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Effects of Allergen Avoidance at High Altitude on Children with Asthma or Atopic Dermatitis

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ABSTRACT

Patients with atopic diseases benefit from a high-altitude climate, the effectiveness of which may be related to established house dust mite allergy. A relationship between these variables and disease severity as well as inflammatory activity has not been previously studied. The study objectives were: (1) to assess changes in inflammatory levels for children and adolescents with asthma or atopic dermatitis during a 4-week inpatient rehabilitation stay at high altitude, (2) to examine the role of house dust mite sensitization, and (3) to compare the results for the two diagnostic groups. A total of 115 children and adolescents aged 10–16 years were enrolled in the study: 60 suffered from asthma and 55 from atopic dermatitis. The prevalence of house dust mite sensitization was 36.52%. Urine and blood samples were collected on admission to an inpatient rehabilitation clinic and at their discharge 1 month later. Urinary eosinophil protein X (U-EPX) and serum eosinophil cationic protein (S-EPC)-levels were analyzed. Informed consent from the parents was obtained for each participant. A 4-week period of high-altitude allergen avoidance results in significant improvement in disease severity (as assessed by FEV_1 and SCORAD, respectively). A significant decrease in U-EPX levels during that period was observed. House dust mite sensitization did not influence the results. The lack of an association between house dust mite sensitization status and degree of improvement suggests that all children with an atopic disease benefit from such a stay. (Pediatr Asthma Allergy Immunol 2004;17[1]:15–24.)

INTRODUCTION

ATOPIC DERMATITIS (AD) and asthma are chronically relapsing diseases characterized by inflammation of the skin or the airways, respectively. For both conditions, the role of eosinophils as important effector cells in inflammation is well established. Several recent studies suggest that eosinophil cationic protein (ECP) levels are related to bronchial hyperreactivity in asthmatic patients[1,2] and to skin condition in patients with AD.[3–6] It is necessary to collect blood samples to determine ECP levels. However, invasive studies are not easily performed in children. Therefore, several authors have studied whether eosinophil protein X in urine could be indicative of inflammatory activity. The results of these studies are promising:

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Increased levels of urinary eosinophil protein X (U-EPX) appear to decrease pulmonary function in asthma[1,2,7,8] and increase disease activity in AD.[5] The findings of these previous studies suggest that eosinophil proteins in serum and urine may reflect ongoing inflammation. Czech et al.[3] conclude that eosinophil markers provide a more precise basis for monitoring disease activity than a clinical scoring system.

Asthma and AD are multifactorial diseases, and many factors or conditions can make symptoms of AD and asthma worse, further triggering the already overactive immune system. These exacerbating factors can be broken down into two main categories: irritants (like wool, detergents, or cigarette smoke) and allergens (e.g., pollens, molds, or dander from pets). Emotional factors and some infections can also influence the course of disease. In recent years, there is more conclusive evidence that sensitization to house dust mite allergens is one important factor in the development and deterioration of atopic diseases. The western way of living (e.g., central heating, double glazing, and soft furnishings) provides ideal conditions for house dust mites (HDM) to reproduce. Therefore, control of exposure with HDM should be an integral part of the disease management in sensitized patients. The results of a recent meta-analysis[9] do not support chemical or physical methods as effective treatments.

It is well known that changes in climate can influence the course of atopic diseases. Especially living in a high-altitude climate has been reported to be associated with significant improvements.[1,6] High-altitude climate is associated with a reduction of environmental pollution, and a reduction, or even absence of pollen and HDM. This diminished exposure to allergens has been postulated to be responsible for the positive effects of high-altitude climate. Recently, several studies have investigated the effects of high-altitude climate on inflammatory activity in asthmatic children sensitized to HDM. Their results suggest that natural allergen avoidance in high-altitude climate decreases the eosinophil phase of inflammation and the eosinophil counts in sputum; correspondingly serum levels of ECP and EPX are reported to rise as a consequence of allergen exposure.[1,10–14] Furthermore, preliminary data are available for the positive influence of high-altitude climate on adults with AD.[6] In summary these data support the positive effects of allergen avoidance on eosinophil markers.

