61-07-18-05).

The study included patients under the age of 90 years with a histological diagnosis of plaque psoriasis, either with or without psoriatic arthritis, who provided their informed consent to participate in the study. The control group consisted of healthy individuals over age 18 with no evidence of psoriasis.

Exclusion criteria were as follows: patients with other forms of psoriasis (erythrodermic, pustular, guttate); patients under the age of 18 years; patients that refused to give informed consent to participate in the study; patients with spondyloarthropathies, rheumatoid arthritis, autoinflammatory diseases, hyperparathyroidism, thyroid diseases, renal insufficiency, malignant diseases, alcoholism, liver diseases, or malabsorption; and relatives of subjects from the test and control groups.

Demographic and clinical data

Basic identification and demographic data, such as first name, last name, sex, and age, were recorded for patients with psoriasis and for the control group. Patient history data were collected, which covered the onset of the disease, any coexisting comorbidities, the presence of psoriatic arthritis, and medications taken. Involvement of the skin and the disease severity were evaluated in the psoriasis group using the Psoriasis Area and Severity Index (PASI) score (24). In addition, the psoriasis group was categorized into three subgroups based on the PASI score, with scores of 0–10 classified as mild, 10–20 as moderate, and 20 or higher as severe (25). The impact of psoriasis on the patient's daily physical, mental, and social life was determined using the Dermatology Life Quality Index (DLQI) scale (26).

Laboratory tests

Blood samples were obtained from the cubital vein during outpatient examinations conducted between 8 and 10 am. For the analytes, blood was drawn into a test tube designed for biochemical tests without anticoagulants (a vacutainer with a red cap, manufactured by Bacton Dickinson). One hour after blood collection, the test tube was centrifuged for 10 minutes in a laboratory centrifuge at 3,000 revolutions per minute to separate the serum. The separated serum portion was then stored in a refrigerator at a temperature of –20 °C until the analysis. The serum was subjected to testing for concentrations of the following antibodies: IgA- and IgG-AGA, IgA- and IgG-tTG, and IgA- and IgG-DGP. The methods employed to determine antibody concentrations were as follows.

IgA- and IgG-AGA were assessed using a method based on the xMAP® Luminex technology Bead-based Multiplex Assay, using the Luminex 200 immunochemical system (Luminex Corporation, Austin, Texas, USA, and Theradiag Reagents, Croissy Beaubourg, France). Serum antibody concentrations greater than 20 AU/ml were considered positive.

IgA- and IgG-tTG were determined using a method based on the xMAP® technology Luminex Bead-based Multiplex Assay with the Luminex 200 immunochemical system. Serum concentrations above 20 AU/ml were considered positive.

IgA- and IgG-DGP were measured using a method based on xMAP® Luminex Bead-based Multiplex Assay technology with the Luminex 200 immunochemical system. Serum concentrations exceeding 20 AU/ml were regarded as positive.

Statistical analysis

Categorical data were represented by absolute and relative frequencies. Differences between categorical variables were tested with the chi-squared test and, if necessary, with Fisher's exact test. The normality of the distribution of numerical variables was tested with the Shapiro–Wilk test. Numerical data were described by the median and the limits of the interquartile range. The means of the numerical variables of interest were estimated with 95% confidence intervals. The Mann–Whitney *U* test (with the Hodges–Lehmann median difference) was used to test the differences in numerical variables between two independent groups of respondents. The Kruskal–Wallis test (post-hoc Conover test) was used to test differences between three or more independent groups. The association of numerical variables was assessed with the Spearman correlation coefficient ρ (rho). All *p* values are two-sided. The significance level was set at alpha = 0.05. The following statistical programs were used for data analysis: MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium; 2020) and SPSS (IBM Corp., Armonk, NY, USA, 2015).

