British Journal of Dermatology 2000; **142:** 44–51.

Psoriasis patients with antibodies to gliadin can be improved by a gluten-free diet

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Accepted for publication 19 August 1999

Summary In a previous screening study, 16% of patients with psoriasis had IgA and/or IgG antibodies to gliadin (AGA). The aim of the present study was to evaluate the effect of a gluten-free diet (GFD) in 33 AGA-positive and six AGA-negative psoriasis patients. Of the 33 AGA-positive patients, two had IgA antibodies to endomysium (EmA) and 15 an increased number of lymphocytes in the duodenal epithelium, but in some this increase was slight. Two patients had villous atrophy. A 3-month period on a GFD was followed by 3 months on the patient's ordinary diet. The severity of psoriasis was evaluated with the psoriasis area and severity index (PASI). The examining dermatologists were unaware of the EmA and duodenal biopsy results throughout the study. Thirty of the 33 patients with AGA completed the GFD period, after which they showed a highly significant decrease in mean PASI. This included a significant decrease in the 16 AGA-positive patients with normal routine histology in duodenal biopsy specimens. The AGA-negative patients were not improved. After GFD, the AGA values were lower in 82% of those who improved. There was a highly significant decrease in serum eosinophil cationic protein in patients with elevated AGA. When the ordinary diet was resumed, the psoriasis deteriorated in 18 of the 30 patients with AGA who had completed the GFD period. In conclusion, psoriasis patients with raised AGA might improve on a GFD even if they have no EmA or if the increase in duodenal intraepithelial lymphocytes is slight or seemingly absent.

Key words: duodenum, endomysium, gliadin, gluten-free diet, psoriasis

In the last few years, we have observed 14 patients with severe and/or refractory psoriasis and concomitant, but silent, coeliac disease who showed a long-standing improvement or total remission of their psoriasis when the coeliac disease was revealed and treated with a gluten-free diet (GFD). We have also observed a few psoriasis patients with IgA antibodies to gliadin (AGA) and normal duodenal histopathology who displayed a marked improvement of their psoriasis when they adhered to a GFD and worsening when their ordinary diet was resumed.

It is nowadays generally accepted that gluten sensitivity may be present without a flat small bowel mucosa. Marsh[1] and Marsh and Crowe[2] have demonstrated a spectrum of changes in the gluten-sensitive mucosa and have termed them pre-infiltrative, infiltrative-hyperplastic, flat-destructive and atrophic-hypoplastic.

We therefore considered it important to determine whether gluten sensitivity (ascertained by measurement of serum AGA) is common among psoriasis patients and in such cases test whether a GFD might have an effect on the skin disease. In order to classify the small bowel mucosa [normal, increased numbers of intraepithelial lymphocytes (IEL) or coeliac disease], the patients were asked to undergo gastroscopy with duodenal biopsy before the diet period. We also measured antibodies to endomysium (EmA) in the patients' sera, as EmA are considered to be more specific than AGA in the diagnosis of coeliac disease.

In a previous screening study of 302 patients with psoriasis, 16% were found to have IgA and/or IgG AGA.[3] Only in one of 11 IgA AGA-positive patients

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from this group screened for antibodies to reticulin/EmA was this result positive. Thirty-three patients with elevated AGA and six with normal AGA underwent duodenal biopsy, and 15 of 33 AGA-positive patients (40%) showed an increase in the number of IEL and of γ/δ + T lymphocytes, while no such increase was seen in the six AGA-negative patients.[4] The increase was usually discrete, and only two of these patients displayed typical histopathological features of coeliac disease, with partial villous atrophy. However, in the duodenal stroma most patients had an increased number of mast cells[5] and eosinophils.[6] This was also observed in psoriasis patients without AGA.

In this report, we present the results of an open study of GFD in AGA-positive psoriasis patients with regard to the effect on the psoriasis area and severity index (PASI),[7] and on the levels of AGA and eosinophil cationic protein (ECP), which is elevated in psoriasis.[6] A group of patients with AGA was followed up during a 3-month period on GFD and subsequently for 3 months on a normal diet. A small group of patients with normal AGA levels was also included.

