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Evaluation of psoriasis patients with long-term topical corticosteroids for their risk of developing adrenal insufficiency, Cushing's syndrome and osteoporosis

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ABSTRACT

Purpose: In this study, we will investigate the possible side effects of psoriasis patients using long-term topical corticosteroids (TCS) such as adrenal insufficiency, Cushing's Syndrome (CS) and osteoporosis and determine how these side effects develop.

Material and Methods: Forty-nine patients were included in the study. The patients were divided into two groups based on the potency of the topical steroid they took and the patients' ACTH, cortisol and bone densitometer values were evaluated.

Results: There was no significant difference between the two groups regarding the development of surrenal insufficiency, CS and osteoporosis. One patient in group 1 and 4 patients in group 2 were evaluated as iatrogenic CS. ACTH stimulation tests of these patients in group 2 showed consistent results with adrenal insufficiency, while no adrenal insufficiency was detected in the patient in Group 1. Patients who used more than 50g of superpotent topical steroids per week compared to patients who used 50g of superpotent topical steroids per week. It was identified that patients who used more than 50g of superpotent topical steroids had significantly lower cortisol levels, with a negatively significant correlation between cortisol level and the amount of topical steroid use ($p < .01$).

Osteoporosis was detected in 3 patients in group 1 and 8 patients in Group 2. Because of the low number of patients between two groups, statistical analysis could not be performed to determine the risk factors.

Conclusions: Our study is the first study that we know of that investigated these three side effects. We have shown that the development of CS, adrenal insufficiency and osteoporosis in patients who use topical steroids for a long time depends on the weekly TCS dosage and the risk increases when it exceeds the threshold of 50 grams per week. therefore, our recommendation would be to avoid long-term use of superpotent steroids and to choose from the medium-potent group if it is to be used.

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Iatrogenic cushing's syndrome; osteoporosis; psoriasis; adrenal insufficiency; topical corticosteroid

Introduction

Plaque psoriasis is a chronic inflammatory skin condition characterized by erythematous, squamous plaques (1). Topical corticosteroids (TCS) which are the first-line treatment for mild psoriasis are frequently used in combination with other therapies for moderate to severe cases. Prolonged and high-dose use of TCS can lead to systemic absorption, resulting in systemic side effects. Although it is well known that TCS can induce systemic side effects, there is limited research on the factors that affect their development (2–4).

Since topical corticosteroids can be obtained from pharmacies without a prescription in our country, a large number of psoriasis patients who have been using topical steroids for a long time applied to our clinic. In most of these patients, systemic side effects were present in addition to topical side effects. We aimed to investigate the occurrence of adverse effects such as adrenal insufficiency, Cushing's Syndrome (CS) and osteoporosis in patients using long-term TCS and the factors affecting these side effects. This study is important, because it is the first study conducted with a patient group in which these three diseases were investigated.

Material and method

The study included 49 patients diagnosed with psoriasis, who were seen at the dermatology outpatient clinics of Health Sciences University Diskapi Yildirim Beyazit Training and Research Hospital in Ankara, Turkey, between September 2016 and August 2018 and were known to use long-term TCS. Patients who included in the study had used super-potent/potent topical steroids as monotherapy, applying at least 50 grams (g) per week for a minimum of one month. Patient data including age, gender, contact information, family and personal medical history, duration of psoriasis, name of TCS, dermatological and systemic examination findings (such as moon facies, buffalo hump, striae, acne, hirsutism,

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pleatore, central obesity) and Psoriasis Area and Severity Index (PASI) were obtained from patient records at the time of their initial visit.

Data from patients referred to the endocrinology department for possible CS were retrospectively reviewed by an endocrinologist, and relevant information was documented in the case evaluation form. Patients were stratified into subgroups based on TCS usage duration, those who used less than 52 weeks or longer (5), and those who used 50 g or more than 50 g per week (6). Patients who received other treatments for psoriasis simultaneously, such as topical treatments, phototherapy or systemic therapy, and patients who received systemic steroid therapy for any reason, were excluded from the study. Additionally, patients under 18 years of age, those with a prior diagnosis of osteoporosis, adrenal insufficiency, or CS, individuals with a history of drug use or systemic illnesses known to cause osteoporosis or CS, patients with malignancies, pregnant or breastfeeding women were not included in the study.

