2 Studies on patients with atopic diseases at the Environmental Research Station Schneefernerhaus (UFS)[1]

Eberlein B.[2, 3], Huss-Marp J.[3], Pfab F.[3], Fischer R.[4], Franz R.[2], Schmitt M.[2], Leibl M.[2], Allertseder V.[2], Gloning J.[2], Kriegisch M.[3], Hennico R.[3], Latotski J.[3], Ebner von Eschenbach C.[3], Darsow U.[2], Behrendt H.[3], Huber R.[4], Ring J.[2]

Correspondence:
Prof. Dr. Bernadette Eberlein
Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, Biedersteiner Str. 29; D-80802 München, Germany
Tel. +49-89-4140-3191; Fax +49-89-4140-3145
E-mail: bernadette.eberlein@tum.de

Abstract

Mountain climate therapy takes advantage of specific climatic conditions to treat chronic allergic diseases. The aim of the study was to investigate effects of a 5-day observation period on atopic diseases at the Environmental Research Station Schneefernerhaus (UFS; Umweltforschungsstation).

18 patients with grass pollen-induced rhinoconjunctivitis, atopic ezcema or asthma and 11 non-allergic controls were included in this study. Skin physiology parameters, changes of the respiratory and nasal functions, subjective symptoms and blood parameters were measured during a 5-day observation period in the Environmental Research Station Schneefernerhaus at the moderate altitude mountain region (Zugspitze; 2650 m alt.) compared to a low altitude area (Munich; 519 m alt.).

Histamine induced itch decreased significantly. Several of the skin physiology parameters changed significantly during the observation period (decrease of skin hydration, increase of skin smoothness, skin roughness, skin scaliness and pH-value). In patients with atopic eczema, the SCORAD (Severity Scoring of Atopic Dermatitis) and the scores of the DIELH (Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen) did not change significantly. Parameters of nasal function (rhinomanometry, eosinophil cationic protein (ECP) in nasal secretions) did not change significantly. The vital capacity (VC) decreased significantly, several other parameters of lung function (FEV1/VC, PEF, MEF 50, MMFEF 25/75) showed a slight, but statistically significant improvement. ECP (eosinophil cationic protein) and IL-33 in the serum and parameters of blood count changed significantly.

In dependence on the atopic disease the benefit of a moderate altitude mountain climate sojourn over a period of 5 days differed – especially itching of the skin and asthma parameters improved. Assessing the parameters during a longer observation periods in alpine climate would be useful.

The methodology used can serve as a suitable template for qualified studies on the effect of climate therapy.

Key words: mountain climate therapy, atopic diseases, atopic eczema, asthma, rhinoconjunctivitis allergica, skin physiology parameters, rhinomanometry, parameters of lung function, Umweltforschungsstation Schneefernerhaus, Zugspitze

---

[1] This study was published as Brief Communication: Eberlein, B. et al. Influence of alpine mountain climate of Bavaria on patients with atopic diseases: studies at the Environmental Research Station Schneefernerhaus (UFS – Zugspitze) – a pilot study. Clinical and Translational Allergy 2014; 4: 17

[2] Department of Dermatology and Allergy Biederstein, Technical University Munich, Germany

[3] Center of Allergy and Environment (ZAUM, Zentrum Allergie und Umwelt), Technische Universität München and Helmholtz Center Munich

[4] Medizinische Klinik Innenstadt, Fachbereich Pneumologie, Ludwig-Maximilians-Universität München

2

2.1 Introduction

Allergies have increased in most countries of the world in recent decades. Prevalence rates of 20 to 30 % of the total population are estimated today. Particularly common allergic diseases are allergic rhinoconjunctivitis (if seasonally occurring "hay fever", allergic asthma bronchiale, atopic eczema (atopic dermatitis, anaphylaxis (maximum variant of an acute allergic reaction with life-threatening character, allergic contact dermatitis (one of the most common occupational diseases) and the manifold spectrum of food and drug intolerance reactions.

Allergies are typical environmental diseases; they are based on genetic susceptibility via a misdirected reaction of the effector organ immune system against natural and anthropogenic substances from the environment. Air pollutants and allergens can influence each other in many ways (1, 2).

Climate therapy comprises the use of certain climatic conditions in the treatment of chronic diseases. In allergy, maritime and moderate altitude mountain zones are of interest. Mountain climatotherapy can be performed in moderate altitude (relative height of > 2000 m) and low altitude (> 500–2000 m alt.) (3).

