

## CLINICAL REPORT

# Calcium Channel Blockers Intake and Psoriasis: A Case-control Study

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***In vitro* evidence suggests that intracellular calcium metabolism influences keratinocyte differentiation. However, only a few reports have described exacerbation of psoriasis or psoriasiform eruptions due to intake of calcium channel blockers. We conducted a case-control study to evaluate the association between exposure to calcium channel blockers and psoriasis. Data were obtained through a retrospective assessment of the files of 150 patients hospitalized for psoriasis or psoriasiform eruptions and 150 matched control patients. Exposure to calcium channel blockers was recorded in case and control patients. It was found that 13/150 patients hospitalized for psoriasis consumed calcium channel blockers. Calcium channel blockers were associated with precipitation of new-onset psoriasis ( $n = 2$ ), as well as with the exacerbation of psoriasis ( $n = 11$ ). The calcium channel blockers were as follows: nifedipine ( $n = 10$ ), felodipine ( $n = 2$ ) and amlodipine ( $n = 1$ ). The median latent period between the beginning of intake of calcium channel blockers and precipitation or exacerbation of psoriasis was 28 months (range 4–143 months). A stepwise multivariate logistic regression analysis demonstrated that intake of calcium channel blockers was significantly associated with psoriasis, as compared to the control group ( $p = 0.018$ ). Our study implies a possible role of calcium channel blockers as precipitating or exacerbating factors in patients with psoriasis. Key words: psoriasis; calcium; channel blockers; beta blockers; drug reactions.**

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Drugs known to influence the onset or course of psoriasis are lithium, anti-malarial agents, non-steroidal anti-inflammatory drugs and beta-blockers. Angiotensin-converting enzyme inhibitors and miscellaneous agents have also been associated with psoriasis (1–11). Drugs may act by precipitation of new-onset psoriasis, in one of its defined forms, as a psoriasis-like (psoriasiform) eruption or by exacerbation of pre-existing psoriasis.

*In vitro* evidence suggests that calcium metabolism is important in the differentiation of keratinocytes and may be involved in the pathogenesis of psoriasis (12, 13). A literature search revealed only two reports of psoriasiform eruptions associated with intake of calcium channel blockers (14, 15).

We conducted a case-control study in order to evaluate the association between exposure to calcium channel blockers and precipitation or exacerbation of psoriasis.

## PATIENTS AND METHODS

### Patients

The study included 150 patients hospitalized for psoriasis or psoriasiform eruptions in the Department of Dermatology at the Soroka University Medical Center, between 5 May 1989 and 30 April 1999. Patients who were hospitalized more than once for psoriasis were included only at the first admission. Excluded from the study were patients for whom a diagnosis of psoriasis or psoriasiform eruption was not definite (e.g. patients with palmo-plantar pustulosis).

Inclusion criteria for the control group were determined in view of previous dermato-epidemiologic studies in psoriasis (16) and severe cutaneous drug reactions (17). Patients admitted to the same dermatology department in the same years, matched for age and sex, were selected as controls. Inclusion criteria for control patients were as follows: 1) acute dermatological diseases, unrelated to drug intake (e.g. acute contact dermatitis), 2) dermatological diseases unrelated to internal diseases, immunosuppression or immunosuppressive therapy (e.g. excluding patients with pemphigus vulgaris).

A total of 161 control patients were eligible for evaluation. After performing a review process, 11 controls were excluded from the study, leaving 150 control patients for the analysis. The admitting diagnoses of the control patients were as follows: 54 patients (36.1%) had acute contact dermatitis, 35 (23.3%) had skin infections (consisting mainly of cellulitis), 11 (7.3%) had insect bites, and 50 (33.3%) had miscellaneous conditions (consisting mainly of various forms of dermatitis or photodermatoses not related to drug intake). The characteristics of all patients are presented in Table I. Patients' characteristics with respect to gender and age were similar in the case and control groups.