Patients who used TCS for an extended period were evaluated for cortisol and adrenocorticotropic hormone (ACTH) levels in peripheral venous blood samples collected between 06:00–08:00 h, following a minimum 8-h fasting period. Cortisol levels below 6.7 µg/dL (normal range: 6.7–22.6 µg/dL) and ACTH levels below 10 pg/mL (normal range: 10–46 pg/mL) were considered 'suppressed' and patients with these values are referred to the endocrinology department. In the endocrinology department, a 250 µg ACTH stimulation test was performed on patients with suppressed cortisol and ACTH levels or only suppressed cortisol levels. Cortisol levels were measured before and at 30, 60 and 90 min after drug administration.

Cortisol levels exceeding 18–20 µg/dL at any time are indicative of normal adrenal reserve, while levels below 18 µg/dL indicate adrenal insufficiency. Patients diagnosed with adrenal insufficiency were monitored at monthly intervals to assess their morning fasting cortisol values. The date when cortisol levels returned to the normal range was recorded to determine the hypothalamic-pituitary-adrenal axis recovery time.

Patients undergoing on long-term steroid therapy were also evaluated for osteoporosis by performing bone mineral densitometry. Bone mineral density was assessed using the dual-energy X-ray absorptiometry (DEXA) method. Osteoporosis and osteopenia diagnoses were made according to the criteria outlined by the World Health Organization.

In this research, the data obtained from the participants were analyzed using the SPSS 15.0 IBM package program. Since the number of groups constituting the sample is below 30, non-parametric tests were used in all evaluations. Descriptive analysis methods were used in the evaluation of sociodemographic data. Mann Whitney U was used when making comparisons between groups. Additionally, Spearman Correlation methods were used to examine the relationship between dependent variables. The level of statistical significance was accepted as $p < .05$.

Findings

A total of 49 patients with psoriasis were enrolled in the study. Group 1 consisted of 24 patients who used potent topical corticosteroids (TCS) such as mometasone furoate lotion, mometasone furoate pomade, and betamethasone dipropionate ointment, while Group 2 comprised 25 patients who used superpotent TCS (clobetasol propionate). There were no statistically significant differences between the two groups regarding average age, duration of illness, disease severity and average weekly amount of steroid use (Table 1).

Both groups 1 and 2 were further divided based on the amount of TCS use per week (less or more than 50 g per week) and total duration of TCS use (less than or longer than 52 weeks) and analyzed separately. In Group 2, it was found that the cortisol levels of patients using super-potent TCS more than 50 grams per week (mean = 9.09 µg/dL, $U = 34$, $p < .05$) were significantly lower than cortisol levels of patients using 50 grams per week (mean = 16.73 µg/dL).

The ACTH and cortisol values, femoral neck T and Z scores and L1-L4 T score values of the patients in group 1 and group 2 are shown in the table (Table 2). While a significant difference was found between the groups only in terms of ACTH values, no significant differences were observed in cortisol values, DEXA femoral neck T scores and Z scores, DEXA L1-L4 T and Z scores or the presence of osteoporosis. ACTH values in group 2 (avg = 20.96) were significantly lower than those in group 1 (avg= 30.42) ($U = 194$, $p < .05$).

There were 1 patient in Group 1 and 4 patients in Group 2 with values below the threshold for ACTH and cortisol. All 5 patients with low ACTH and cortisol levels were diagnosed with iatrogenic CS based on their clinical features, ACTH and cortisol levels and a history of external TCS uses. Adrenal insufficiency was detected in 4 patients. The mean recovery time of the axis was calculated as 2 ± 0.81 months (Table 3).

When evaluating the cushingoid findings in the patients, all 5 patients had moon facies, central obesity, and buffalo hump. Acne

Table 1. Distribution of the sample groups according to age, PASI, duration of illness, weekly amount.

	Group 1 ($n = 24$)	Group 2 ($n = 25$)
Age	54	46.38
Duration of illness (years)	14.58	16.86
Mean PASI at presentation	12.17	12.44
Weekly amount of topical steroid use (g)	62.29	87
Active substance of topical steroid used	**number of patients**	**number of patients**
Mometasone furoate lotion (class 4)	6	0
Mometasone furoate pomade (class 2)	13	0
Betamethasone dipropionate ointment (class 2)	5	0
Clobetasol propionate (class 1)	0	25

Table 2. ACTH, cortisol and DEXA results.