Results

Patient characteristics

The research was conducted on 112 subjects, of whom 52 (46.4%) were subjects from the control group and 60 (53.6%) were patients with psoriasis. There was no statistically significant difference in the distribution of subjects by sex between the psoriasis and control groups (x^2 test, $p = 0.845$). The median age of the subjects was 49 years (interquartile range 39 to 58 years) in a range from 23 to 88 years. There were 32 men and 20 women in the control group.

The median age of the control group was 47.5 years (interquartile range 38 to 57 years).

There was no statistically significant difference in age between the patients in the test group and the control group (Mann–Whitney *U* test, $p = 0.389$). Furthermore, 43 (71.7%) of the patients suffered from plaque psoriasis, and 17 (28.3%) suffered from both psoriatic arthritis and plaque psoriasis. Patients with psoriatic arthritis had a longer median disease duration of 240 months (interquartile range: 138–333 months) compared to those with plaque psoriasis (Mann–Whitney *U* test, $p = 0.005$). Regarding therapy, the majority received local treatment (50%), whereas 15 (25%) patients were treated with systemic or biological therapies. The median duration of psoriasis was 120 months, ranging from 4 months to 600 months (50 years). PASI scores ranged from 0 to 47, and DLQI scores ranged from 0 to 25. Additional patient information is presented in Tables 1 and 2.

Antibody profile

Regarding AGA, concentrations of IgA-class antibodies were significantly higher in patients, median 6 AU/ml, compared to the healthy control group, with a median IgA-AGA of 2.5 AU/ml (Mann–Whitney *U* test, $p = 0.04$). Furthermore, IgG-class antibody concentrations were significantly higher in patients, median 3.5 AU/ml, compared to the control group, with a median of 1 AU/ml (Mann–Whitney *U* test, $p = 0.03$; Table 3).

Furthermore, 20 patients (33.3%) had positive IgA-AGA, which was significantly higher compared to the healthy control group, in which 15 (25.0%) patients were positive (x^2 test, $p = 0.001$). Significantly more patients, 15 of them (25.0%), had positive IgG-AGA, compared to the control group, in which two (3.8%) were positive (x^2 test, $p = 0.002$; Fig. 1).

There were no significant differences in IgA- and IgG-AGA when considering the duration of the disease and PASI index (Table 4).

Regarding antibodies to tissue transglutaminase tTG, concentrations of IgG-class antibodies were significantly higher in patients, median 1 AU/ml, compared to the control group (Mann–Whitney *U* test, $p = 0.003$). There were no significant differences between the groups in the serum concentrations of IgA-tTG (Table 5).

Table 1 | Height, mass, and body mass index differences between control group and psoriasis patients.

Variable	Median (interquartile range)		Difference*	95% CI	*p*†
	Control	Psoriasis			
Height, cm	168.0 (164.0–175.8)	173.5 (165.3–180.0)	4	0–7	0.08
Weight, kg	76.5 (64.0–91.5)	90.0 (75.0–106.3)	11	4–18	0.004
Body mass index, kg/m²	26.7 (23.0–29.7)	29.3 (25.2–35.2)	3.01	0.8–5.2	0.01

*Hodges–Lehmann median difference; †Mann–Whitney *U* test.

Table 2 | Distribution of subjects by consumption of nicotine products and alcohol, physical activity, diagnosis and therapy by group.

Factor	Patients, *n* (%)			*p**
	Control	Psoriasis	Total	
Nicotine consumption	19 (36.5)	22 (36.7)	41(36.6)	0.99
Alcohol consumption	17 (32.7)	25 (41.7)	42 (37.5)	0.33
Physical activity	12 (23.1)	28 (46.7)	40 (37.5)	0.009
Diagnosis				
Plaque psoriasis	—	43 (71.7)	43 (71.7)	—
Psoriatic arthritis	—	17 (28.3)	17 (28.3)	
Therapy				
Local	—	30 (50.0)	30 (50.0)	—
Systemic therapy	—	15 (25.0)	15 (25.0)	
Biologic therapy	—	15 (25.0)	15 (25.0)	

*x^2 test.