Increasing altitude implies climatic changes in the following factors: air pressure, oxygen partial pressure, temperature, water vapour pressure, UV radiation, global radiation and reduction of allergens such as house dust mite. Some of these factors are considered as "stimulating", the relative purity of the air and low allergen content as protective factors (4).

From the experience of special rehabilitation clinics in the moderate high mountains, especially in Davos, Switzerland, we know since decades that the mountain climate exerts a favorable influence on numerous inflammatory diseases of the skin and respiratory system. Especially the climatic situation in moderate high mountains (5) has been proven in many studies to be particularly effective in the treatment of allergic respiratory and skin diseases, with most long-term studies in Davos (6,7). From patients with atopic eczema (AE) treated in the German Hospital for Dermatology and Allergy Davos (Switzerland) some 94 % returned either completely free or with considerably improved symptoms (4). Also in patients with asthma mountain climate therapy is a well-established therapeutic option (5).

The effects of mountain climate include normalization of misguided immune responses (T cell responses, IgE levels, changes in cutaneous reactivity, histamine and allergen pricktest thresholds), influences on vegetative parameters such as sweating, and beneficial effects on the subjective symptom itching. The nature of these effects, especially with regards to the only more recently elucidated pathophysiological reactions of the allergic inflammatory cascade, is investigated only to a limited extent. Increased cortisol and catecholamine levels as well as modulation of lymphocyte regulatory functions might be mechanisms explaining the effects of climate therapy in these disorders (8, 9).

Many patients – especially those with severe forms of the above-mentioned diseases – cannot be subjected to allergological testing in the lowlands under the conditions of daily life at all. This is due to the fact that either the skin organ or the respiratory tract constantly show symptoms and must be treated, which prevents the patient from testing, or strong symptoms occur immediately when the medication is discontinued, which makes testing impossible. For such patients, moderate high mountain conditions are particularly valuable for providing them with a further treatment strategy. Compared to Davos (1.600 m) the altitude in Bavaria with Oberjoch (approx. 1200 m) and Berchtesgaden-Buchenhöhe (approx. 900 m) are still relatively low. With a height of 2650 m, the UFS offers a location comparable to that of the Jungfraujoch in Europe.

It was the aim of this study to follow objective and subjective parameters in patients suffering from rhinoconjunctivitis and/or atopic eczema, asthma over a 5 days observation period in the Environmental Research Station Schneefernerhaus (UFS) at the Zugspitze (2650 m alt.) in the alpine mountain climate of Bavaria compared to lowland in Munich (518 m alt.). Clinical symptoms, skin and lung parameters, blood parameters and self-assessed health status were analyzed.

2.2 Materials and methods

2.2.1 Study Design

Five-day observation periods at the Environmental Research Station Schneefernerhaus (UFS) were performed with groups up to 10 patients and/or controls in July/August 2008, March 2009 and July 2009. Skin physiology parameters, changes of the respiratory and nasal functions, subjective symptoms and blood parameters were measured 3 to 4 days in Munich before the sojourn at the UFS (t1), at the first and second day (t2) and at the fourth and fifth (t3) day during the sojourn at the UFS as well as about 4 weeks later in Munich (t4). All participants reached the UFS by railway within four hours. All study procedures were conducted according to the Declaration of Helsinki. The local Ethical Committee approved the study. Patients had given informed consent.

2.2.2 Patients

18 patients (6 males, 12 females; mean age: 30 years, range: 24–43 years) with grass-pollen induced rhinoconjunctivitis, atopic eczema or asthma and 11 non-allergic controls (4 males, 7 females; mean age: 26 years, range 18–32 years) were included in the study. Characteristics of patients are shown in Tab. 1.

2.2.3 Diagnostic criteria

Atopic eczema was diagnosed according to the criteria of Hanifin and Rajka, the UK working party and Ring et al. (10,11,12). Asthma in adults was diagnosed according to Global Strategy for Asthma Management and Prevention (13).

2.2.4 Blood tests

A maximum of 20 ml per blood sampling time (maximum 3 time points) was required. The total IgE, a spectrum of specific IgE antibodies (main focus on inhaled allergens), a complete blood count and parameters of inflammation of the skin and respiratory tract (eosinophilic cationic protein ECP and soluble receptors) were determined.