The studies also provide preliminary evidence that monitoring eosinophil activity is a predictive marker for disease severity. Although a number of studies on eosinophil levels in children with asthma exist, there is very little literature concerning eosinophil levels in children with AD. Little is known about the influence of allergen avoidance at high altitude on eosinophil activation in children with either asthma or AD. This is especially true for the hypothesized moderating effect of HDM sensitization.

The present study provides a detailed examination of different markers. The goal of this paper is threefold. (1) We wanted to assess changes in disease severity and inflammatory levels associated with a 4-week in-patient rehabilitation stay. We hypothesized that this stay would be accompanied by a reduction in disease severity reflected by a decrease in U-EPX and S-EPC-levels. (2) We wished to examine the role of HDM allergy for this process. It was hypothesized that patients with HDM-allergy would benefit more from their stay in an environment with reduced concentration of mite allergens. (3) Finally, we wanted to compare the results for the two diagnostic groups.

MATERIALS AND METHODS

Study design and subjects

The reported data are part of a broader study aimed at assessing the long-term effects (over 2 years) of inpatient rehabilitation at high-altitude climate on clinical (disease severity) and psychological (e.g., emotional strain) parameters. We evaluated consecutive inpatients admitted to "Santa Maria" (Oberjoch, Germany), an inpatient rehabilitation clinic specializing in children and adolescents with atopic diseases. The clinic is situated at an altitude of 1200 m above sea level and has a low concentration of allergens. In the samples collected from 44 mattresses at "Santa Maria," no HDM could be found. This suggests, as well as the class 0 guanine test result, that "Santa Maria," is HDM free.[15] During their in-patient rehabilitation stay, children and adolescents were cared for by a multidisciplinary team of physicians, nurses, psychologists, social workers, and other professionals. Inpatient rehabilitation included, for example, supervised medical

treatment, physical exercises, and a structured disease-related patient education program. All interventions aimed to improve not only the physical, but also the psychosocial well being of the chronically ill children and adolescents.

To be included in the study, children and adolescents had to fulfill several criteria: (1) confirmed diagnosis of either asthma or AD, or both according to national and international guidelines.[16,17] (2) At least moderate disease activity had to exist. For asthma this was defined by the frequency of asthma attacks during the last year.[18] This parameter reflects the long-lasting disease course; because all children were medically treated at the beginning of the study and we felt it to be unethical to withhold medication FEV_1% and medication status could distort the underlying disease severity. For AD, SCORAD[19] had to be 25 points or higher. (3) Children and their parents had to be German speaking. (4) Children could not be mentally handicapped. (5) Children had to be aged between 10 and 16 years. (6) Children had not to have participated in another rehabilitation stay throughout the duration of the study. Study participation was voluntary, and informed consent was given by the parents or the children themselves (if they were older than 14 years). The study was performed between December, 1996, and May, 1998. During that time, a total of 115 children and adolescents met these inclusion criteria and agreed to have blood samples taken. The reported clinical and immunological data were collected at enrollment (T1) and at discharge 1 month later (T2).

Immunologic parameters

Participants were determined to have clinically relevant mite sensitization if they had positive radioallergosorbent test (RAST) results to *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* of at least 3 points on a scale ranging from 0 to 4. This procedure should make sure that the allergic sensitization is of clinical relevance and acuity. RAST results of 3 points and higher could be considered as a proof for an allergic sensitization.[20]

Spirometry measurements

All asthma patients performed a spirometry test at inclusion and at discharge from the clinic (1 month later). The lung function was measured with the body plethysmograph (Master Screen Body, Jaeger GmbH, Höchberg, Germany). The best of three FEV_1 measures was chosen for the statistical analysis. The results are presented as a percentage of predicted value for sex and height.