All patients had a negative finding of IgA-tTG, and only one patient from the psoriasis group had a positive finding of IgG-tTG (Table 6).

Regarding DGP, concentrations of IgA-DGP were significantly higher in patients, median 1.5 AU/ml, compared to the healthy control group (Mann–Whitney *U* test, $p = 0.02$). There were no significant differences between the groups in the serum concentrations of IgG-DGP (Table 7).

In the psoriasis group, significantly more patients, nine of them (15.0%), had positive IgA-DGP, compared to the control group, where one (1.9%) of the patients was positive (Fisher's exact test, $p = 0.02$). There was no significant difference in the distribution of patients according to IgG-DGP by groups (Table 8).

Table 3 | Difference in serum concentrations of anti-gliadin antibodies.

Antibody (AU/ml)	Median (interquartile range)		Difference*	95% CI	*p*†
	Control (*n* = 52)	Psoriasis (*n* = 60)			
IgA-AGA	2.5 (1.5–8.0)	6.0 (1.0–32.5)	3	0 to 8	0.04
IgG-AGA	1.0 (0.0–3.5)	3.5 (0.5–14.0)	1	0 to 4	0.03

IgA-AGA = immunoglobulin A anti-gliadin antibodies, IgG-AGA = immunoglobulin G anti-gliadin antibodies.
*Hodges–Lehmann median difference; †Mann–Whitney *U* test.

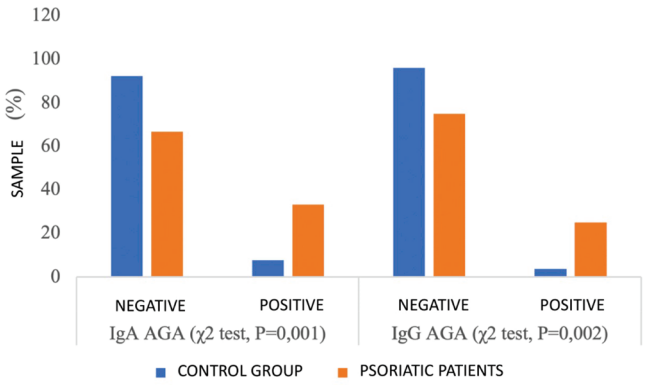

Figure 1 | Distribution of subjects by status of anti-gliadin antibodies by group. IgA-AGA = immunoglobulin A anti-gliadin antibodies, IgG-AGA = immunoglobulin G anti-gliadin antibodies.

Table 4 | Difference in psoriasis duration and Psoriasis Area and Severity Index (PASI) by immunoglobulin A and immunoglobulin G anti-gliadin antibodies (sample *n* = 60).

Antibody (AU/ml)	Duration, months	PASI index
IgA-AGA		
Negative, median (interquartile range)	120 (24–240)	8 (2.5–15.8)
Positive, median (interquartile range)	132 (18–246)	10.8 (4.6–22.1)
Difference*	0	3
95% CI	−72 to 72	−2 to 9
p†	0.98	0.29
IgG-AGA		
Negative, median (interquartile range)	96 (14–120)	15.3 (4.3–21.4)
Positive, median (interquartile range)	180 (12–333)	8.6 (4.5–15.2)
Difference*	72	−2.4
95% CI	−24 to 216	−11.9 to 5.5
p†	0.17	0.58

PASI = Psoriasis Area Severity Index, IgA-AGA = immunoglobulin A anti-gliadin antibodies, IgG-AGA = immunoglobulin G anti-gliadin antibodies.
*Hodges–Lehmann median difference; †Mann–Whitney *U* test.

Table 5 | Difference in serum concentrations of antibodies to tissue transglutaminase.