Patients and methods

All patients had previously taken part in a screening study concerning the occurrence of AGA among psoriatic patients.[3] IgA AGA > 50 U/L and IgG AGA > 12 U/L were considered elevated according to the reference values. Forty-nine patients with elevated values of IgA AGA and/or IgG AGA and 12 patients without such antibodies were asked if they were willing to undergo gastroscopy with duodenal biopsy and thereafter to try to adhere to a GFD for 3 months. Thirty-three patients with antibodies and six without antibodies agreed to participate (mean ± SD age 43 ± 13 years, range 18–70, with psoriasis for mean ± SD 20 ± 13 years, range 1–42). Clinical and laboratory data are given in Table 1. There had been no changes in the psoriasis treatment during the last month before the trial. Reasons for unwillingness to participate were: (i) unwillingness to undergo gastroscopy; (ii) inability to adhere to the diet for practical reasons; and (iii) inability to attend for examination once a month for 6 months. One patient with mild psoriasis also had palmoplantar pustulosis. In addition to psoriasis, two women (both with AGA) had hypothyroidism which was being treated with levothyroxine.

The project was approved by the local Ethics Committee and all patients had given their informed consent.

Study design

The study started with a 3-month period on a GFD followed by a second 3-month period on the patient's ordinary diet. The trial always started in the autumn or early winter. Before and repeatedly during the first period, the patients received detailed information from a dietician about the GFD. All patients were examined by the same dermatologist once a month throughout the study in an unblinded assessment. The severity of the psoriasis was assessed by use of the PASI scoring system.[7] The patients were allowed to decrease their

Table 1. Anamnestic and clinical data, levels of IgA and IgG antibodies to gliadin (AGA) in serum, and duodenal scores

	IgA AGA > 50 U/L IgG AGA ≤ 12 U/L	IgA AGA > 50 U/L IgG AGA > 12 U/L	IgA AGA ≤ 50 U/L IgG AGA > 12 U/L	IgA AGA ≤ 50 U/L IgG AGA ≤ 12 U/L
Men/women (*n*)	15/8	3/2	1/4	4/2
PASI score < 5/5 < 10/≥ 10 (*n*)	10/9/4	3/1/1	4/0/1	2/0/4
Arthritis (*n*)	3	1	0	3
Previous treatment (*n*)				
Bath-PUVA/methotrexate/etretinate	6/5/5	0/0/1	2/1/1	3/2/2
Ongoing treatment (*n*)				
Methotrexate 5–7·5 mg/week	1	0	0	2
Etretinate 40–50 mg/day	1	1	1	0
UVB/bath-PUVA	5/1	2/0	1/0	1/1
Mainly emollients	12	3	3	1
IgA AGA (U/L, mean ± SD)	87 ± 67 (*n* = 23)	160 ± 118 (*n* = 5)	25 ± 11 (*n* = 5)	20 ± 6 (*n* = 6)
IgG AGA (U/L, mean ± SD)	4 ± 3 (*n* = 23)	59 ± 46 (*n* = 5)	33 ± 32 (*n* = 5)	2 ± 0·8 (*n* = 6)
Duodenal score < 1/1 < 2/≥ 2–3 (*n*)[a]	11/6/4	3/1/1	3/1/1	6/0/0

[a] Gastroscopy and duodenal biopsies failed in two patients. PASI, psoriasis area and severity index; UV, ultraviolet; PUVA, psoralen UVA.

ordinary treatment (both topical and systemic) if there was an improvement.

Before the trial, gastroscopy with duodenal biopsy was performed as previously reported.[4] The examining dermatologists were unaware of the results of histopathological examination of the duodenal biopsy specimens throughout the study. Details about the duodenal biopsy histology and immunohistology (CD45 +, CD3 +, γ/δ + T cells, tryptase + mast cells and EG2 + eosinophils) in this patient group have been published previously.[4–6] The data shown for duodenal biopsy scores (0–3) in this paper refer to the semi-quantitative evaluation of mononuclear cells present in the duodenal epithelium in haematoxylin and eosin (H&E) stained sections described previously. One mononuclear cell or fewer per four epithelial cells was considered normal (= score 0). In specimens scored as 3, there was a pronounced infiltration of mononuclear cells in the epithelium.[4]

After the 3-month follow-up, patients with an abnormal histopathology (score ≥ 1) were asked by the gastroenterologist (G.H.) if they would undergo a second gastroscopy to see if the mucosal changes had improved.

