Glucocorticoid receptor expression in the skin of psoriatic patients compared with control skin: correlation with stress and disease activity and severity

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Background
Although the role of topical glucocorticoids treatment in psoriasis is well established, the expression of glucocorticoid receptors (GRs) in psoriatics has not yet been studied.

Objective
To study the expression of GRs in 20 psoriatics compared with 20 matched controls and correlate the results to disease severity and activity, and life stress.

Patients and methods
In this case–control study, two skin biopsy specimens from each psoriatic patient's involved and clinically uninvolved skin and one biopsy specimen from each control were evaluated for GRs expression using immunohistochemistry. The results were correlated to psoriasis area and severity index, physician's global assessment for psoriasis activity (PGA-Ps), and psoriasis life stress inventory (PLSI).

Results
A significant increase in GR expression was found in psoriatic involved skin compared with uninvolved and control skin ($P=0.044$ and $P=0.033$, respectively), with a correlation between expression levels in involved epidermis and both involved dermis and clinically uninvolved epidermis ($P=0.044$ and $P=0.05$, respectively). Despite the absence of a significant difference between patients with different grades of psoriasis area and severity index, significantly higher expression was found in psoriatic involved and uninvolved skin of highly stressed patients compared with less stressed patients ($P<0.001$ and $P=0.01$, respectively). Expression in both involved and uninvolved skin correlated with PLSI and PGA-Ps scores, and both PLSI and PGA-Ps correlated to each other ($P<0.05$).

Conclusion
Higher GR expression in psoriatic involved skin compared with uninvolved and control skin, with correlation to disease activity, and high life stress indicate the reciprocal relationship between inflammation, stress response, and glucocorticoid signaling pathways. Correlation between expression in uninvolved skin and psoriasis activity suggests a prepsoriatic phenotype in psoriatic patients' clinically uninvolved skin.

Keywords:
glucocorticoid receptors, immunohistochemistry, psoriasis, stress

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Introduction

Psoriasis is a chronic inflammatory autoimmune skin disease with faulty signals that speed up the growth cycle of skin cells [1]. Glucocorticoids (GCs), important regulators of epidermal growth, differentiation, and homeostasis, are used extensively in the topical treatment of psoriasis [2]. In addition to epidermal growth regulation, GCs exert potent immunosuppressive and anti-inflammatory actions in a cell type-specific manner, largely through the interruption of cytokine-mediated pathways [3]. GCs exert their actions through specific receptors, the glucocorticoid receptors (GRs), which have been characterized in cultured human skin fibroblasts and keratinocytes (KCs), but their localization *in vivo* has not been established [4]. GRs belong to the nuclear receptor subfamily, which includes receptors for estrogen and thyroid hormones, retinoic acid, and vitamin D [5]. Although the role of GCs as a topical treatment in psoriasis is well established, the expression of GRs in psoriatic skin has not yet been studied. It can be variable and consequently lead to different therapeutic responses to steroid treatment in psoriasis. However, this remains to be elucidated.

The aim of this work was to study the expression of GRs in psoriatic and apparently normal skin of patients compared with normal controls and correlate the results to disease severity, and activity, as well as life stress. This will aid better understanding of the pathogenesis of psoriasis.

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Patients and methods

Patients

Twenty patients with psoriasis vulgaris and 20 age-matched and sex-matched controls were included in the current case–control study. Patients were selected from among the inpatients' section and the outpatients' clinics of the Dermatology, Venereology, and Andrology Department, Faculty of Medicine, Ain Shams University, and controls were selected from among healthy volunteers who were attending the Plastic Surgery Department for cosmetic reasons, after signing an informed consent. The study was carried out according to the Declaration of Helsinki principles, and was approved by the ethical committee of Faculty of Medicine, Ain Shams University. Patients were subjected to a full assessment of history including smoking, menstrual history, disturbed sleep pattern, onset, course, and duration of illness, presence of any precipitating or aggravating factors such as trauma, infection or drugs, history of other skin or systemic diseases, and history of any current or previous treatments of psoriasis or other diseases, especially those that affect the immune system, and the date of stopping them. A careful general examination, including BMI, joint examination, and assessment of clinical manifestations suggestive of any systemic or endocrinal disease, likely to influence GC and GR levels, was performed. All patients were subjected to screening laboratory tests including complete blood picture, erythrocyte sedimentation rate, serum albumin and electrolytes (sodium, potassium, and calcium levels), random blood glucose, liver enzymes (ALT, AST), kidney function tests (serum urea and creatinine), and urine analysis.

Patients who had untreated psoriasis vulgaris with various degrees of severity were included in the study, and patients with any dermatological and/or systemic diseases that could affect the outcome of the study, patients who had received any topical treatment of psoriasis within the previous 2 weeks or any systemic treatment of psoriasis or phototherapy during the last month before the study, patients receiving GCs, patients with any other autoimmune disease, or those taking any medication that affects the immune system, and female patients who had received any hormonal contraceptives were excluded.