### Methods

Data were collected retrospectively from the patients' files, recording demographic and clinical characteristics, as well as data on the exposure to calcium channel blockers. Drug intake was recorded as indicated in the files, with no time limitation for assessment of drug exposure.

### Determination of the index date

For case patients with new-onset psoriasis, the index day was defined as the first day of the appearance of rash. For case patients with exacerbated psoriasis, an index date was defined as a generalized spread of lesions in a patient with stable psoriasis or the appearance of erythroderma or of generalized pustular psoriasis. In the case of patients with psoriasiform eruptions, the index date was determined as the day of appearance of the rash. For control patients with chronic dermatoses, the index date was defined as the date of exacerbation of the disease leading to hospitalization. In control patients with acute dermatoses, the index date was defined as date of appearance of the dermatological disease.

### Statistics

A statistical analysis was performed to compare intake of drugs by case and control patients, as previously described (17). Drugs were grouped on the basis of similar chemical structure or pharmacological

effect. Chi-square test or Fisher's exact test were used as necessary. A stepwise multivariate logistic regression model was used for analysis.

A calculation assuming a 10% exposure to calcium channel blockers in the case of patients and a 1% exposure to calcium channel blockers in controls showed that a target sample size of 121 cases and 121 controls would give an 80% chance to reject the null hypothesis at  $p=0.05$  level of significance.

## RESULTS

Calcium channel blockers were taken by 13 patients (9 men and 4 women) in the case group compared to 3 patients in the control group. The mean age of these 13 patients was  $64.1 \pm 8.9$  years. Patient and control characteristics are presented in Table I. Two patients had new-onset psoriasis and 11 patients had an exacerbation of pre-existing disease. Three patients had psoriatic arthritis and 10 patients had characteristic nail involvement. Three patients had palmo-plantar psoriasis and one patient had a positive family history of psoriasis.

The calcium channel blockers taken by the patients were as follows: nifedipine (10 patients), felodipine (2 patients) and amlodipine (1 patient) (Table II). The median latent period between the intake of calcium channel blockers and the precipitation or exacerbation of psoriasis was 28 months, ranging from 4 to 143 months. Seven patients took concomitantly beta-blockers (atenolol-5 patients, propranolol-1 patient, metoprolol-1 patient and a combination of propranolol and atenolol-1 patient).

A stepwise logistic regression analysis revealed that intake

of calcium channel blockers was significantly associated with psoriasis ( $p=0.018$ ) (Table III).

## DISCUSSION

In previous case reports and studies, efforts were made to identify drugs associated with psoriasis (1–11). In the current study, a case-control study was performed in order to estimate the role of exposure to calcium channel blockers in patients with psoriasis. A stepwise multivariate logistic regression analysis demonstrated that intake of calcium channel blockers was significantly associated with psoriasis, as compared to the control group ( $p=0.018$ ).

The use of calcium channel blockers was associated with precipitation of new-onset psoriasis as well as with exacerbation of psoriasis, but there was no association with psoriasis-form eruptions. Because of the small size of the study it was not possible to perform sub-group analyses according to the onset of psoriasis or sub-type of psoriasis.

In our study, we could not demonstrate a significant association between beta-blockers intake and psoriasis when using the multivariate model, which is contrary to previous observations (1, 2, 4–8). As 7/13 patients (53.8%) who took calcium channel blockers also took beta-blockers, it is possible that calcium channel blockers and beta blockers imposed a synergistic influence in our patients. However, our results may represent our patient population only, and should be repeated in additional cohorts in order to clarify possible complex

Table I. Patients' characteristics

	Case patients (n = 150)	Control patients (n = 150)
Male/female (ratio)	94/56 (1.68)	94/56 (1.68)
Age (years)		
Mean $\pm$ SD	45.1 $\pm$ 17.8	46.3 $\pm$ 17.9
Median (Range)	45 (13–88)	44 (14–87)
Admitting diagnoses	Plaque-type psoriasis (n = 133)	Acute contact dermatitis (n = 54)
	Psoriasiform eruption (n = 5)	Skin infections (n = 35)
	Guttate psoriasis (n = 6)	Insect and spider bites (n = 11)
	Generalized pustular psoriasis (n = 6)	Miscellaneous (n = 50)