Skin condition

On admission and discharge, the clinical severity of the AD was determined by a dermatologist (A.F.G.) using an established scoring system, the SCORAD index.[19] Briefly, the total score consists of ranking for three parameters (extent, intensity, and subjective symptoms). Extent (A) expresses the body surface involved; intensity (B) describes the condition of the skin (erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and dryness of nonaffected skin). Subjective symptoms (C) are pruritus and sleep loss.

Laboratory analyses

All laboratory analyses were done in the morning hours (8 to 9 o'clock), and on the same day skin condition respectively spirometry were assessed.

Urine samples: Urine was collected at the time of clinical evaluation. The samples were immediately frozen at −20°C. U-EPX was measured by using a radioimmunoassay (EPX RIA; Pharmacia Biosystems, Freiburg, Germany). Creatinine levels were determined using the Jaffé-method to detect renal insufficiency. U-EPX levels were expressed in μg/mmol creatinine. The detection threshold was 8 ng/mL.

Blood samples: Venous blood samples were drawn into vacutainers at the time of the admission and 4 weeks later. After clotting at room temperature for 60–120 min, the samples were centrifuged for 10 min and sera were frozen and stored at −20°C. S-ECP levels were analyzed using radioimmunoassay (RIA) kits (Pharmacia Biosystems, Freiburg, Germany). ECP concentrations were expressed in μg/L.

Statistics

Statistical analyses were performed using the statistical package SPSS for Windows®, release 9.0. Results are presented as means + SD. First we tested for significant differences between the two diagnostic groups. As significant differences existed, we included diagnosis as factor in all further analysis to control that influence.

Comparisons between diagnostic groups (asthma or AD) and sensitization status (positive or negative for HDM) were made using a repeated measures general linear model (GLM). Eta^2 was used as a measure of variance explained by a given factor (time, diagnosis, time × diagnosis etc). All data were normally distributed. The Pearson correlation coefficient was calculated and tested for statistical significance. Probability (p) values of less than 0.05 were considered statistically significant.

RESULTS

Subject characteristics

Demographic data are shown in Table 1. A total of 115 children and adolescents were included; 60 suffered from asthma and 55 from atopic dermatitis. In 42 (36.52%) of the children, HDM sensitization could be confirmed; the percentage was nearly twice as high in the asthma (45%) compared to the AD group (27.27%). Mean ages of the asthmatic children and children with AD evaluated were 12.83 years (SD = 1.91) and 12.13 years (SD = 1.81), respectively. In all subgroups, boys and girls were almost equally distributed. Groups of children with and without HDM sensitization were comparable in respect to all recorded characteristics (e.g., age, gender, disease severity). As expected FEV_1 scores in asthmatic children were high. Data from medication taken confirm the higher disease severity reflected by the frequencies of asthma attacks: 86.6% of the children and adolescents took long-acting beta-2-agonists or theophylline on a regular basis (for at least 4 weeks). Children with AD suffered from more severe disease activity than children with asthma ($\chi^2 = 7.23$; $p = 0.06$).

Lung function values and skin condition

Repeated clinical examination of the patients at admission and at discharge indicated a significant clinical improvement over time both for asthma-patients ($F = 12.43$; $p = 0.001$; $Eta^2 = 0.202$; $FEV_1\%$ from 95.27 to 99.38%) and for AD-patients ($F = 184.5$; $p = 0.000$; $Eta^2 = 0.811$; SCORAD from 49.66 to 26.62 points). In both groups, the interaction between time and HDM status did not prove to be significant.