Methods

Evaluation of psoriasis distribution, morphology, extent, and severity was performed, with calculation of the psoriasis area and severity index (PASI) score (maximum total score of 72) [6]. PASI scores were then categorized into mild psoriasis (<15), moderate psoriasis (15–25), and severe psoriasis (>25) [7].

We assessed the stress experienced by the patients using the modified version of the psoriasis life stress inventory (PLSI), by Rakhesh *et al.* [8]. The resulting scores ranged from 0 to 54, which were expressed as a percentage. On the basis of the PLSI percentage scores, we divided our patients into two groups: less stress-reactive group, with a PLSI score of less than 22.5%, and a high-stress group, with a PLSI score of more than 22.5%.

The modified physician's global assessment (PGA) of psoriasis activity (PGA-Ps), by Chandran *et al.* [9], was used to rate our psoriatic patients on a scale from clear or inactive to severe or most active. The activity of psoriasis was scored on an 11-point (0–10) numerical rating scale, with 0 representing inactive disease and 10 representing the most active disease.

Two 4 mm punch biopsies were obtained from each of the 20 patients: one from the center of psoriatic lesion and one from clinically uninvolved skin 5 cm away from the lesion. One skin biopsy specimen was obtained from an anatomically matched site of each volunteer (representing the control specimen). Each specimen was prepared for histopathological examination. Routine hematoxylin and eosin stain was used for routine histopathological examination. Immunohistochemistry (IHC) was performed for evaluation of GR in psoriatic involved skin versus uninvolved skin versus control skin using the primary polyclonal rabbit antibody [GR (H-300), sc-8992; Santa Cruz Biotechnology Inc., Dallas, Texas, USA] raised against amino acids 121–420 of GR of human origin, thus enabling the detection of both GRs α and β. The secondary antibody (Universal Kit) used biotinylated Goat Anti-Rabbit IgG (H + L) (Alexa Fluor, Catalog Number A-21076; Life Technology, Carlsbad, California, USA). Color was developed using aminoethylcarbazole chromogen. Positive GR reactions appeared red in color in the nuclei. The percentage of cells positive for GRs was assessed in five high power fields ($\times 400$) in each specimen, and the mean was used for statistical analysis. Counting was carried out using a Leica Q500 MC image analyzer computer system controlled by Leica Qwin 500 software (Leica, Cambridge, UK). According to the percentage of positive cells, above 0 and up to 30% was considered a mild reaction, 31–60% a moderate reaction, and more than 60% a strong reaction.

Statistical analysis

The data collected were analyzed using the statistical package for social science (SPSS 15.0.1 for windows, 2001; SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test (K–S test) was used for testing normality of the distribution of data. Student's *t*-test was used to compare between two groups of parametric data, the paired *t*-test to compare between involved and uninvolved skin of patients, and the analysis of variance test to compare between more than two groups of parametric data. Correlation analysis (using Pearson's method) was used to assess the strength of the association between two quantitative variables. *P* value was considered insignificant if more than 0.05, significant if 0.05 or less, and highly significant if 0.001 or less.

Results

Clinical data

Among the patients, there were 10 men and 10 women, mean age 38.9 ± 6.6 years (30–50 years), and also among the controls there were 10 men and 10 women, matched mean age 35.6 ± 5.8 years (32–47 years). The median

disease duration was 5.55 years (0.1–11 years). According to the PASI score, the patients were divided into three groups. Group A included seven patients with mild psoriasis; their PASI score ranged from 1.0 to 10.8 (6.0 ± 3.9). Group B included five patients with moderate psoriasis; their PASI score ranged from 16.2 to 25.0 (18.2 ± 3.8). Group C included eight patients with severe psoriasis; their PASI score ranged from 26.1 to 50.9 (37.1 ± 11.0). According to PLSI, the score of the less stress-reactive group (two patients) ranged from 18.5 to 22.2% (20.89 ± 1.76), whereas in the high-stress group (seven patients), it ranged from 27.8 to 64.8% (53.42 ± 12.78).

Glucocorticoid receptor expression in patients

Overall, the patients studied showed variable GR expression in both involved and clinically uninvolved skin. Table 1 summarizes psoriatic patients' disease severity, PLSI scores, PGA-Ps scores, and the results of GR expression in clinically uninvolved as well as involved skin. Six patients were found to express GR strongly in the epidermis of clinically uninvolved skin: one with mild disease, one with moderate disease, and four with severe psoriasis.