Table II. Characteristics of 13 patients with psoriasis and intake of calcium channel blockers

Patient no.	Age/sex	Effect on psoriasis	Calcium channel blockers intake	Latent period (months)*	Family history of psoriasis	Nail involvement	Psoriatic arthritis	Concomitant use of beta-blockers
1	50/F	Exacerbation	Nifedipine	12	–	+	–	+
2	50/M	Exacerbation	Nifedipine	36	–	+	–	+
3	55/M	Exacerbation	Nifedipine	7	–	+	–	–
4	58/M	Exacerbation	Nifedipine	143	–	+	+	–
5	59/M	Exacerbation	Nifedipine	84	–	+	–	+
6	63/M	Exacerbation	Amlodipine	24	–	+	–	–
7	66/F	New onset	Nifedipine	52	+	+	+	–
8	70/M	Exacerbation	Nifedipine	34	–	–	–	+
9	70/F	Exacerbation	Felodipine	13	–	+	–	–
10	70/M	New onset	Felodipine	4	–	+	–	+
11	73/M	Exacerbation	Nifedipine	20	–	–	–	+
12	73/M	Exacerbation	Nifedipine	32	–	+	–	–
13	76/M	Exacerbation	Nifedipine	Unknown	–	–	+	+

\*Latent period was defined as the time lag between the beginning of intake of a drug and the appearance of psoriasis de-novo or exacerbation of psoriasis (for definition of exacerbation of psoriasis, see text).

Table III. Stepwise multivariate model for cardiovascular drugs suspected of being associated with psoriasis vulgaris

Drug	Case patients (n = 150)	Controls (n = 150)	Crude p-values	Multivariate p-values	Multivariate odds ratios (95% confidence intervals)
	No. (%) of patients exposed				
Calcium channel blockers	13 (8.7%)	3 (2%)	0.02	0.018	3.5 (1.3–16.6)
Beta-blockers	12 (8%)	3 (2%)	0.034	Not in model	–
ACE inhibitors	9 (6%)	6 (4%)	0.43	Not in model	–

ACE = Angiotensin converting enzyme.

associations between psoriasis and intake of beta blockers or calcium channel blockers.

The latent period between the intake of calcium channel blockers and precipitation or exacerbation of psoriasis was long (median duration: 28 months). This protracted latency is similar to the long latent period between the beginning of intake of beta-blockers and the precipitation or exacerbation of psoriasis, estimated as 1–3 years (1, 2, 4–7). No explanation has been suggested for the long latent period.

Only 1/13 patients (7.7%) who took a calcium channel blockers had a positive family history of psoriasis, as compared to 26/137 (19.0%) patients who did not take calcium channel blockers in the study. We may therefore presume that calcium channel blockers can exert their influence on psoriasis, regardless of a genetic background.

The possible influence of calcium channel blockers on psoriasis may ensue from their effect on keratinocyte differentiation, which is dependent on intracellular calcium levels (12). Derangement in calcium metabolism has been suggested as a possible mechanism for the influence of beta-blockers on psoriasis (18–20). This may also imply an effect of calcium channel blockers on psoriasis. A recent study has demonstrated that calcium influx, which is needed in the processing of profilaggrin to filaggrin, a final event in the cornification of epidermal cells, was inhibited by the calcium channel blocker nifedipine (13).

The current study was designed to test the potential impact of calcium channel blockers on psoriasis. Although our results are supported by *in vitro* evidence (12, 13), we suggest that a further large-scale dermato-epidemiologic study, using analytic epidemiologic methods, is needed to elucidate the relationship between intake of calcium channel blockers, beta-blockers or other drugs and the precipitation or exacerbation of psoriasis.

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