Table 1. Demographic Data of the Patients at Baseline

	Asthma group (n = *60)*		*Atopic dermatitis group* (n = *55)*	
	With HDM	*No HDM*	*With HDM*	*No HDM*
Sample size	27	33	15	40
Age (years)				
Mean (±SD)	12.56 (±1.87)	13.06 (±1.94)	11.8 (±1.37)	12.25 (±1.94)
Sex ratio M:F	15:12	19:14	7:8	20:20
$FEV_1\%$	95.21 (±9.90)	93.98 (±18.63)		
SCOARD			52.63 (±15.57)	49.69 (±11.76)
Disease severity				
Moderate	32.23%[a]	41.82%[a]	12.24%[b]	32.73%[b]
Severe	12.37%[a]	12.37%[a]	16.33%[b]	34.69%[b]

With HDM = with high level of HDM sensitization.
No HDM = with or without low level of HDM sensitization.
[a]According to the guidelines.[18]
[b]According to the guidelines.[21]

TABLE 2. GLM RESULTS FOR ECP AS DEPENDENT VARIABLE BY DIAGNOSIS AND HDM SENSITIZATION AS BETWEEN FACTORS

Variable	F *value*	p *value*	*Eta*^{2}
Time	0.142	0.707	0.001
Diagnosis	4.128	0.045	0.038
HDM sensitization	0.388	0.053	0.004
Time * diagnosis	0.473	0.493	0.004
Time * HDM sensitization	0.702	0.404	0.007
Diagnosis * HDM sensitization	0.458	0.500	0.004
Time * diagnosis * HDM sensitization	0.420	0.518	0.004

Immunological parameters

S-ECP: Table 2 summarizes the results of the statistical analyses for S-ECP. We observed a significant main effect for diagnosis on the multivariate level. The variance explained by the main factor diagnosis was low (3.8%). Post hoc analyses revealed that asthma and AD patients showed a slightly different time course: Whereas the ECP values of the asthma patients remained stable over time, a slight but not statistically significant increase was observed for the AD patients (see Fig. 1). There was only a significant difference between both groups at discharge, with AD patients showing higher levels than asthma patients (see horizontal bars). Sensitization status did not influence the EPC levels, neither as main factor nor in connection with time (time * sensitization, n.s.) nor diagnosis (diagnosis * sensitization, n.s.).

U-EPX: As shown in Table 3, the main effects for time and diagnosis proved to be significant. U-EPX levels in the AD patients were significantly higher than in the asthma patients at admission and at discharge. Both groups showed a significant decrease over time (see Fig. 2). The variance explained in the U-EPX levels by time was 28.2% and 10.1% by diagnosis. HDM status did not influence this decrease over time (see Fig. 3): Both subgroups profited over time.

To elucidate the different inflammatory levels in asthma compared with AD patients, correlations with disease severity were calculated. There was no significant correlation between ECP-levels at admission and

