

# Association between Coeliac Disease and Psoriasis: Italian Primary Care Multicentre Study

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## Key Words

Psoriasis · Immune-mediated diseases · Coeliac disease · Primary care

## Abstract

**Background:** Studies assessing the association between coeliac disease (CD) and psoriasis show conflicting results. **Objective:** To assess in the primary care setting the prevalence of CD in patients with psoriasis and the response to a gluten-free diet (GFD) in subjects with psoriasis and CD. **Methods:** We enrolled 218 patients with psoriasis and 264 controls. Coeliac screening was carried out in all subjects (Eurospital, Trieste, Italy). In subjects with a positive serology, the diagnosis of CD was confirmed histologically. **Results:** Nine (4.1%) psoriatic patients had positive anti-tissue transglutaminase antibodies compared to only 1 among controls

(0.4%,  $p < 0.05$ ; OR 2.03, 95% CI 1.42–90.11). The diagnosis of CD was confirmed histologically in all 10 subjects. At 6 months GFD was associated with a great improvement of skin lesions in 7 out of 8 patients with psoriasis. **Conclusion:** Our multicentre primary care study showed an high prevalence of CD in psoriasis and an improvement of skin lesions in CD under GFD.

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## Introduction

Coeliac disease (CD) is an immune-mediated gluten-dependent enteropathy characterized by atrophy of the intestinal villi which improves when the causal antigen is removed through a gluten-free diet (GFD). Recent epidemiological studies showed a higher prevalence of CD in

the general population than previously reported at about 1% of the western population [1, 2]. The availability of accurate, noninvasive and widely available serology tests in the last decade has led to a corner in terms of prevalence and clinical patterns of CD [1, 2]. The presentation of CD with the classic picture of a malabsorption syndrome is less common while patients often present with extraintestinal manifestations such as anaemia, persistent hypertransaminasaemia, neurological disorders and a series of autoimmune diseases [1–3]. Among the extraintestinal diseases associated with CD, several skin disorders have been reported; among them dermatitis herpetiformis is the best recognized [4].

Psoriasis is a chronic relapsing autoimmune skin disorder characterized by scaling, erythema and less commonly pustulation. Arthritis is reported in 5–20% of patients affected by psoriasis [5, 6]. In 1971, Marks and Shuster [7] described for the first time a ‘psoriatic enteropathy’ in a small group of patients with severe psoriasis. It was characterized by histological changes similar to those commonly observed in CD [7]. Several studies investigating the possible association between CD and psoriasis were subsequently published. However, due to contrasting data the available results are inconclusive [8–14]. Most of the few available data on the effects of GFD on psoriatic skin lesions are contained in case reports [14–17].

To clarify the link between psoriasis and CD, we assessed (1) the prevalence of CD in patients affected by psoriasis in the Italian primary care setting and (2) the effect of GFD on psoriatic lesions in patients with a diagnosis of CD.

## Methods

Nineteen primary care practices adhering to GIGA-CP (Italian Group for Primary Care Gastroenterology) or SNAMID (National Society of Medical Education in General Practice) participated in this prospective multicentre study. Eleven primary care practices were located in Northern Italy, four in Central and four in Southern Italy, with a total registered population of about 21,700 persons.

Adult (age 18–80 years) patients with a diagnosis of psoriasis as codified in the computerized records of the participating practices were contacted by phone. A baseline evaluation involving an examination by a dermatologist (one for each practice) was performed in all subjects enrolled. Skin biopsy was performed in doubtful cases only. Only patients with a confirmed diagnosis of psoriasis were enrolled.

At enrollment patients underwent a standardized interview in order to assess the characteristics of psoriasis, i.e. type, duration, presence of arthritis, specific ongoing treatments and gastrointes-

**Table 1.** Characteristics of psoriatic patients included in the present study

	Plaque psoriasis	Other types <sup>a</sup>
Patients	187 (86%)	31 (14%)
Age, years	53 ± 12	56 ± 15
Disease duration, years	11 ± 3	13 ± 5
Systemic therapies	29 (16%)	18 (58%)
Arthritis	35 (19%)	8 (25%)
Initial PASI score	9 ± 2	16 ± 4

Figures represent number with percentage in parentheses or mean ± standard deviation.

<sup>a</sup> Inverse/flexural, erythrodermic, pustular, guttate.

**Table 2.** Prevalence of GI symptoms in the patients with psoriasis enrolled in the present study

GI symptoms	n (%)
Heartburn/acid regurgitation	59 (27%)
Dyspepsia	29 (13%)
Nausea/vomiting	9 (4%)
Abdominal pain/discomfort	24 (11%)
Bloating	34 (16%)
Diarrhoea	18 (8%)
Constipation	13 (6%)

tinal (GI) symptoms. The severity of psoriasis was evaluated by means of a standardized clinical index at baseline and at the follow-up visits using the psoriasis area and severity index (PASI) [6]. It combines the severity (erythema, induration and desquamation of the skin) and the overall percentage of the affected area [6].