Antibody (AU/ml)	Median (interquartile range)		Difference*	95% CI	*p*†
	Control (*n* = 52)	Psoriasis (*n* = 60)			
IgA-tTG	0 (0–0)	0 (0–1)	0	0 to 0	0.06
IgG-tTG	0 (0–1)	1 (0–2)	0	0 to 1	0.003

IgA-tTG = immunoglobulin A anti-tissue transglutaminase antibodies, IgG-tTG = immunoglobulin G anti-tissue transglutaminase antibodies.
*Hodges–Lehmann median difference, †Mann–Whitney *U* test.

Table 6 | **Distribution of subjects based on anti-tissue transglutaminase antibody status between control and psoriasis groups.**

Antibody	Patients, *n* (%)			*p**
	Control	Psoriasis	Total	
IgA-tTG				
Negative	52 (100.0)	60 (100.0)	112 (100.0)	
Positive	0 (0.0)	0 (0.0)	0 (0.0)	
IgG-tTG				
Negative	52 (100.0)	59 (98.3)	111 (99.1)	› 0.99
Positive	0 (0.0)	1 (1.7)	1 (0.9)	
Total	52 (100.0)	60 (100.0)	112 (100.0)	

IgA-tTG = immunoglobulin A anti-tissue transglutaminase antibodies, IgG-tTG = immunoglobulin G anti-tissue transglutaminase antibodies.
*Fisher's exact test.

Table 7 | **Difference in serum concentrations of antibodies to deaminated gliadin peptide.**

Antibody (AU/ml)	Median (interquartile range)		Difference*	95% CI	*p*†
	Control (*n* = 52)	Psoriasis (*n* = 60)			
IgA-DGP	1.0 (0.0–1.0)	1.5 (0.0–4.5)	0	0 to 1	0.02
IgG-DGP	1.0 (0.0–1.5)	1.0 (0.0–2.0)	0	0 to 1	0.39

IgA-DGP = immunoglobulin A anti-deaminated gliadin peptide antibodies, IgG-DGP = immunoglobulin G anti-deaminated gliadin peptide antibodies.
*Hodges–Lehmann median difference; †Mann–Whitney *U* test.

Table 8 | **Distribution of subjects to the status of anti-deaminated gliadin peptide antibodies by group.**

Antibody	Patients, *n* (%)			*p**
	Control	Psoriasis	Total	
IgA-DGP				
Negative	51 (98.1)	51 (85.0)	102 (91.1)	0.02
Positive	1 (1.9)	9 (15.0)	10 (8.9)	
IgG-DGP				
Negative	52 (100.0)	57 (95.0)	109 (97.3)	0.25
Positive	0	3(5.0)	3 (2.7)	
Total	52 (100.0)	60 (100.0)	112 (100.0)	

IgA-tTG = immunoglobulin A anti-tissue transglutaminase antibodies, IgG-tTG = immunoglobulin G anti-tissue transglutaminase antibodies.
*Fisher's exact test.

Psoriatic arthritis

The difference in the value of serum concentrations of AGA between psoriasis patients with or without psoriatic arthritis was not significant (Table 9). There was no significant difference in the value of serum concentrations of tTG considering the form of the disease (Table 10). However, IgA-DGP were significantly higher in the group of patients with psoriatic arthritis compared to patients with plaque psoriasis only (Mann–Whitney *U* test, $p = 0.005$; Table 9).

Regarding the correlation of disease severity with general symptoms, inflammatory markers, and antibodies, based on the PASI index, the sample was divided into those with mild (0–10), medium-severe (10–20), and severe (> 20) forms of the disease. Men had a significantly more severe form of the disease compared to women (Fisher's exact test, $p = 0.01$), whereas there was no significant difference in the severity of the disease in relation to whether it was plaque psoriasis or psoriatic arthritis. There was no correlation between the severity of the disease and the antibody profile (Table 10).