2.2.5 Measurements

2.2.5.1 Dermatological examination

The examination of the skin was carried out in a standardised manner by trained physicians. The focus of the study was set on the qualitative and quantitative description of atopic eczema. The severity of the atopic eczema was determined by the SCORAD (scoring index for atopic dermatitis). This is a standardised survey tool developed for this purpose, which records the parameters of extent, intensity (divided into the criteria erythema, edema/papules, wetness/crusts, excoriations, lichenification, dryness) and subjective symptoms (daytime pruritus and sleep loss). (14)

2.2.5.2 Skin prick test

The skin prick test was performed on the volar sides of the forearms. Commercial extracts of grass pollen allergens in various dilutions as well as saline and histamine solutions were used as controls. The reactions were evaluated after 15 minutes and categorized according to the diameter of the wheal and flare reaction. A wheal diameter of ≥ 3 mm was defined as positive. Tests in which the negative control was positive or in which there was no positive reaction (including positive control) were excluded from the final evaluation.

Itch intensity after prick testing of histamine was rated on a computerized visual analogue scale (VAS) ranging from 1 to 100, where 0 was defined as ‘no itch’ and 100 as ‘maximum itch’. The scale was anchored at one-third of the VAS, defined to patients as the ‘scratch threshold’ (15).

Tab. 1: Clinical characteristics, skin tests, determination of total and specific IgE in the patient group (41)

Patient number	Age (years)	Sex	Atopic disease	Prick-test (positive)	Total IgE (IU/ml)	Specific IgE (CAP-class)
01	31	f	Asthma, AR	birch, grass, cat, celery	275	D. pter. 2, cat 2, dog 3, hazelnut 2, celery 1, grass 4, birch 4, hazel 3
02	25	f	AR	D. pter., birch, grass, mugwort	964	D. pter. 3, celery 3, grass 6, birch 4, hazel 5, wheat flour 3, rye 5, mugwort 3
03	25	f	AR	D. pter., cat, grass, mugwort	79.4	D. pter. 3, cat 1, grass 2, rye 2, mugwort 2
04	31	f	AR	hazel, celery, Alt. alternata	14.2	grass 2
05	23	f	Asthma, AR	D. pter., birch, dog, cat	134	D. pter. 4, cat 2, dog 2, grass 3
06	24	f	AE, Asthma, AR	grass	161	D. pter. 5, grass 2, mugwort 1, ambrosia 1
07	24	f	AE, Asthma	trees, mugwort, birch, D. pter., alder, grass, hazel	2248	D. pter. 4, cat 3, celery 3, grass 3, birch 5, wheat flour 3, mugwort 3, ambrosia 3, latex 2
08	30	m	AE, AR	trees, birch, D. pter., alder, grass, hazel, dog, cat	1822	D. pter. 6, cat 4, grass 5, birch 3, wheat flour 1, mugwort 1, milk 2
09	28	m	AR	trees, mugwort, birch, blatella, D. far., D. pter., alder, grass, hazel, dog, cat, ambrosia, herbage	226	D. pter. 4, cat 2, hazel nut 3, grass 2, birch 3, mugwort 2, ambrosia 1
10	25	f	AD	grass, cat, herbage	113	cat 3, grass 4
11	18	m	Asthma	D. far., D. pter., grass	493	D. pter. 2, grass 5, ambrosia 1
12	20	m	AE, Asthma, AR	trees, birch, D. far., D. pter., alder, hazel, aspergillus, ambrosia	56.2	D. pter., 3, birch 3
13	20	f	AE, Asthma	negative	136	negative
14	27	m	AE, Asthma, AR	trees, birch, D. pter., alder, grass, hazel, dog, cat, horse, Alternaria tenuis, ambrosia	1455	D. pter. 3, cat 5, grass 3, birch 6, wheat flour 2, mugwort 3, egg white 2, codfish 2, Cladosporium herbarum 3
15	24	f	AE, Asthma, AR	trees, birch, D. far., D. pter., alder, grass, hazel, dog, cat, herbage, horse	159	D. pter. 4, cat 2, grass 2, birch 3
16	26	f	AD	Mugwort, grass, herbage	8.7	grass 3
17	32	m	AR	trees, birch, alder, grass, herbage, ambrosia	142	D. pter. 1, cat 2, grass 4, birch 2, wheat flour 1, ambrosia 2
18	28	f	Asthma, AR	trees, birch, D. far., D. pter., alder, grass, hazel, herbage,	77.5	D. pter. 3, celery 1, grass 3, birch 4, ambrosia 2

Abbreviations: AD: atopic diathesis; AE: atopic eczema; AR: allergic rhinitis; D. far.: Dermatophagoides farinae; D. pter.: Dermatophagoides pteronissinus; f: female; m; male

2.2.5.3 Measurement of skin physiological parameters (Fig. 1)

Parameters of skin function, especially with regard to the barrier function of the upper skin layers (16), were investigated under the conditions of the altitude climate:

Fig. 1: Measurement of skin physiology parameters

2.2.5.4 Sebum content

A sebumeter (SEBUMETER SM 810, Courage and Khazaka electronics GmbH, Köln, Germany) was used for the quantitative measurement of skin surface fat. The measurement was based on fat spot photometry. The mat tape of the sebumeter was brought into contact with skin (here forehead). It became transparent in relation to the sebum on the surface of the measurement area. Then the tape was inserted into the aperture of the device and the transparency was measured by a photocell. The light transmission represented the sebum content and the result was displayed in µg/cm^2.