Blood samples

Blood samples were drawn at baseline and at 3 and 6 months for assays of serum levels of IgA AGA and IgG AGA and at 0 and 3 months for measurement of serum ECP as previously described.[6] ECP values > 16 μg/L were considered elevated.[6] Baseline serum samples were also analysed/re-analysed for IgA EmA with the same technique as previously reported.[3] All blood samples were analysed after completion of the study.

Statistics

The degree of significance was tested with the non-parametric Wilcoxon signed rank test for paired two-group comparison.

Results

Antibodies to endomysium and gliadin in relation to the duodenal score for intraepithelial lymphocytes

As shown in Table 2, only two patients were EmA-positive. One had an EmA titre > 1 : 160 and a duodenal score of 3 with partial villous atrophy. The other patient, who had an EmA titre of 1 : 10, had a duodenal score of 1·13. Of the 13 AGA + EmA – patients with a duodenal score ≥ 1, one had partial villous atrophy and five others a score of ≥ 2–3. In two IgA AGA + EmA – men, the gastroscopy had to be interrupted because of nausea, but both patients completed the trial with GFD.

Table 2. IgA and/or IgG antibodies to gliadin (AGA) and IgA antibodies to endomysium (EmA) in relation to the duodenal score for intraepithelial lymphocyte infiltration

	AGA + EmA +		AGA + EmA –		AGA –	
	n	%	*n*	%	*n*	%
Duodenal score < 1	0	0	16	55	6	100
Duodenal score ≥ 1[a]	2	100	13	45	0	0

[a] In two cases gastroscopy had to be interrupted because of nausea (see text).

Compliance to gluten-free diet and drop-outs

All patients tried to adhere to the diet, but practical dietary problems were experienced by a few patients on some occasions. Among the 33 patients with AGA there were three drop-outs. One woman discontinued the trial after 2 weeks because of gastrointestinal symptoms. She had raised IgG AGA and a duodenal H&E score of 2. In another woman the psoriasis improved but she did not come for the last check-up (raised IgA AGA and duodenal score of 1·3), and the third patient, a man with raised IgA AGA and duodenal biopsy score of 2, was unable to adhere to the diet because of personal and practical problems. These three patients had a history of moderate to severe psoriasis, all with unsatisfactory responses to previous psoriasis treatments.

Although all six patients without AGA adhered to the diet, one of them required a higher dosage of methotrexate after 2 months, and in another patient methotrexate treatment had to be started after 2 months on GFD. Only PASI scores from four patients with normal AGA are therefore included.

Gluten-free period: 0–3 months

Of the 39 patients who started the trial, 34 completed all visits during the 3 months without reporting a need to increase their treatment, either systemic or topical. Eight patients (all AGA-positive) reduced their systemic or topical treatment during the GFD period: etretinate (two), non-steroidal anti-inflammatory drugs (NSAIDs) (one), topical corticosteroids (five). No patients with

Table 3. Effects of 3 months on a gluten-free diet in different groups of psoriasis patients with and without IgA and/or IgG antibodies to gliadin (AGA)

	Improved		No change		Worse	
	n	%	*n*	%	*n*	%
All AGA + (*n* = 30)	22	73	3	10	5	17
IgA AGA + IgG AGA − (*n* = 21)	15	71	3	14	3	14
IgA AGA + IgG AGA + (*n* = 5)	4	80	0	0	1	20
IgA AGA − IgG AGA + (*n* = 4)	3	75	0	0	1	25
Duodenal score < 1 (*n* = 16)[a]	12	75	1	6	3	19
Duodenal score ≥ 1 (*n* = 12)	8	67	2	17	2	17
IgA EmA +	2	100	0	0	0	0
AGA − (*n* = 6)	0	0	2	33	4	67
Lower IgA and/or Ig G AGA (*n* = 22)[b]	18	82	1	5	3	14
Lower ECP (*n* = 19)[c]	14	74	1	5	4	21

ECP, eosinophil cationic protein; [a] duodenal biopsies missing in two patients, improved; [b] value missing in two patients, both improved; [c] value missing in three patients, all improved.

elevated AGA needed to increase their ordinary psoriasis treatment during the trial.