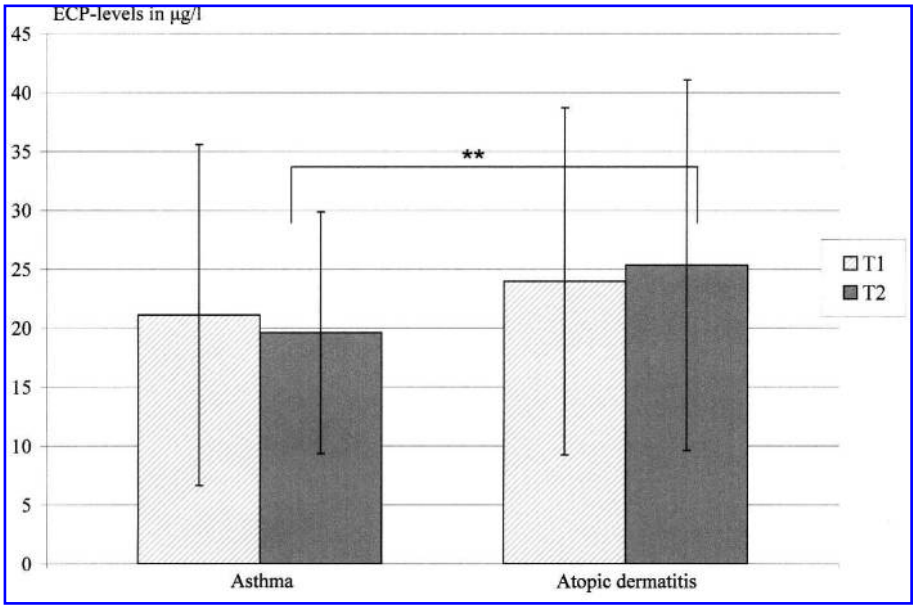

FIG. 1. Mean ECP levels over time in children with asthma and AD, respectively (the horizontal bars mark the significant difference).**$p < .01$.

TABLE 3. GLM RESULTS FOR U-EPX AS DEPENDENT VARIABLE BY DIAGNOSIS AND HDM SENSITIZATION AS BETWEEN FACTORS

Variable	F *value*	p *value*	*Eta*^{2}
Time	36.583	0.000	0.282
Diagnosis	10.461	0.002	0.101
HDM sensitization	1.147	0.287	0.012
Time * diagnosis	2.699	0.104	0.028
Time * HDM sensitization	2.190	0.142	0.023
Diagnosis * HDM sensitization	0.176	0.675	0.002
Time * diagnosis * HDM sensitization	0.000	0.990	0.000

disease severity ($r = 0.097$), but a slightly significant relationship to U-EPX levels ($r = 0.223$; $p = 0.025$). A multivariate analysis with disease severity as between factor (based on the corresponding guidelines for asthma[18] and AD[21]) revealed no significant influence on ECP ($F = 1.84$; $p = 0.18$), but as expected, a significant main effect for the U-EPX analysis ($F = 11.21$; $p = 0.001$; eta$^2 = 0.111$). Independent of their disease severity, all groups decreased the U-EPX levels over time ($F = 2.343$; $p = 0.129$).

Correlational analyses

At inclusion, neither S-ECP nor U-EPX values were correlated with SCORAD scores ($r = 0.096$ rsp, $r = 0.021$) in children with AD. The corresponding values for discharge also did not prove to be significant ($r = 0.204$ rsp, $r = 0.184$). Test results obtained for partial correlations taking HDM into account revealed no relationship between clinical status and inflammatory markers. FEV_1 scores correlated significantly with ECP levels at admission ($r = -0.372$; $p = 0.007$) and at discharge ($r = -0.290$; $p = 0.027$). No significant correlations were found between FEV_1 and U-EPX. HDM status did not change the correlational pattern.

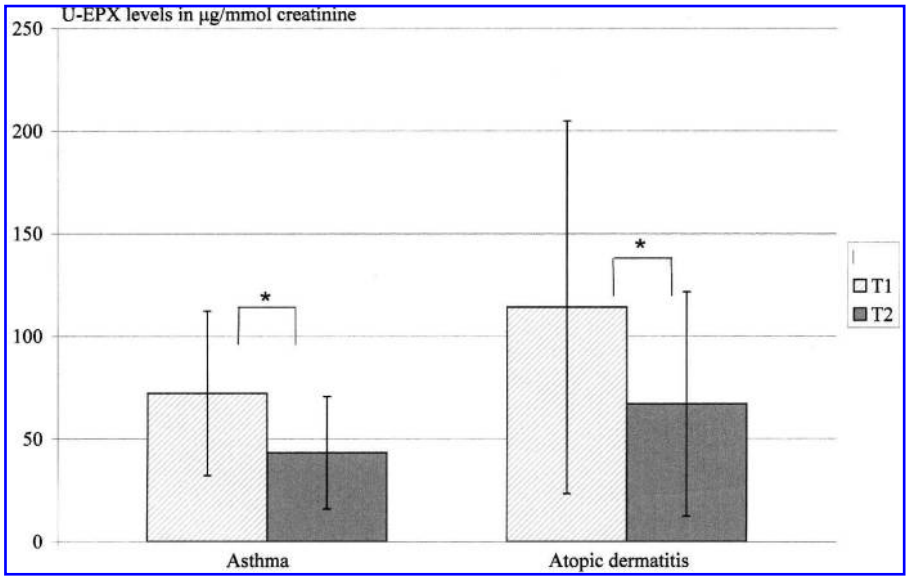

FIG. 2. Mean U-EPX levels over time in children with asthma and AD, respectively (the horizontal bars mark the significant main effects for time and diagnosis). *$p < .05$.