Figures 1–3 show variable grades of GR expression in both psoriatic skin and clinically uninvolved skin of some of the studied patients. Generally, GR were expressed in KCs, Munro's microabscesses, dermal fibroblasts, and dermal infiltrating leukocytes.

Glucocorticoid receptor expression in controls

The control specimens showed positive GR expression in nuclei of some cells in both the epidermis and the dermis; KCs showed moderate expression (47.68 ± 10.56%) and dermal fibroblasts showed mild expression (19.35 ± 4.51%) (Fig. 4).

Glucocorticoid receptor expression in patients' involved versus uninvolved skin versus controls' specimens

Collectively, there was a significant increase in GR expression in the epidermis of psoriatic involved skin compared with epidermis taken from both uninvolved and control skin ($P = 0.044$ and $P = 0.033$, respectively), and a highly significant increase in GR expression in the dermis of psoriatic involved skin compared with that of uninvolved skin as well as control skin ($P < 0.001$). However, GR expression in uninvolved skin did not show any statistically significant difference compared with the control skin (Table 2).

Glucocorticoid receptor expression in patients' subgroups

Grading of psoriasis as assessed by the PASI score was not significantly reflected on GR expression in either the epidermis or the dermis of psoriatic involved skin ($P = 0.75$ and $P = 0.995$, respectively), as well as those of uninvolved skin ($P = 0.104$ and $P = 0.995$, respectively) (Table 3).

Highly stressed patients showed significantly higher GR expression in involved and uninvolved epidermis compared with the less stress-reactive group ($P < 0.001$ and $P = 0.01$, respectively) (Table 4).

Data correlations

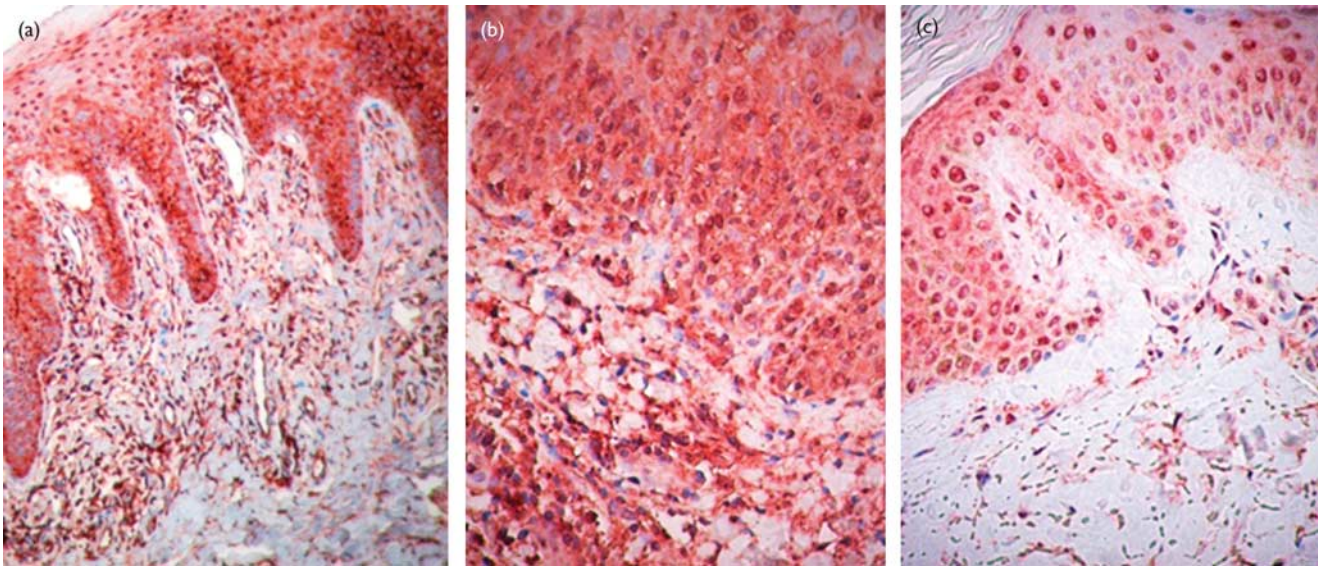
A significant positive correlation was found between GR expression in the epidermis and dermis of involved skin ($r = 0.454$; $P = 0.044$), epidermis and dermis of uninvolved skin ($r = 0.440$; $P = 0.05$), as well as epidermis

Table 1. Psoriasis life stress inventory scores, physician's global assessment scores for psoriasis activity, and the results of glucocorticoid receptor expression in uninvolved as well as diseased skin in the groups of patients studied