All improvements in psoriasis occurred gradually. In a few patients with initial improvement, worsening was observed during viral or streptococcal infections and during stressful periods. In no patient was increased swelling or any other sign of increased activity in the joints observed during the first 3 months on GFD, in contrast to the findings during the subsequent 3 months on the ordinary diet.

Table 3 gives the percentage and numbers that were improved, unchanged or worse, and Table 4 the mean PASI scores before and after the GFD in various subgroups. Twenty-two of 30 patients (73%) with raised IgA and/or IgG AGA had a lower PASI score after 3 months on GFD and were classified as improved. The percentage of improved patients was similar in all AGA + subgroups; thus, this percentage was similar in the AGA + groups with duodenal scores of < 1 and ≥ 1. Both patients with positive EmA as well as four others with a duodenal score of 2–3 improved.

As shown in Table 4, patients with elevated IgA AGA and/or IgG AGA showed a highly significant decrease in their mean PASI score after 3 months on a GFD. Of the six patients without AGA there was no change in two and a pronounced deterioration in four (Table 3). Patients with an initial mean PASI ≥ 5 showed a greater reduction in their mean PASI than those with an initial mean PASI < 5 (Table 4).

The individual values for IgA AGA varied widely and the mean ± SD values before and after 3 months on GFD did not differ significantly (96 ± 108 vs. 80 ± 72 U/L, *n* = 33), whereas the mean ± SD value for IgG AGA decreased from 10·1 ± 15·4 to

Table 4. Psoriasis area and severity index (PASI) score (mean ± SD) before and after a 3-month gluten-free diet in subgroups of patients with various initial levels of antibodies to gliadin (AGA) and duodenal biopsy findings

Patients	*n*	PASI before	PASI after	*P*-value
All raised IgA and/or IgG AGA	30	5·5 ± 4·5	3·6 ± 3·0	0·001
All IgA AGA > 50 U/L	26	7·9 ± 5·7	4·1 ± 3·1	0·004
IgA AGA > 50 U/L, IgG AGA ≤ 12 U/L	21	5·2 ± 3·3	3·7 ± 2·7	0·008
IgA AGA > 50 U/L, IgG AGA > 12 U/L	5	7·1 ± 8·0	5·0 ± 4·7	0·225
IgA AGA ≤ 50 U/L, IgG AGA > 12 U/L	4	5·0 ± 5·4	1·5 ± 0·8	0·144
Normal IgA/IgG AGA	4[a]	8·9 ± 6·4	10·2 ± 7·9	0·465
Raised IgA/IgG AGA, duodenal score < 1	16	6·1 ± 4·9	4·2 ± 3·8	0·008
Raised IgA/IgG AGA, duodenal score ≥ 1	12	4·5 ± 2·8	2·8 ± 1·7	0·126
Raised AGA, initial PASI ≥ 5	14	9·0 ± 4·3	5·5 ± 3·5	0·002
Raised AGA, initial PASI < 5	16	2·4 ± 1·3	2·0 ± 1·1	0·286
Raised AGA, only emollients	18	3·7 ± 2·2	2·8 ± 1·4	0·029
Raised AGA, previously requiring PUVA, methotrexate, retinoids	11	7·9 ± 5·9	4·5 ± 3·6	0·016
ECP decrease ≥ 30%, raised AGA	15	7·3 ± 5·3	4·2 ± 3·6	0·007
ECP decrease < 30%, raised AGA	11	3·5 ± 2·6	3·2 ± 1·9	0·374

ECP, eosinophil cationic protein; PUVA, psoralen ultraviolet A. [a] See text.

Table 5. Individual psoriasis area and severity index (PASI) scores at months 0, 3 and 6 in patients with raised levels of antibodies to gliadin in whom serum eosinophil cationic protein decreased by ≥ 30% at 3 months compared with the baseline value. Gluten-free diet (GFD) months 0–3, normal diet months 3–6