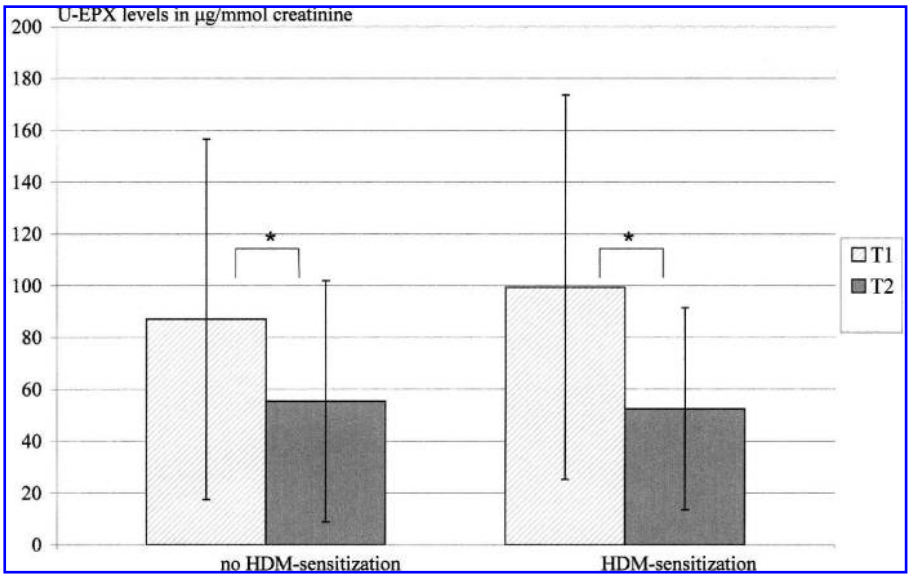

FIG. 3. Mean U-EPX levels over time in children with a high level of HDM sensitization compared to those of children without or with a low level of HDM sensitization (the horizontal bars mark the significant decrease in U-EPX levels over time in both groups). *$p < .05$.

DISCUSSION

The aims of this longitudinal study were to investigate the short-term effects of allergen avoidance in high-altitude climate assessed by clinical and inflammatory parameters for both children with asthma and AD, respectively. It was of specific interest to study influence of HDM sensitization on these effects. Therefore, we collected data from a consecutive sample of 115 children and adolescents with asthma or AD during their 4-week inpatient stay in a clinic situated in a high-altitude climate. To test the influence of HDM allergy on the course of immunological parameters, we divided the group into those with high and those with low or no HDM sensitization on the basis of their RAST results.

The results of this report confirm previous clinical investigations that atopic patients benefit from inpatient rehabilitation in high-altitude conditions as assessed by clinical and inflammatory markers (e.g., refs. 6,10–11,22,23). Asthmatic patients showed a significant decrease in U-EPX while FEV_1 values increased. A significant decrease in the U-EPX level was also observed in the group with AD, along with a significant improvement in skin condition. Moreover, we found a significant decrease in total eosinophil count for children with asthma ($F = 5.55$; $p = 0.022$; $Eta^2 = 0.089$). At present, this is the first demonstration of the effect of comprehensive inpatient rehabilitation at high altitude on S-ECP and U-EPX in children with AD. Our results support the value of such a stay to control disease activity for children with atopic diseases.