	Mild psoriasis group (7 patients)[a]			Moderate psoriasis group (5 patients)[a]			Severe psoriasis group (8 patients)[a]		
Characteristics	*N* (%)	Range	Mean ± SD	*N* (%)	Range	Mean ± SD	*N* (%)	Range	Mean ± SD
PLSI score %[b]									
Less stressed	2 (10)	18.5–22.2	20.35 ± 2.62	4 (20)	20.4–22.2	21.75 ± 0.9	1 (5)	18.5	–
Stressed	5 (25)	29.6–61.1	49.62 ± 14.49	1 (5)	59.3	–	7 (35)	27.8–64.8	55.3 ± 12.84
PGA-Ps score[c]	7 (35)	0–8	3.57 ± 2.37	5 (25)	1–8	3.6 ± 2.7	8 (40)	2–10	6.63 ± 2.5
GR% in psoriatic epidermis									
Mild	1 (5)	26	60.71 ± 19.1	0 (0)	–	52.8 ± 10.13	1 (5)	20	57.63 ± 19.65
Moderate	2 (10)	48–60		4 (20)	43–51		2 (10)	40–54	
Strong	4 (20)	62–84		1 (5)	70		5 (25)	62–80	
GR% in psoriatic dermis									
Mild	4 (20)	15–22	38.29 ± 26.16	2 (10)	21–30	43.8 ± 22.15	3 (15)	24–28	41.38 ± 16.42
Moderate	1 (5)	51		1 (5)	33		3 (15)	34–46	
Strong	2 (10)	63–80		2 (10)	65–70		2 (10)	61–67	
GR% in uninvolved epidermis									
Mild	4 (20)	20–30	36.43 ± 17.39	2 (10)	30	43.2 ± 19.28	1 (5)	21	59.63 ± 22.88
Moderate	2 (10)	38–47		2 (10)	33–48		3 (15)	40–60	
Strong	1 (5)	70		1 (5)	75		4 (20)	63–90	
GR% in uninvolved dermis									
Mild	6 (30)	9–28	20.43 ± 12.04	5 (25)	10–22	13.2 ± 5.07	4 (20)	7–23	26.5 ± 15.22
Moderate	1 (5)	44		0 (0)	–		4 (20)	33–46	
Strong	0 (0)	–		0 (0)	–		0 (0)	–	

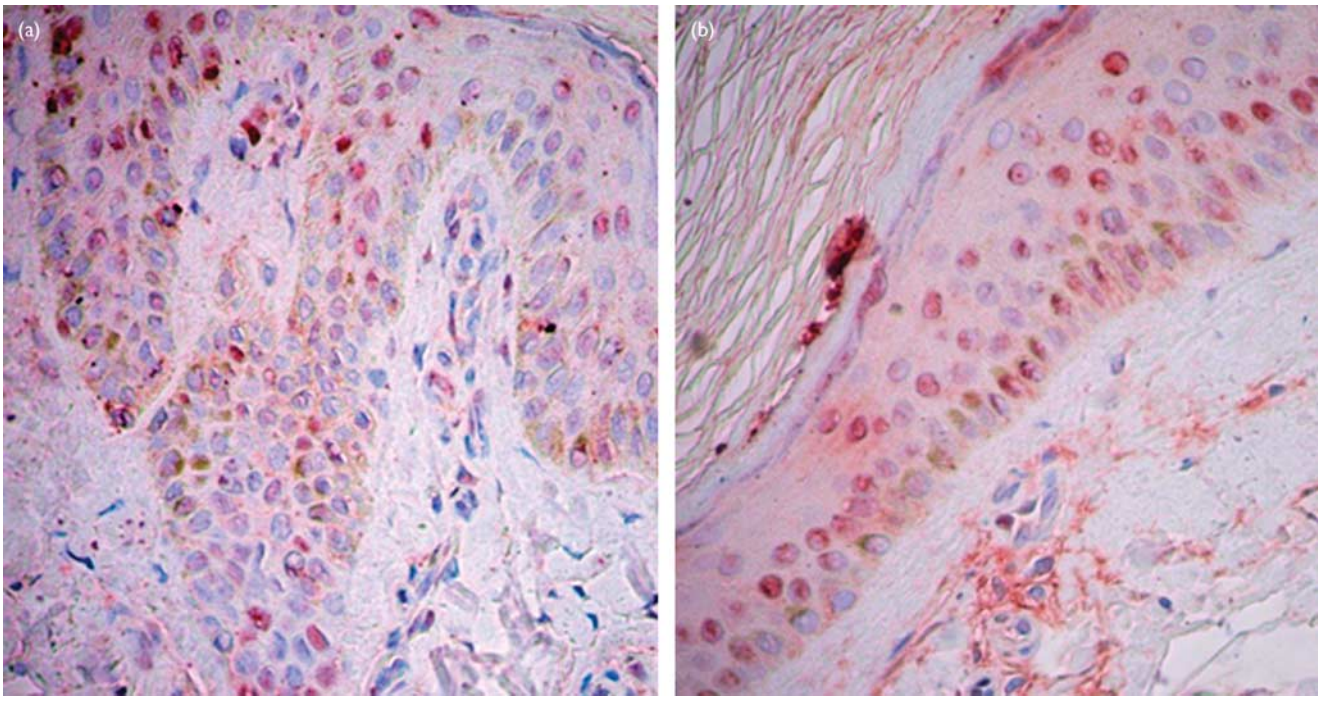
GR, glucocorticoid receptor; PGA-Ps, physician's global assessment for psoriasis activity; PLSI, psoriasis life stress inventory.
[a]According to psoriasis area and severity index; mild psoriasis (<15), moderate psoriasis (15–25), and severe psoriasis (>25).
[b]According to PLSI; less stress-reactive group, with a PLSI score of <22.5%, and high-stress group, with a PLSI score of >22.5%.
[c]The activity of psoriasis was scored by physician's global assessment on an 11-point (0–10) numerical rating scale, with 0 representing inactive disease and 10 representing the most active disease.