	Group 1 ($n = 24$)		Group 2 ($n = 25$)	
Screening for ACTH /adrenal insufficiency	*n*	%	*n*	%
above 10 pg/ml	23	95.8	23	92
below 10 pg/ml	1	4.2	2	8
Screening for cortisol/adrenal insufficiency	*n*	%	*n*	%
above 6.7 µg/dL	23	95.8	21	84
below 6.7 µg/dL	1	4.2	4	16
DEXA femoral neck according to the T score	*n*	%	*n*	%
normal	15	62.5	17	68
osteopenia	9	37.5	6	24
osteoporosis	0	0	2	8
DEXA L1-L4 according to the T Score	*n*	%	*n*	%
normal	13	54.1	11	44
osteopenia	8	33.3	8	32
osteoporosis	3	12.5	6	24

Table 3. Sociodemographic and clinical characteristics, ACTH, cortisol values and time of axis recovery of five patients screened for adrenal insufficiency.

Patient	Group	Age	Gender	ACTH	Cortisol	Axis recovery time (month)	Duration of steroid use (month)	Amount of steroid use (g/week)	PASI
1.	1	88	M	10	6.12	–	48	100	18
2.	2	53	M	15	1.03	1	24	150	6.4
3.	2	37	M	<5	0.01	2	60	50	36.9
4.	2	58	M	26.9	0.23	2	36	100	38
5.	2	56	F	<5	0.05	3	500	350	10

M: male F: female.

Table 4. Sociodemographic and clinical characteristics and DEXA scores of patients diagnosed with osteoporosis.

Patient	Group	Gender (age)	Smoking	DEXA femoral T-score	DEXA L1-L4 T score	DEXA femoral Z-score	DEXA L1-L4 Z score	duration of steroid use (month)	the amount of steroid use (g/week)
1.	1	M (71)	–	−0.5	−2.6	−0.7	−2	48	90
2.	1	M (37)	–	−1.1	−2.7	−0.9	−2.7	12	50
3.	1	F (54)	–	−1.2	−3	−0.8	−3	48	60
4.	2	M (53)	–	−1.5	−2.7	−1.1	−1.8	120	50
5.	2	M (31)	+9 packages/year	−1.1	−2.6	−0.7	−2	150	50
6.	2	M (50)	+5 packages/year	−1.4	−3.2	−1.1	−2.7	120	50
7.	2	F (28)	–	0.5	−2.5	0.6	−2.5	12	50
8.	2	M (79)	–	−1.4	−3.5	−1.5	−2.5	3	50
9.	2	M (68)	–	−2.6	−2.7	−2	−0.7	130	150
10.	2	F (56)	–	−2.7	−2.3	−2.1	−2	500	350
11.	2	M (37)	+10 packages/year	−0.9	−0.2	−0.7	−2.1	60	50

was observed in only the second patient, and no cushingoid findings were observed in the other 44 patients. Liver and kidney function tests, complete blood counts and serum electrolyte levels (sodium, potassium, chloride, calcium, phosphorus) were all within normal ranges for all patients.

Osteroporosis was diagnosed in 3 patients in group 1 and 8 patients in group 2 according to T and *Z* scores (Table 4). Due to the small number of patients, statistical analysis could not be performed between the groups. Biochemical tests for the 11 patients diagnosed with osteoporosis were retrospectively analyzed in the hospital's automation system. Calcium (Ca), parathormone (PTH), vitamin D, phosphorus, thyroid-stimulating hormone (TSH) and T4 levels were recorded. Biochemical data for the first patient could not be obtained. Ten patients had low 25-OH vitamin D levels. The patients were also evaluated for other secondary causes of osteoporosis such as DM, chronic liver disease, chronic kidney disease, plasma cell dyscrasia, thyroid diseases, hyperparathyroidism, connective tissue diseases. None of the patients had any comorbidities.

Discussion

In this study, we aimed to identify the factors contributing to the suppression of the HPA axis, the development of osteoporosis and these systemic side effects caused by TCS in patients with plaque-type psoriasis who have used TCS for an extended duration.