2.2.5.5 Skin hydration

To determine the skin hydration, a corneometer (CORNEOMETER CM825, Courage and Khazaka electronics GmbH, Köln, Germany) was used to determine the moisture content of the outer layer of the epidermis (stratum corneum) by means of a capacitive measuring method. Changes in the skin surface hydration resulted in a change in the capacitance of a precision capacitor due to the change of a dielectric medium. This was evaluated electronically and displayed as a corneometer value. The value scale ranged from 1–150 units. For measurement, the active front face of the probe head, coated with special glass, was placed on the flexor side of the forearm. The corneometer reading was displayed after 1 second.

2.2.5.6 PH-value

The pH-value of the skin surface provides important information about the condition of the skin and its protective acid mantle. Since the skin's surface with its excretions and high moisture content comes very close to the properties of an "aqueous solution", it is suitable for immediate pH measurement. The sensor for pH measurement on the skin surface of the skin-pH-meter (SKIN-pH-METER PH 900, Courage and Khazaka electronics GmbH, Köln, Germany) was characterised by the fact that its active part was designed as a flat surface in order to be able to measure on the skin (here: flexor side of the forearm). The measurement was based on a high quality combined electrode, where both glass H+ ion sensitive electrode and additional reference electrode were placed in one housing. It was connected to a probe handle containing the measurement electronics. The result of the measurement within seconds was displayed with an accuracy of 0.1 pH.

2.2.5.7 Skin roughness (Fig. 2)

Skin roughness can be determined by means of an impression procedure to determine the skin surface texture. Replicas were taken from the flexor side of the forearm with a polyether impression material (Permadyne Garant 2:1, ESPE, Seefeld, Germany) according to a previous publication (16). Each skin print is measured with the aid of a commercially available surface measuring device (VisioScan VC98 with the software SELS 2000, Courage and Khazaka electronics GmbH, Köln, Germany). For the description of skin roughness, those parameters were chosen that have proven to be particularly meaningful for the description of the skin surface texture (skin scaliness, skin smoothness).

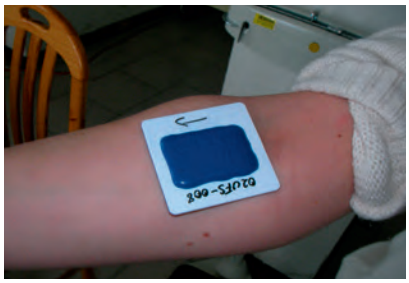

Fig. 2: Replica of the skin surface for measurement of skin roughness

2.2.5.8 Transepidermal water loss

A tewameter (Tewameter TM 300, Courage and Khazaka electronics GmbH, Köln, Germany) was used to determine the transepidermal water loss as a measure of the skin barrier function. The physical basis for measuring the evaporation of water on a surface is the diffusion law discovered by Adolf Fick:

$$\frac{dm}{dt} = -D \cdot A \cdot A \cdot \frac{dp}{dx}$$

(A = surface (m^2); m = water transported (g); t = time (h); D = diffusion constant (= 0.0877 g/m(h(mm Hg))); p = vapour pressure of the atmosphere (mm Hg); x = distance from skin surface to point of measurement (m))

The diffusion current dm/dt indicates how much mass is transported per time unit. The diffusion current is proportional to the surface A of the perpendicularly penetrating interface and the change in density per unit of displacement length dp/dx. D is the diffusion coefficient of water vapour in atmospheric air. This law is only valid within a homogeneous diffusion zone. This is approximately created by a hollow cylinder open on both sides, the shorter side of which is placed on the skin (open chamber measurement). The water evaporating from the surface of the skin evaporates through the cylinder on the opposite side. The resulting density gradient is indirectly measured and evaluated by two pairs of sensors (temperature and relative humidity) in the cylinder. The values are given in g/hm^2. The transepidermal water loss was measured according to the guidelines of Pinnagoda et al. (17) on the flexor side of the forearm. This parameter is of particular importance as it can be used to detect very small disorders of the skin barrier function both in healthy skin and in patients with atopic eczema, which already show elevated levels of TEWL in non-affected areas.