Figure 1.



Case number 15 (severe psoriasis, with psoriasis life stress inventory of 61.1% and physician's global assessment for psoriasis activity of 9). (a) Scanning power showing psoriasiform epidermal hyperplasis and club-shaped dermal papillae with a prominent increase and dilatation of papillary blood vessels [immunohistochemistry (IHC) for glucocorticoid receptor (GR), × 100]. (b) Another field showing prominent strong expression of GR in the nuclei of epidermal cells (90%) and in dermal cells (70%) of psoriatic skin (IHC for GR, × 560). (c) Prominent strong expression of GR in the nuclei of epidermal cells (87%) and moderate expression in dermal cells (44%) of uninvolved skin (IHC for GR, × 400).

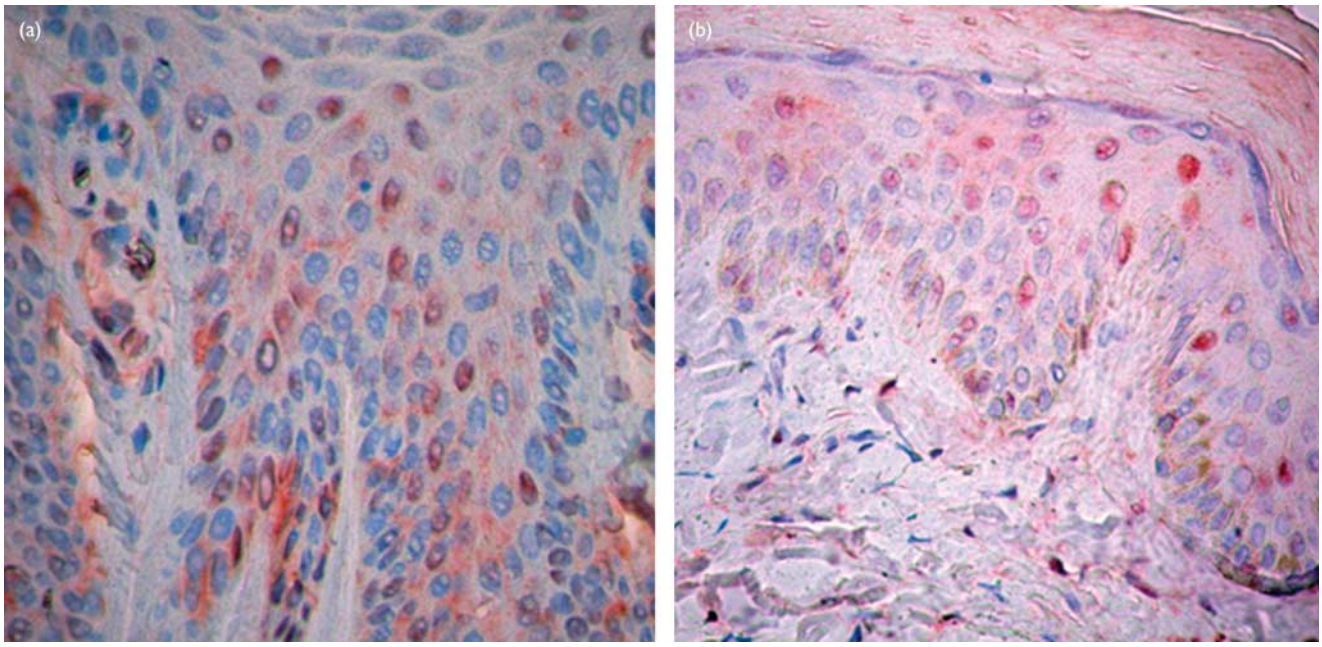
Figure 2.