In contrast to the results of other studies, the improvement in lung function and skin condition, respectively, were not associated with a significant reduction in S-ECP levels. However, we observed a significant decrease in U-EPX levels over time. These different observations for the time-related changes in S-ECP and U-EPX were paralleled by a significant correlation between clinical assessment (FEV_1, SCORAD) and U-EPX but not S-ECP. Our findings support the conclusions of other studies[2,8] that the effects of treatment can be monitored as well by U-EPX levels as by S-ECP levels. In our study, U-EPX proved to be the more sensitive marker. Using U-EPX for monitoring has the advantage of being noninvasive, because blood samples are often difficult to obtain. In addition, as Cottin *et al.*[24] pointed out, U-EPX may be a useful marker of eosinophil degranulation in vivo.

In addition, we found no significant correlation between ECP levels and disease severity.[25] We can only speculate about the reason for the missing relationship. Contrary to our results, e.g., Pucci[5] found a stronger

correlation between SCORAD and EPC than U-EPX. On the other hand, they reported that for the subgroup of children with moderate to severe forms of AD U-EPX was better related to clinical severity. Moreover, 11.9% of the patients showed only low levels of S-ECP and U-EPX. In sum, we hypothesize that the inclusion of only moderate to severe AD forms can explain our results. Further research is clearly needed to find out why some patients with high SCORAD scores present only low eosinophil involvement.

Consistent with the literature, children with AD showed higher mean S-ECP and U-EPX levels than children with asthma.[24] This observation could not be explained by the fact that a higher percentage of children with AD had a severe medical condition, compared with children with asthma. The lower ECP levels in the children with asthma may reflect a good medical, mainly anti-inflammatory, treatment that they receive from their local physician. High FEV_1 values at study enrollment are consistent with this interpretation.

We divided our patients into those who were highly sensitized to HDM and those who were not or only slightly sensitized to HDM. Evaluation of changes in clinical and inflammatory levels over 4 weeks showed a significant decrease in several parameters in both groups. Therefore, we can conclude that independent of allergic sensitization to HDM children can benefit from comprehensive in-patient rehabilitation at a high-altitude climate. This observation would contradict the conclusion that HDM avoidance is the major factor for the observed benefits. On the other side, univariate analyses revealed that in the group of children with asthma, HDM-sensitized children showed a greater reduction in U-EPX levels than asthmatic children without such a sensitization. Further studies should focus on this issue.

There are some limitations to our study. Due to the lack of an untreated control group in their home environment, we were unable to ascertain whether allergen avoidance in a high-altitude climate of patients participating in an inpatient rehabilitation stay causes the observed improvements. Comprehensive inpatient rehabilitation also means supervised medical treatment with better adherence to prescribed medicine, taking part in relaxation and educational programs, etc. It is always difficult to rule out the relevant causal factor because it would be unethical to withhold effective treatment approaches. Results from other studies (e.g., refs. 12, 23) suggest benefits from allergen avoidance despite regular anti-inflammatory treatment. These reports support our conclusion that allergen avoidance is an important factor the documented positive effects. But certainly allergen avoidance is not the only factor improving disease status, otherwise children and adolescents without HDM sensitization would not have benefitted so clearly from their inpatient stay. Inpatient rehabilitation at high altitude not only means allergen avoidance but also, for example, better compliance with the treatment plans or stress reduction. Changes in other exacerbating factors will add to the reported effects of the inpatient stay. Furthermore, it must be mentioned that our results concerning the potentially differential influence of HDM sensitization is only based on the determination of specific immunoglobulin E (IgE) antibodies against HDM. Prick skin testing and/or atopy patch testing (for AD patients) were not performed. Convincing evidence exists in the literature that RAST classes 3 and 4 can be considered as a proof for the clinical sensitization and reflect the clinical acuity.[20] To our knowledge, this is the first study that focuses on the effects of HDM sensitization status on clinical and immunological parameters for children with asthma or AD staying in an inpatient clinic in a high-altitude climate.

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