Topical corticosteroids are the primary and most frequently utilized medications for cases of localized plaque psoriasis. They possess various effects, including anti-inflammatory, antiproliferative, antimitotic, immunosuppressive and vasoconstrictive properties. Topical corticosteroids are classified into seven classes based on their vasoconstrictive effects, super potent TCS are included in class 1 (for example; clobetasol propionate cream and ointment) (2,4–6). While localized side effects of TCS are commonly observed, systemic side effects occur when the drug enters the systemic circulation through the epidermis and dermis. One of systemic side effects is the suppression of the HPA axis. Exogenous corticosteroids from external sources lead to hypercortisolemia upon entering the systemic circulation, eventually can stop glucocorticoid production in the adrenal gland. This condition results in HPA axis suppression, which can be of a physiological, resolve quickly or potentially lead to adrenal insufficiency or crisis. However, precise data on the timing of suppression and the necessary dosage and duration of corticosteroid use are currently lacking. We designed a study to find answers to all these questions, we considered psoriasis patients who used uncontrolled TCS for a long time.

When evaluating the HPA axis, the initial assessment should include measuring serum cortisol and ACTH levels in the morning (7,8). In our study, ACTH values were significantly lower in Group 2. Although ACTH alone may not be sufficient to diagnose adrenal insufficiency, this finding suggests a greater risk of suppression associated with super-potent TCS. A significant negative correlation was observed between the quantity of super-potent TCS used and cortisol levels when comparing both groups in terms of the effects of TCS volume and duration of use on ACTH and cortisol levels. These findings indicate that super-potent TCS may have a more pronounced effect on suppressing cortisol levels, with weekly usage amounts being more significant than the duration of use. A study conducted by Cornell et al. showed that the potency of TCS plays a very important role in suppressing cortisol levels, which is consistent with our data (9).

Regarding the development of adrenal insufficiency, we did not find a statistically significant difference between the two groups. However, it was noted that four patients in the super-potent TCS group 2 and only one patient in the potent TCS group 1 had cortisol levels below the normal range. The ACTH stimulation test confirmed adrenal insufficiency in all four patients in group 2 who used super-potent TCS, but adrenal function remained normal in one patient in group 1. Although statistical conclusions cannot be drawn due to the small sample size, it is recommended to keep this information in mind when prescribing super-potent TCS. It typically takes an average of 2 to 4 months for the HPA axis to return to normal after discontinuing steroid use, and in some cases, this period may extend up to 1 year. The mean recovery

time of the axis was calculated as 2 ± 0.81 months in our study. As a result, basal serum cortisol levels should be monitored every 4–6 weeks and systemic corticosteroid support should be administered as needed (e.g. during periods of stress, infection, or before surgical procedures) (7–9).

The amount of weekly use is also an important marker for the suppression of the adrenal axis in addition to the potency of TCS. To understand the amount of weekly use and the effect of amount on the HPA axis, we conducted our study with two subgroups: In group 2, the cortisol levels of patients using more than 50 g of super-strong TCS per week (mean = 9.09 µg/dL, $U = 34$, $p < .05$) were found to be significantly lower than those of patients using 50 g per week (mean = 16.73 µg/dL). In a meta-analysis by Levin et al. cortisol values were found to be low in six of the 13 patients, and it was stated that five of these patients used at least 50 g of clobetasol propionate per week The study emphasized be careful when prescribing more than 50 grams of super-potent TCS per week to patients with dermatological conditions (10). Our study, similar to the data in this meta-analysis, supported that the use of TCS significantly increases the probability of suppression of the HPA axis when it exceeds 50 g per week.