Patient no.	PASI 0	PASI 3	PASI 6	Comments
1	11·1	1·3	10·6	Reduction long-term etretinate months 0–3, increased dosage month 5. Methotrexate added month 6. Duodenal score < 1
2	3·3	1·2	0·8	Duodenal score < 1
3	4·5	2·1	2·0	Duodenal score < 1
4	12·9	1·8	12·2	Reduction long-term etretinate months 2–3, increased dosage months 5–6, later methotrexate. Duodenal score 2·2
5	5·2	3·2	3·4	Only emollients months 0–3. Duodenal score < 1
6	20·4	12·8	16·2	Methotrexate from month 6 because of worsening months 3–6. Duodenal score < 1
7	11·0	9·2	6·3	Methotrexate dosage unchanged months 0–3, increased months 3–6. Duodenal score < 1
8	5·3	3·6	4·5	Only emollients months 0–3, calcipotriol added months 3–6. Duodenal score < 1
9	1·2	1·4	11·8	Long-term etretinate. Non-steroidal anti-inflammatory drug dosage reduced months 0–3; improved joints; severe flare skin lesions, arthritis, gastrointestinal symptoms on normal diet. Duodenal score 3
10	2·0	2·5	3·4	Duodenal score < 1
11	10·2	5·2	11·8	Loose stools months 3–6. Duodenal score 1·13
12	1·6	3·6	4·5	Problems in adhering to GFD. Duodenal score < 1
13	10·8	11·6	8·8	Duodenal score < 1
14	6·8	3·0	13·1	Pronounced worsening of skin lesions months 3–6, no gastrointestinal symptoms; after the trial restart of GFD; subsequent clearance of psoriasis. Duodenal score 3. Positive antibodies to endomysium
15	3·6	1·0	1·5	Duodenal score < 1

8·1 ± 11·7 U/L (n = 34, P = 0·041). However, 82% of the AGA + patients who were improved had a lower IgA and/or IgG AGA value after 3 months on a GFD.

The mean ± SD serum ECP in patients with elevated IgA and/or IgG AGA was 19·4 ± 21·5 μg/L before GFD and 13·2 ± 11·6 μg/L at 3 months (n = 27, P = 0·008); as shown in Table 3, 74% of the patients with improved psoriasis had a lower ECP after GFD than before GFD.

As seen in Table 4, patients exhibiting a decrease in serum ECP of ≥ 30% (arbitrarily chosen) after 3 months on GFD showed a highly significant reduction in their mean PASI score: the mean ± SD elevated ECP value in this subgroup decreased from 23·1 ± 25·6 to 12·5 ± 13·0 μg/L (P = 0·0007). In contrast, patients without a decrease in ECP had a lower mean ± SD initial ECP value (10·6 ± 5·3 μg/L), and a lower initial PASI value, which was essentially unchanged at 3 months.

Duodenal biopsies after 3 months

Seven patients with abnormal histology (score ≥ 1) agreed to undergo a second gastroscopy after 3 months on a GFD. Two of these patients were EmA-positive. None of the specimens showed any obvious improvement compared with the pre-GFD findings. All seven had a lower IgA AGA value than before the GFD and the mean value at 3 months was significantly lower than the mean baseline value (P = 0·018). Five of the seven patients had a lower PASI value at 3 months. In three of the patients with a duodenal score of 2–3 who continued the GFD after the study, the histological features became normalized after 1–2 years.

Clinical course: 3–6 months

Skin. The second part of the study (months 3–6) on a normal diet could not be performed as planned, as 18 of 30 AGA-positive patients required increased systemic (etretinate, methotrexate, ultraviolet radiation) and/or topical treatment because of worsening of their skin lesions. None of the six AGA-negative patients required an increase in their topical or systemic treatment during the 3–6-month period.

Two patients with a duodenal score of 2–3 (both EmA-negative) had a severe flare of their skin condition, with intensely erythematous, oedematous lesions, as well as arthritis and gastrointestinal symptoms (see below). They were unable to continue with their normal diet and had to resume the GFD. A third patient with a duodenal score of 3, villous atrophy, positive EmA and pronounced worsening during months 3–6 (patient 14, Table 5) resumed the GFD after the trial, with subsequent clearance of her psoriasis and with no relapse during the last 4 years.

The other EmA-positive patient with minor lymphocyte infiltration has resumed the GFD on her own initiative and has also experienced an almost total clearance of her moderate to severe psoriasis.

Table 5 shows the individual PASI scores at 0, 3 and 6 months in the patients with a ≥ 30% reduction in their ECP during the first 3 months. The mean ± SD PASI scores in these patients were 7·3 ± 5·3, 4·2 ± 3·6 and 7·4 ± 4·9, respectively (n = 15; PASI 0 vs. PASI 3 P = 0·0007; PASI 3 vs. PASI 6 P = 0·027).