Age- and sex-matched controls without psoriasis were also recruited. The controls were chosen among patients registered at the same primary care practices across Italy. All subjects gave informed consent to participate in the present study.

Levels of serum anti-tissue transglutaminase (anti-tTG) IgA antibodies were assessed by ELISA (Eurospital, Trieste, Italy) in all cases and controls. Titres above 7 arbitrary units/ml were considered positive. Total IgA antibodies were dosed in all subjects in order to exclude a condition of IgA deficiency. In the presence of total IgA deficiency, anti-tTG IgG antibodies were also determined [18].

If coeliac serological screening resulted positive for CD, the diagnosis was confirmed by histology on biopsy samples taken in the distal duodenum during upper GI endoscopy. Other causes of villous atrophy (i.e. food allergy) were excluded before a definitive diagnosis of CD was made. The severity of histological damage was graded according to the modified Marsh classification [19].

Psoriatic patients with evidence of CD followed a GFD for 6 months, under control by a dietitian who also assessed dietary adherence. The severity of psoriasis lesions was evaluated by a dermatologist using the PASI at 3 and 6 months after starting GFD. Significant clinical improvement of psoriasis was defined by an

**Table 3.** Characteristics of the patients with psoriasis and CD

Patient No.	Sex	Age, years	Type of psoriasis, arthritis	Systemic treatment	GI symptoms	Marsh classification
1	F	49	plaque	–	diarrhoea	IIIa
2	M	60	plaque	–	bloating/dyspepsia	IIIc
3	F	27	plaque	–	bloating/diarrhoea	IIIc
4	F	48	guttate	yes	bloating/diarrhoea	IIIc
5	M	71	plaque arthritis	yes	–	IIIb
6	M	54	plaque	–	diarrhoea	IIIc
7	M	37	plaque	–	bloating/dyspepsia	IIIc
8	F	28	guttate arthritis	yes	heartburn/acid regurgitation	IIIb
9	M	64	plaque	–	–	IIIa

improvement of the PASI of  $\geq 50\%$  (PASI-50) or  $\geq 75\%$  (PASI-75) with respect to the pre-GFD value.

Response and adherence to the GFD was monitored by measuring the levels of serum anti-tTG IgA antibodies in all patients with psoriasis and CD at 6-month follow-up. Statistical analysis using the  $\chi^2$  test was conducted to compare the prevalence of CD in cases and controls. A *p* value  $< 0.05$  was considered statistically significant.

## Results

A total of 612 patients with a diagnosis of psoriasis were identified in the computerized records of the participating primary care practices. Among them, 218 were enrolled (males 111, 51%; mean age  $54 \pm 14$  years). In addition, 264 age- and sex-matched controls without psoriasis (males 121, 46%; mean age  $48 \pm 12$  years) participated in the study.

Table 1 summarizes the main characteristics of the psoriatic patients included in the study. A total of 49% of the 218 enrolled patients reported one or more GI symptoms, the most common being heartburn/acid regurgitation (27%) and bloating (16%) (table 2). Nine out of the 218 patients with psoriasis showed positive serology for CD compared to only 1 out of the 264 controls (4.1 vs. 0.4%; *p*  $< 0.05$ , OR 6.5, 95% CI 1.4–90.1). Histology confirmed the CD diagnosis in all subjects with positivity to anti-tTG antibodies. Table 3 summarizes the characteristics of the patients with psoriasis and CD. Interestingly the majority of the 9 patients with CD had a Marsh IIIc histological pattern accounting for complete villous atrophy; the most prevalent GI symptoms observed were bloating and diarrhoea.

All patients with psoriasis and CD adhered to the GFD and completed the 6-month follow-up. All patients

**Table 4.** Impact of GFD on psoriatic lesions at 3- and 6-month follow-up

Patient No.	3-month follow-up	6-month follow-up
1	lost to follow-up	lost to follow-up
2	PASI-50	PASI-75
3	PASI-75	PASI-75
4	PASI-75	PASI-75
5	PASI-50	PASI-75
6	no skin lesions	no skin lesions
7	PASI-75	PASI-75
8	PASI-75	worsening
9	PASI-75	PASI-75

showed negative results for CD serological screening at 6 months, suggesting strict adherence to the GFD. Ongoing treatments for psoriasis were not modified during the follow-up period. Three months after starting the GFD all patients showed a significant improvement in PASI. The clinical improvement was maintained at 6 months in all patients but one, who experienced a worsening of psoriasis (table 4).

## Discussion

The present study assesses for the first time the prevalence of CD in patients with psoriasis in a primary care setting. It shows a significant epidemiological association between CD and psoriasis in the Italian population. At the 6-month follow-up, GFD was associated with a great improvement in 7 out of 8 patients, suggesting a causal association between the two disorders.