Case number 2 (mild psoriasis, with psoriasis life stress inventory of 22.2% and physician's global assessment for psoriasis activity of 4). (a) Moderate expression of glucocorticoid receptor (GR) in the nuclei of epidermal cells (51%) and mild expression of dermal cells (10%) of psoriatic skin [immunohistochemistry (IHC) for GR, × 400). (b) Moderate expression of GR in the nuclei of epidermal cells (40%) and mild expression in dermal cells (7%) of uninvolved skin (IHC for GR, × 560).

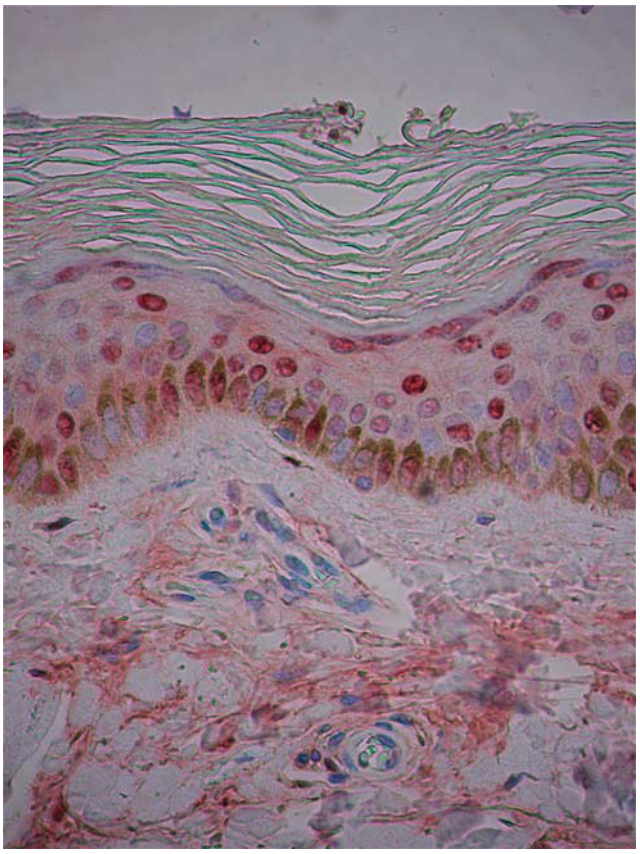
of involved skin and that of uninvolved skin ($r = 0.553$; $P = 0.011$). Neither the age of the patients nor the disease duration was correlated to GR expression in the epidermis or the dermis of either involved or uninvolved skin ($P > 0.05$) (Table 5). There was no significant correlation between the PASI score and GR expression in the epidermis or the dermis of involved skin ($P > 0.05$). However, there was a highly significant positive correlation between PASI score and GR expression in the epidermis of uninvolved skin ($P = 0.001$) (Table 5). Besides, GR

Figure 3.



Case number 4 (mild psoriasis, with psoriasis life stress inventory of 18.5% and physician's global assessment for psoriasis activity of 0). (a) Mild expression of glucocorticoid receptor (GR) in the nuclei of epidermal (26%) and dermal (20%) cells of psoriatic skin [immunohistochemistry (IHC) for GR, × 560]. (b) Mild expression of GR in the nuclei of epidermal cells (30%) and dermal cells (10%) of uninvolved skin (IHC for GR, × 560).

Figure 4.



Mild expression of glucocorticoid receptor (GR) in the nuclei of epidermal cells (49%) and dermal cells (19%) of normal control skin (immunohistochemistry for GR, × 560).

expression in the epidermis of both involved and uninvolved skin was correlated positively with both PLSI and PGA-Ps scores ($P<0.001$ and $P=0.006$ and $P=0.018$ and $P<0.001$, respectively) (Table 5), and both PLSI and PGA-Ps scores were highly correlated to each other ($r=0.752$; $P<0.001$).

Discussion

Sevilla *et al.* [10] have previously shown that GRs are required for skin homeostasis and epidermal barrier competence. GRs were found to mediate GCs repression of basal-cell-specific keratins expression K5 and K14 as well as disease-associated keratins K6, K16, and K17 [11,12]. They repress the expression of disease-related keratins, K6 and K16, even in the presence of epidermal growth factor, known to be involved in the pathogenesis of psoriasis [13,14]. In addition, GRs dysfunction is likely to be involved in the pathogenesis of depression [15], a well-known co morbidity associated with psoriasis [16].