Cushing's Syndrome, is a rare endocrine disorder characterized by prolonged elevation of cortisol levels, it occurs mainly in an iatrogenic form due to prolonged use of exogenous steroids. Clinical manifestations include central obesity, changes in fat distribution leading to dorsocervical and supraclavicular fat pad, facial plethora, moon facies, purple striae, spontaneous ecchymosis, hirsutism, acne and other features contributing to cushingoid appearance in patients (7,8,11,12). In our study, exogenous CS was diagnosed in 5 out of 49 patients and adrenal insufficiency was detected in 4 of these five patients. Although very few case reports have been published in the literature, the rates found in our study, which included only psoriasis cases, indicate that this condition is not very rare and may be overlooked in clinical practice. In all of our patients, the HPA axis returned to normal with the cessation of TCS. Nakamura et al. published a literature review aimed at identifying individuals who developed pathological adrenal sufficiency among 14 adult cases of CS associated with the use of superpotent TCS. All cases used at least 25 grams of clobetasol propionate per week for at least a year. The authors stated that they could not find a case with pathological adrenal insufficiency without CS in the literature and the presence of CS can be a very important clue for adrenal insufficiency (11). There is also a growing acceptance that the suppression of the HPA axis and the development of KS may be influenced by individual differences related to corticosteroid metabolism and glucocorticoid receptor sensitivities (12). Some studies have suggested that some patients may show increased sensitivity to glucocorticoids due to the presence of genetic polymorphisms associated with receptor sensitivity (13). Given these findings, it is reasonable to assume that personal factors, as well as TCS use, play an important role in the development of CS and adrenal insufficiency. Clinicians should take into account individual patient factors when prescribing superpotent TCS and make the necessary warnings to their patients to avoid long-term use.

Corticosteroids are known to cause a reduction in bone mineralization and the suppression of bone formation by affecting the synthesis of sex steroids and negatively affecting calcium metabolism. They are the most common cause of secondary osteoporosis. While these side effects are frequently observed with oral and inhaler forms, there are relatively few reported cases related to TCS use in the literature (14,15). A large cohort study of 723,251 patients who used 200 mg of mometasone furoate per week or an equivalent amount of potent or super-potent topical corticosteroids reported that the use of potent and super-potent topical corticosteroids is indeed a risk factor for osteoporosis. Furthermore, the risk of developing osteoporosis appears to increase with the amount of corticosteroid use (16). In our study, although no statistically significant difference was observed between the two groups, it is noteworthy that of the 11 patients diagnosed with osteoporosis or osteopenia, only 3 were in Group 1, while the remaining 8 were in Group 2. This suggests that prolonged use of super-potent topical corticosteroids may indeed pose a greater risk to bone health.

When we analyzed the DEXA results of 5 patients diagnosed with CS, we found that one patient had osteoporosis, three patients had osteopenia, and only one patient had normal DEXA scores. This underscores the potential role of cushingoid features as a warning sign for doctors to assess patients not only for adrenal insufficiency but also for osteoporosis. Early detection of decreased bone mineral density and the implementation of supportive treatments may offer opportunities for recovery or at least prevent further deterioration of bone health in these individuals.

Conclusion

Our study is the first study that evaluate the side effects of topical steroids, such as CS, adrenal insufficiency and osteoporosis together and address the underlying factors for the development of these side effects. It has been shown that super-strong TCS have a higher tendency to induce adrenal insufficiency, CS, and osteoporosis compared to strong topical corticosteroids, indicating that studies with larger patient groups may yield important results in this regard.

Study limitations encompass its retrospective nature, small sample size and the inability to conduct more extensive statistical analyses due to the limited number of subjects. Additionally, data on patients' body surface areas, baseline DEXA scans and initial values for ACTH and cortisol levels are unavailable. Besides, in our study, the duration of super potent corticosteroid use of patients was significantly longer compared to the use of potent topical steroids. This situation can also be shown as a limitation. Due to all these restrictions, although an exact value related to the duration and amounts of use of topical steroids has not been determined, the data obtained will still be a guide for clinicians.

In summary, it can be assumed that the development of CS, adrenal insufficiency and osteoporosis in patients using topical steroids for a long time depends on the weekly TCS dosage and the risk increases when it exceeds the threshold of 50 g per week. Since none of the patients in our study developed adrenal insufficiency when using class 2 and class 4 TCS, it would be safer to choose steroids in these groups in cases requiring long-term and maintenance TCS administration.

Author contributions

Conception and design: Betul ERDEM, Muzeyyen GONUL, analysis of the data: Muzeyyen GONUL, Betul ERDEM, Ilknur Ozturk Unsal, Seyda Ozdemir Sahingoz, the drafting of the paper: Betul ERDEM, Muzeyyen GONUL revising it critically: Muzeyyen GONUL.

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Data availability statement

Data openly available in a public repository that issues datasets with DOIs.

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