### *Review of the Available Literature*

Most of the available studies investigating the possible association between CD and psoriasis had several limitations or bias leading to inconclusive results: small sample size, lack of controls, low accuracy of serological methods used to screen CD (i.e. anti-gliadin antibodies, AGAs) and the setting, including the design as single-centre studies performed in tertiary centres [8–14, 20].

A recent review of the literature by Bhatia et al. [20] on the available studies assessing the prevalence of serologic markers of CD in psoriasis and the clinical trials evaluating the impact of GFD on psoriatic lesions observed that the majority of the results suggest an association between psoriasis and gluten sensitivity (marked by anti-gliadin IgA positivity), but not necessarily gluten enteropathy [20]. Gluten sensitivity has been distinguished from CD and defined as a reaction to gluten in which allergic and autoimmune mechanisms have been excluded [21]. AGAs may be present, but anti-endomysial/tTG antibodies are negative and the intestinal mucosa is grossly normal. Gluten sensitivity exists as an entity separate from overt CD. Most of these patients do not have CD in any of its forms because they do not have the necessary HLA profile [21].

Only two large clinical trials have been published, both showing an epidemiological link between CD and psoriasis [13, 14]. Birkenfeld et al. [13] analysed the Israeli national medical database: 12,502 adult patients with a diagnosis of psoriasis and a double number of controls were included. In multivariate analysis psoriasis was associated with CD (OR 2.73). However, neither the diagnosis of psoriasis nor CD was validated and the prevalence of CD in study population resulted 0.11%, suggesting underdiagnosis of CD, in contrast with epidemiological studies documenting a prevalence of 1% in the same population. Ludvigsson et al. [14] analysed the registries of 28 pathology departments in Sweden, identifying 28,958 histologically proven patients with CD diagnosed between 1969 and 2008. They demonstrated retrospectively that in the Swedish population, CD was a risk factor for onset of psoriasis (HR 2.05, 95% CI 1.62–2.60). Nevertheless, the authors reported the following limitations: absence of measurement of activity of psoriasis as well as no data on smoking, alcohol consumption and body mass index, which are parameters that may influence the prevalence of psoriasis.

At present, only few data on the effects of GFD on psoriatic symptoms are available, most of them in the form of case reports [15, 16]. In a Swedish study by Michaëls-son et al. [17], 39 patients with psoriasis underwent GFD

for 3 months: 33 with positive AGAs but negative or non-specific histology and 6 with negative serology. Patients with positive AGAs showed a significant improvement of psoriasis (described by PASI improvement) compared to negative AGA cases. The observed clinical improvement correlated with a significant decrease in AGA titres. The results were non-specific since none of the 33 patients with positive AGAs had a diagnosis of CD, rather suggesting gluten sensitivity only.

In the large Swedish study by Ludvigsson et al. [14] the association between CD and psoriasis appeared not to be correlated temporarily since it was proved both before and after the diagnosis of CD. This would suggest that psoriasis was apparently unresponsive to GFD. However, as a crucial limitation of the study the authors reported that no data on dietary compliance were available.

### *Limitations of the Present Study*

In our interventional multicentre study, the patients had a duodenal biopsy-proven diagnosis of CD and adherence to the GFD was verified during the follow-up period. However, the small number of psoriatic patients with evidence of CD cannot be considered a definitive evidence of a causal link between the two disorders through activation of immunological pathways.

Another limitation was that for obvious reasons neither the patients nor the dermatologists who evaluated the PASI scores following the GFD were blinded. It should also be noted that serum anti-tTG IgA used for serological screening of CD has a 67% sensitivity if only partial villous atrophy is present, which characterises about one third of CD patients [22].

### *Physiopathology*

The physiopathologic mechanisms behind the association between psoriasis and CD remain still to be clarified. We hypothesize that the presence of shared genes (at-risk HLA haplotypes), often taken into account to explain the greater prevalence of CD in several autoimmune disorders, might be present in subjects affected by psoriasis [4]. Secondly, CD-related malabsorption may affect psoriasis by causing a vitamin D deficiency status [4]. It is well known that low levels of vitamin D predispose to psoriasis, and that exposure to sun light and topical administration of vitamin D analogues improve psoriatic lesions. This is partly due to immunoregulatory properties of vitamin D [4, 23]. Finally, an abnormal small intestinal permeability common in untreated CD may increase the passage of different immune triggers. T cells are in-

volved in the pathogenesis of both psoriasis and CD. In patients affected by CD, gliadin induces a sensitization of T cells, which may play a role in the pathogenesis of psoriatic lesions [4].

Interestingly, in our study the majority of psoriatic patients with positive serology showed complete villous atrophy. This result is concordant with both hypotheses of vitamin D malabsorption and of abnormal intestinal permeability to immune triggers in CD as a causal link leading to psoriatic lesions.

## Conclusions

Our primary care multicentre study suggests a causal association between CD and psoriasis, encouraging further larger and double-blind interventional clinical trials to confirm these preliminary observations on GFD as an alternative therapy for psoriasis.

## Disclosure Statement

The authors have no conflict of interest to declare.

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