Arthritis and arthralgia. Two patients (both EmA-negative) experienced disabling deterioration of their arthritis and one patient had pronounced worsening of his arthralgia. All three had an elevated IgA AGA level and an increased duodenal score. One of the two patients with arthritis developed tender, swollen, erythematous wrists and ankles and sausage-like toes and fingers during the first month after resuming the normal diet, and the other patient with arthritis, mainly in the shoulder and sacroiliac joints, suffered severe pain and stiffness. Both these patients resumed the GFD and improved, with reduced requirements for NSAIDs/retinoids.

Gastrointestinal symptoms. In two patients severe diarrhoea developed (the same two patients as had a flare of their arthritis: see above), although previously they had had only minor or no gastrointestinal symptoms. In contrast, one patient (EmA-positive) with a duodenal score of 3 and marked worsening of her psoriasis (patient 14, Table 5) had no gastrointestinal symptoms on reintroduction of gluten-containing food. The mean ± SD values for IgA AGA at 3 and 6 months were 99 ± 91 and 155 ± 298 U/L, respectively.

Discussion

This study on effects of GFD has shown that in psoriasis patients who have IgA or IgG AGA the psoriasis can be improved by avoiding gluten in food. The positive effects were observed not only in patients with an increased number of lymphocytes in the duodenal epithelium, but also in some patients with seemingly normal epithelium. These results may be compatible with those of Marsh[1] and Marsh and Crowe,[2] which indicated that gluten sensitivity can be present even in patients with an apparently normal mucosa.

Only two of the patients with elevated levels of IgA AGA had IgA EmA. One of these had partial villous atrophy. The other patient, with a low IgA EmA titre, had only a very slightly increased number of IEL. Both patients resumed the GFD after the end of the study and have now shown almost total clearance of their moderate to severe psoriasis for several years. In addition, some of the AGA + EmA – patients in this study have also had long-term improvement of their psoriasis.

It takes time to learn to manage and adhere to a GFD, and practical problems are encountered when the patient travels, visits restaurants, etc. A few of our patients reported that strict avoidance of gluten had not been possible on such occasions. Three months may also be too short a time to learn to manage the diet and a longer time would probably have given more information. The fact that none of the patients who had a second duodenal biopsy showed improved histology despite the fact that the AGA values were reduced in all of them may also indicate that a longer trial with GFD would be preferable. An alternative would be a long-term trial with GFD for 12 months followed by 12 months on a normal diet. Six-month periods would be less suitable, as most psoriasis patients improve during the summer.

On the other hand, in the light of our experience from patients with silent coeliac disease and psoriasis who have started GFD and have improved, it seems reasonable to assume that some tendencies towards effects on the skin might be observed and evaluated after 3 months, particularly if the patients are followed up when they resume their ordinary diet.

This study was not performed as a double-blind trial with regard to the GFD, but the evaluating dermatologists were unaware of the duodenal histopathology. EmA and ECP were assayed after the end of the study. A double-blind cross-over study would have been difficult to arrange. Furthermore, the results of the study have shown that it was important to follow the clinical course on resumption of the ordinary diet, which in some patients provoked a marked worsening of the psoriasis.

Even if the PASI scoring is done by the same person throughout a study, the evaluation of similar lesions may vary somewhat. As a complementary test, three target lesions were also evaluated, and the results were the same as for the PASI scores (data not shown). Psoriasis can fluctuate in intensity 'spontaneously' and can also be influenced by factors such as stress and infections. It may be argued that the changes observed in our patients might have been spontaneous or