Table 9 | **Difference in serum concentrations of antibodies to gliadin, tissue transglutaminase, and deaminated gliadin peptide by type of disease.**

Antibody (AU/ml)	Median (interquartile range)		Difference*	95% CI	*p*†
	Only plaque psoriasis (*n* = 43)	With psoriatic arthritis (*n* = 17)			
IgA-AGA	6 (1.0–20.8)	11 (1.8–54.5)	3	−2 to 13	0.32
IgG-AGA	1 (0.0–9.3)	8 (1.0–15.5)	4	0 to 9	0.07
IgA-tTG	0 (0.0–1.0)	0 (0.0–1.0)	0	0 to 0	0.34
IgG-tTG	1 (0.0–2.0)	1 (0.0–2.0)	0	−1 to 1	0.91
IgA-DGP	1 (0.0–2.0)	4 (1.0–16.0)	3	1 to 5	0.005
IgG-DGP	1 (0.0–2.0)	1 (0.8–4.0)	1	0 to 1	0.12

IgA-AGA = immunoglobulin A anti-gliadin antibodies, IgG-AGA = immunoglobulin G anti-gliadin antibodies, IgA-tTG = immunoglobulin A anti-tissue transglutaminase antibodies, IgG-tTG = immunoglobulin G anti-tissue transglutaminase antibodies, IgA-DGP = immunoglobulin A anti-deaminated gliadin peptide antibodies, IgG-DGP = immunoglobulin G anti-deaminated gliadin peptide antibodies.
*Hodges–Lehmann median difference; †Mann–Whitney *U* test.

Table 10 | **Correlation of disease severity with antibody profile.**

Antibody	Number (*n*) of patients by disease severity (%)				*p**
	Mild (34)	Mild to severe (13)	Severe (13)	Total (60)	
IgA-AGA					
Negative	24 (71)	9/13	7/13	40 (67)	0.57
Positive	10 (29)	4/13	6/13	20 (33)	
IgG-AGA					
Negative	25 (74)	9/13	11/13	45 (75)	0.78
Positive	9 (26)	4/13	2/13	15 (25)	
IgA-tTG					
Negative	34 (100)	13/13	13/13	60 (100)	—
Positive	0 (0)	0/13	0/13	0 (0)	
IgG-tTG					
Negative	34 (100)	13/13	12/13	59 (98)	0.43
Positive	0	0	1/13	1 (2)	
IgA-DGP					
Negative	29 (85)	12/13	10/13	51 (85)	0.70
Positive	5 (15)	1/13	3/13	9 (15)	
IgG-DGP					
Negative	32 (94)	12/13	13/13	57 (95)	› 0.99
Positive	2 (6)	1/13	0	3 (5)	
Total	34 (100)	13/13	13/13	60/100	

IgA-AGA = immunoglobulin A anti-gliadin antibodies, IgG-AGA = immunoglobulin G anti-gliadin antibodies, IgA-tTG = immunoglobulin A anti-tissue transglutaminase antibodies, IgG-tTG = immunoglobulin G anti-tissue transglutaminase antibodies, IgA-DGP = immunoglobulin A anti-deaminated gliadin peptide antibodies, IgG-DGP = immunoglobulin G anti-deaminated gliadin peptide antibodies.
*Fisher's exact test.

Discussion

In recent years, there has been a significant increase in knowledge about celiac disease, including its pathogenesis, epidemiology, clinical presentation, and diagnostic methods. It is important to note that celiac disease can manifest with a range of extraintestinal symptoms, particularly in atypical forms, which can be categorized into neurological, endocrinological, rheumatological, and dermatological manifestations (27). A study by Humbert et al. classified skin manifestations related to celiac disease into four main groups: autoimmune diseases (such as herpetiform dermatitis), allergic diseases (including urticaria and atopic dermatitis), inflammatory conditions (such as plaque psoriasis), and other conditions (such as chronic ulcerative stomatitis) (28). In addition, sporadic case reports have mentioned other skin conditions that may be associated with celiac disease, such as vitiligo and alopecia areata. The potential connection between celiac disease and psoriasis derives from the fact that patients with psoriasis are more prone to other autoimmune diseases compared to the general population (29). The exact mechanism explaining the association between psoriasis and celiac disease is not yet known, but the following hypotheses have been proposed: increased permeability of the small intestine, found in both psoriasis (30, 31) and celiac disease, is a possible link between the two diseases (32). Furthermore, T cells play a key role in the pathogenesis of psoriasis and celiac disease. Patients with psoriasis have an increased number of CD4+ lymphocytes in the blood, dermis, and epidermis

(33). On the other hand, in celiac disease, gliadin stimulates the sensitization of CD4+ lymphocytes, and this may be the trigger for the appearance of psoriatic changes on the skin.