Immunoreactive GRs were found to be highly expressed in cultured human skin fibroblasts, KCs, and Langerhans' cells, whereas they were less expressed in melanocytes [4]. Besides, GRs were characterized in peripheral blood mononuclear leukocytes (PBMLs) [17]. In accordance with ex-vivo studies, we found GRs to be expressed *in vivo* by epidermal KCs and dermal fibroblasts, in addition to infiltrating leukocytes. Moreover, we found a significant increase in GR expression in psoriatic plaques compared with uninvolved and control skin. In addition, GR

Table 2. Glucocorticoid receptor expression in involved skin compared with uninvolved skin and control skin

Cases				Controls			
GR expression	Mean ± SD (%)	Range (%)	*P*	GR expression	Mean ± SD (%)	Range (%)	*P*
Involved epidermis	57.50 ± 16.99	26–84	0.044*	Epidermis	47.68 ± 10.28	28.8–62.7	0.033*
Uninvolved epidermis	47.4 ± 21.87	20–90					0.959
Involved dermis	40.9 ± 20.58	15–80	<0.001**	Dermis	19.35 ± 4.51	11–28.8	<0.001**
Uninvolved dermis	21.05 ± 12.86	7–46					0.589

Paired *t*-test was used to compare involved and uninvolved skin of the patients, and Student's *t*-test was used for comparisons of cases versus controls.
GR, glucocorticoid receptor.
*$P \leq 0.05$ (significant).
**$P \leq 0.001$ (highly significant).

Table 3. Comparison between patients with different psoriasis area and severity index scores on glucocorticoid receptor expression in the epidermis and the dermis of psoriatic areas, as well as uninvolved skin, using the one-way analysis of variance test

	PASI score (mean ± SD) (%)				
GR expression	Mild	Moderate	Severe	*F*	*P*
Involved epidermis	60.71 ± 19.10	52.8 ± 10.13	57.63 ± 19.65	1.250	0.535
Involved dermis	38.29 ± 26.16	43.8 ± 22.15	41.38 ± 16.42	0.078	0.962
Uninvolved epidermis	36.43 ± 17.39	43.2 ± 19.28	59.63 ± 22.88	4.351	0.114
Uninvolved dermis	20.43 ± 12.04	13.2 ± 5.07	26.5 ± 15.22	5.425	0.066

GR, glucocorticoid receptor; PASI, psoriasis area and severity index.

Table 4. Comparison between highly stressed and less stressed groups in terms of glucocorticoid receptor expression in involved and uninvolved skin

	Mean ± SD		
GR expression	Less stressed	Highly stressed	*P*
GR expression in diseased epidermis	41.14 ± 12.79	66.31 ± 11.64	<0.001**
GR expression in diseased dermis	33.57 ± 19.07	44.85 ± 21.00	0.253
GR expression in nondiseased epidermis	33.43 ± 10.37	54.92 ± 22.99	0.010*
GR expression in nondiseased dermis	19.14 ± 11.84	22.08 ± 13.73	0.639

GR, glucocorticoid receptor.
*$P \leq 0.05$ (significant).
**$P \leq 0.001$ (highly significant).

Table 5. Correlation results between patients' age, disease duration, and psoriasis area and severity index score with glucocorticoid receptor expression in the epidermis and dermis of involved and uninvolved skin

	Involved epidermis	Involved dermis	Uninvolved epidermis	Uninvolved dermis
Age				
r	−0.026	0.208	0.057	−0.041
P	0.912	0.379	0.660	0.881
Disease duration				
r	0.055	−0.094	−0.0234	−0.0207
P	0.819	0.695	0.320	0.381
PASI				
r	0.237	0.210	0.691	0.371
P	0.314	0.375	0.001**	0.108
PLSI				
r	0.768	0.387	0.595	0.049
P	<0.001**	0.092	0.006*	0.836
PGA-Ps				
r	0.523	0.278	0.912	0.390
P	0.018*	0.236	<0.001**	0.089

PASI, psoriasis area and severity index; PGA-Ps, physician's global assessment of psoriasis activity; PLSI, psoriasis life stress inventory.
*$P \leq 0.05$ (significant).
**$P \leq 0.001$ (highly significant).

expression in psoriatic epidermis correlated with expression in psoriatic dermis. This is the first study to evaluate the expression of GRs in psoriasis; to the best of our knowledge, there have been no previous studies similar to our study.

There is a clear evidence of a reciprocal relationship between inflammatory and GC signaling pathways. One possibility is that interleukin (IL)-1-induced decreases in GR shuttling from cytoplasm to nucleus may lead to

reduced autoregulation of receptor expression and thus a compensatory GR upregulation [15]. In addition, inhibition of prednisolone-induced GR translocation as well as GR-mediated gene transcription in human epidermal cells were induced by tumor necrosis factor (TNF)-α [18]. As both IL-1 and TNF-α are elaborated in psoriasis, they can influence the expression and function of GRs.