'placebo' effects. However, the opposite trends, with improvement during the GFD period accompanied by lower AGA and ECP values, and worsening in most of the patients when resuming their ordinary diet, indicate that the diet influenced the psoriatic process. Particularly impressive were two patients (both EmA-negative), who suffered an acute, severe flare of their skin lesions and arthritis when they resumed the normal diet. The tendency to improvement on GFD in this patient group is in conformity with our experience in sporadic patients with psoriasis and silent coeliac disease who have become free from psoriasis or much improved for years after the initiation of a GFD. A few of those observed in more recent years have been EmA-positive, whereas EmA was not checked in the first patients observed.[8] Whether the AGA+ EmA− patients in this study have a different type of gluten sensitivity from patients with coeliac disease, or the same type but much milder, is not yet known. The increased number of γ/δ + T lymphocytes in the duodenal epithelium, which was significantly correlated with the serum level of IgA AGA, may indicate that there is a relationship between psoriasis and coeliac disease in AGA− psoriasis patients.[4] However, there are EmA-negative patients with gluten enteropathy. For example, in a study on the diagnosis of gluten-sensitive enteropathy, Feighery *et al.* found that 13% of patients with a histological diagnosis of coeliac disease were EmA-negative.[9] Elevated AGA levels in psoriasis patients might represent some other type of sensitivity to gluten with an (auto)antigen other than endomysium transglutaminase. It is possible that this might also be true for EmA-negative patients with coeliac disease.

Most patients with a decreased PASI score after 3 months on a GFD had lower AGA and/or lower ECP values than before the GFD. The pronounced decrease in the ECP level after the GFD period in most of the AGA-positive patients indicates that the GFD influenced the activity of the eosinophil granulocytes, causing a reduction in the release of ECP, which might have had a favourable effect on the psoriasis activity.

A decrease in the ECP level after GFD has not been reported previously. It might be induced via effects on lymphocytes, but other mechanisms are conceivable as two of the AGA-negative patients without an increase in IEL in the duodenum and without any active treatment of their psoriasis also showed a marked decrease in ECP after 3 months. Most of our psoriasis patients (AGA-positive and AGA-negative) have increased numbers of eosinophils[6] and mast cells[5] in the duodenal stroma, and direct effects of gluten on these cells might be possible. Although the group of patients without AGA showed no clinical improvement, the group was too small to exclude the possibility that there are some AGA-negative patients who might benefit from a GFD.

The mechanism of the effect of a GFD in AGA-positive psoriasis patients is not known. There might be a reactivity to some antigen that is present in both the intestinal mucosa and skin and is also linked to gluten. A non-specific effect may also be possible, e.g. via cytokines induced in the gut. For instance, an upregulation of keratinocyte growth factor after activation of lamina propria T cells has been reported.[10] This may be of importance for the epithelial hyperplasia in the mucosa, and possibly also for the epidermal proliferation in the psoriatic skin. The fact that patients with an increased number of lymphocytes in the duodenal epithelium have a significantly larger number of mast cells in non-involved skin than those with no such increase may indicate a communication between the skin and gut.[11] It might also be speculated that the GFD improved the profound disturbance of the macrophage function which was present in some of our patients *in vivo*. Patients with psoriasis, dermatitis herpetiformis and coeliac disease have all been found to have the same type of pronounced impairment in the ability to clear immune complexes.[12]

There are several examples of associations between diseases in the skin and the gut, e.g. dermatitis herpetiformis, pyoderma gangrenosum and acrodermatitis enteropathica. There is also evidence of an increased risk for Crohn's disease in psoriasis.[13] Some case reports on patients with coeliac disease and concomitant psoriasis in whom the psoriasis has cleared on GFD have been published.[14–16] Our previous and present results indicate that there is a subgroup of psoriasis patients, often with moderate or severe psoriasis, sometimes with an unsatisfactory response to conventional treatment, with hidden gluten sensitivity, which can be of great relevance for their psoriasis. Many of these patients have no or only minor gastrointestinal symptoms. Some have very subtle, if any, mucosal changes and most seem to have no EmA. Nevertheless their psoriasis can improve on a strict GFD. Others may have a classical, but silent, coeliac disease with IgA EmA, which (regardless of the skin disease) should be treated with life-long GFD. In our experience from such patients, this regimen can induce long-term remission or improvement of the disease.

It is therefore important to try to identify this subgroup of psoriasis patients. Screening for IgA and IgG AGA in patients with moderate and severe psoriasis may be a valuable tool in this respect. Absence of EmA does not exclude the possibility that the psoriasis can improve on a GFD. The intestinal mucosa needs further studies in both AGA-positive and AGA-negative psoriasis patients.

Acknowledgments

We thank the dietician Mia Hjelm for all advice and support throughout the dietary trial. This project was supported by grants from the Swedish Psoriasis Association, the Edvard Welander Foundation and the Swedish Foundation for Health Care Sciences and Allergy Research.

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