The main objective of this study was to investigate the potential link between psoriasis, AGA, tTG and DGP. In the past, the assessment of serum antibodies served as a supplementary method, with mucosa biopsies considered the gold standard for diagnosis. However, with the emergence of more specific antibodies, serological diagnostics have gained prominence, making it possible to detect the disease in adults.

In our study, the positivity and serum concentration of IgG- and IgA-AGA was significantly higher in patients suffering from psoriasis and psoriatic arthritis compared to the control group. Regarding the serology of celiac disease, IgG-AGA are more sensitive but less specific than IgA-AGA. Considering the specificity and sensitivity of both these tests, they should be used in pairs. Positive AGA can be found in patients with autoimmune liver diseases, connective tissue diseases, and inflammatory bowel diseases, as well as in healthy subjects (34). Recently, AGA have taken their place in the diagnosis of non-celiac hypersensitivity (35). In their sample of 302 patients with psoriasis, Michaelsson et al. found positive IgA-AGA in 16% of patients. A statistically significant difference between IgG-AGA was not determined in that study. Later, the same group of authors placed 33 AGA-positive patients and six patients negative to the same antibodies on a gluten-free diet for 3 months. The patients that followed a gluten-free diet showed significant improvement, recorded by a decrease in the PASI index. In patients that were negative for AGA, there was no improvement (17). Similar results were obtained in a sample of 97 psoriasis patients by Kolchak et al., who found positive AGA in 14% of patients and in 2% of the control group. After implementing a gluten-free diet, the improvement of psoriatic changes was present in all patients, but a significant decrease in the PASI index was recorded in those with a higher AGA titer (36). In addition, Trancone and Jabri suggest that in some patients psoriasis should be understood as a phenomenon of non-celiac gluten hypersensitivity, which has recently been increasingly recognized and for which efforts have been made to define it as a separate entity. In these patients, the site of gluten immunization is most likely extraintestinal, and tissue transglutaminase is not considered a major antigen because 16% of psoriasis patients have high levels of both IgA- and IgG-AGA in the absence of tTG. Those patients show significant improvement in psoriatic changes when placed on a gluten-free diet (37).

As stated in the introduction, the use of AGA as a test has been almost completely abandoned, and it has been replaced by highly predictive tests such as EMA, DGP, and tTG. Based on this, our study used tTG and DGP, which are known to be more specific tests for the serological diagnosis of celiac disease. Significantly higher serum concentrations of IgG-tTG were recorded in the psoriasis group, whereas there was no difference in IgA antibodies. Results similar to these were published by Nagui et al., whose study found an elevated serum concentration of AGA in the psoriasis group without a statistically significant difference in the positivity of tTG and EMA (14). Higher serum concentrations and positivity of IgA-DGP were also recorded in the psoriasis group. DGP are the newest antibodies in the serological diagnosis of celiac disease. Their use allows higher diagnostic precision compared to AGA. Research has shown that they are less sensitive than EMA and tTG, whereas their specificity is higher than antibodies to tTG. The simultaneous use of antibodies to tTG and DGP is a very effective diagnostic tool for the diagnosis of celiac disease (38). It should also be emphasized that IgA-DGP are not sufficient for the diagnosis of celiac disease (6). However, IgG-DGP have high diagnostic accuracy, comparable to IgA-tTG (39). According to some authors, the use of IgG-DGP is recommended instead of IgA-tTG in patients with IgA deficiency (40). In addition to positive serology, a possible correlation between positive antibodies to celiac disease and the severity of the disease would be additional evidence for the link between antibodies to celiac disease and psoriasis. In this study, no significant difference was recorded in relation to the positivity of IgA- and IgG-AGA regarding the duration of the disease and the PASI index. A study by Akbulut et al. also found a higher positivity of AGA compared to the control group, without correlation with the PASI score and the duration of the disease (10). A study by Lindquist et al., which included patients with psoriatic arthritis and plaque psoriasis, demonstrated a higher prevalence of IgA-AGA compared to the control group (15).