It was suggested that the activation of immune responses and the release of inflammatory cytokines may play a role in the pathophysiology of depression and stress response. Increased concentrations of IL-1, IL-6, and TNF-α, as well as their soluble receptors, have been found in the peripheral blood and/or cerebrospinal fluid of depressed patients [19]. In the current study, GR expression in the epidermis of patients' involved and uninvolved skin was found to be correlated positively with the PLSI score. These findings indicate the close interrelation between psoriasis activity, stress, and GRs expression/signaling for further functional studies. Thus, GR expression may be useful in predicting high-stress responders, and may be used in the future to guide treatment plans.

There was also a significant positive correlation between GR expression in the epidermis of psoriatic patients' involved and uninvolved skin, and both were correlated positively with psoriasis activity as determined by the PGA-Ps score, which correlated to the PLSI score. These findings again indicate the mutual relation between psoriasis activity and stress response.

Of relevance to interactions between cytokines and GR, it was reported that antidepressants show the capacity to inhibit cytokine production both *in vitro* and *in vivo* [20]. For example, amitriptyline decreased lipopolysaccharide-stimulated release of IL-1-β and TNF-α from a mixed glial culture [21]. At the same time, antidepressants were used successfully as adjuvant therapy in depressed psoriatic patients [16,22]. These data indicate that consideration should be given to therapeutic strategies that both augment GR function and/or inhibit inflammatory pathways for the treatment of psoriatic patients with psychological impact.

It was found in the present study that six (30%) of the patients expressed GRs strongly in the epidermis of uninvolved skin. Körver *et al.* [23] studied keratin expression in psoriatic lesions versus apparently normal distant skin and they found that there was homogenous expression of K6 in the center of lesions, whereas in the inner margin, K6 expression was patchy, with coexpression of K6 and K10 in single cells. In uninvolved skin, the expression of β1 integrin was decreased and K15 expression was lost, indicating a prepsoriatic phenotype, which they considered the first step in a psoriatic cascade. On the basis of the previous study by Körver *et al.* [23], it is assumed that strong GRs expression could be a marker of a prepsoriatic phenotype in uninvolved skin, as a reflection of the systemic inflammatory nature of psoriasis. Although GR expression did not vary with the PASI score and did not correlate with duration of disease, there was a highly significant positive correlation between the PASI score and GR expression in the epidermis taken from uninvolved skin. These findings again reinforce the possible prepsoriatic phenotype of uninvolved skin in psoriatic patients because of systemic rather than local inflammation.

In this study, there were no significant correlations between age and GR expression in the epidermis and dermis of either diseased or control skin. Similarly, Aljubeh *et al.* [24] showed no differences in the binding capacity of PBML' GR characteristics on the basis of patients' weight or age, whereas Tanaka *et al.* [25] found an age-related decrease in the number of GRs in PBML only between extremes of age: patients younger than 20 years and elderly patients.

In an attempt to study GR expression and characteristics in relation to serum cortisol level, Huizenga *et al.* [17] studied PBMLs-GR expression in patients with Cushing's syndrome compared with controls. They found that receptor downregulation does not occur in PBMLs from patients with endogenous Cushing's syndrome. However, there seemed to be a reduced ligand affinity, which possibly reflects receptor modification in response to exposure to the continuously high cortisol levels in patients with Cushing's syndrome. This assumption was substantiated by the fact that in one patient, a normalization of the ligand affinity was observed after complete remission of the disease [17]. However, previous studies on abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis in psoriatic patients have yielded controversial results. In contrast to Weigl [26], who found excess serum cortisol level in patients with erupting psoriasis, Thaller *et al.* [27] reported unusually low cortisol levels. Nevertheless, no particular neuroendocrine profile of HPA axis responsiveness was identified in psoriatic patients by Karanikas *et al.* [28]. However, Atzeni *et al.* [29] linked improvement in psoriasis to higher serum cortisol levels relative to other adrenal hormones. Evers *et al.* [30] also showed that psoriatic patients with persistent high daily stressors had lower cortisol levels compared with other patients. Further studies on larger psoriatic population are needed to establish certain findings on possible dysregulation in the HPA axis, and abnormal cortisol levels with correlation to GR expression and function.

Conclusion

Higher GR expression in psoriatic involved skin compared with uninvolved and control skin, with correlation to disease activity, and high life stress indicates the reciprocal relationship between inflammation, stress response, and GC signaling pathways for future correlation with functional studies and possible dysregulation in the HPA axis. The presence of a group of patients expressing GRs strongly in the epidermis of clinically uninvolved skin indicates a prepsoriatic phenotype in distant uninvolved skin of patients with active disease, as evidenced by the correlation between GR expression in uninvolved skin and psoriasis activity. These results pave the way toward adoption of therapeutic strategies that augment GR

function and/or inhibit inflammatory pathways, and tackle both psoriasis and its psychological impact.

Limitations

The absence of a correlation with possible dysregulation in the HPA axis and serum cortisol levels are limitations.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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