Furthermore, a 2018 review article on dietary recommendations for psoriasis and psoriatic arthritis by Ford et al. (Medical Board of the National Psoriasis Foundation) strongly recommend a gluten-free diet in patients with psoriasis and diagnosed celiac disease as a significant therapeutic option. There is also a recommendation for a 3-month diet that does not contain gluten in patients with positive serological markers for celiac disease. This group of authors certainly recommends screening for celiac disease if patients report gastrointestinal problems or have close relatives with celiac disease (41). Based on the results of our research, in which we found a significant correlation between patients with psoriasis and elevated concentrations of IgA- and IgG-AGA and elevated concentrations of IgA-DGP, without a statistically significant correlation with IgA- and IgG-tTG, we tend to assume that psoriatic changes in patients could be skin manifestations of non-celiac hypersensitivity, according to the theory we described above. On the other hand, in certain cases positive DGP and positive tTG could be a sign of a potential or asymptomatic form of celiac disease, which needs to be confirmed or ruled out by additional diagnostic methods.

In contrast to the previously described studies, a study by Engin et al. (based on the description of the sample and subjects, it was very similar to our study) found that IgA- and IgG-AGA, as well as IgA- and IgG-tTG, were not significantly higher in patients with psoriasis compared to the control, but the authors do not offer an explanation for this. Nonetheless, the authors claim that only hypertensive psoriasis patients had significantly higher IgA-AGA titers compared to normotensive psoriasis patients (4.2 U/ml vs. 2.3 U/ml, $p = 0.005$). It has been shown that adaptive and innate immunity is associated with arterial hypertension by increasing the stiffness of blood vessel walls. Therefore, the possibility of hypertension as a comorbidity is increased in people with psoriasis and celiac disease. Previously unrecognized common human leukocyte antigen (HLA) haplotypes or genome loci may predispose to all three diseases. Furthermore, patients with hypertension probably have poor eating habits rich in gluten, which represents a risk of developing psoriasis and celiac disease. These patients are also prone to obesity, a known risk factor for psoriasis (42).

In this study, the aim was not to investigate the relationship between celiac disease and psoriasis, and so screening for celiac disease was not conducted. Instead, the study explored the relationship between positive celiac disease–specific antibodies and the disease severity of psoriasis. Thus we did not manage to find

a significant correlation between positive antibodies and higher disease severity, which was previously shown (17, 36, 37), but our psoriasis patients did have higher concentrations of antibodies than healthy controls, which still emphasizes the possibility of non-celiac hypersensitivity in psoriasis patients.

A limitation of our study is that no gluten-free diet was implemented for the patients with further follow-up to establish whether it would have any effect on PASI and DLQI. Moreover, EMA was not tested due to technical constraints, which is another limitation of the research. Another possible limitation of the study is its small sample size, and therefore further research is desirable.

Conclusions

Patients with psoriasis have a higher serum concentration of IgG-AGA, IgA-AGA, IgA-DGP, and IgG-tTG compared to healthy patients. Although there was no correlation with the severity of the disease expressed by the PASI index and celiac-specific antibodies in our psoriasis patients, based on previous research as well as our results, we believe that for patients with positive serology for celiac disease it would be advisable to implement a 3-month gluten-free diet. Further research should be conducted to investigate possible benefits of a gluten-free diet in psoriasis patients.

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