2.2.5.9 Alkali resistance test

The alkali resistance test assesses the alkaline resistance of the skin. For this purpose, a skin area was moistened with 0.5 M NaOH solution for 2 × 10 minutes and covered with a small glass platelet. In between was a 10-minute drying and observation area. The control was 0.9 % aqueous saline solution. The TEWL was then measured over both areas.

2.2.5.10 Laser Doppler flowmetry (Fig. 3)

By means of Laser-Doppler Imager (Moor Instruments, Axminster, England) it was possible to measure the skin blood circulation without contact. A low energy laser was guided over the surface of the skin (here both forearms) in a meandering manner by a mirror that can be rotated on two axes. The light was scattered through the static surface and the moving blood. The double shifted and unchanged light components were directed to two detectors via the movable scanning mirror and the incoming mixed signal was used to calculate the parameter Flux (proportional to the blood flow). The value was given in device-specific units.

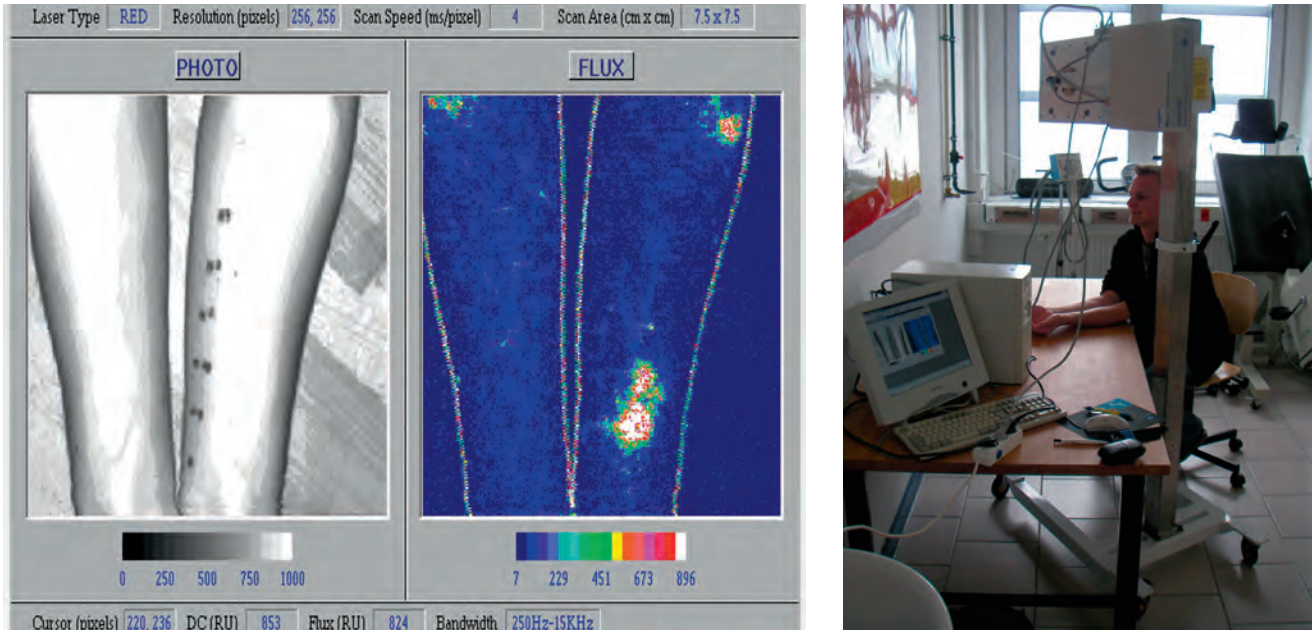

Fig. 3: Laser Doppler Flowmetry

2.2.6 Respiratory parameters

2.2.6.1 Peak flow measurement

The severity of a breathing disorder can be assessed by peak flow measurement. This method measured the maximum exhalation flow (peak flow) at forced expiration at the mouth in l/s or l/min. The mouthpiece of the peak flow meter (Mini-Wright-Peak-Flow-Meter, Clemente Clark, Essex, England) was attached to the mouth and the pointer is positioned at 0 l/min. The patient breathed deeply while standing, held the device horizontally, covered the mouthpiece with his or her lips and exhaled through the device as fast and powerfully as possible. The value was read above the pointer. In healthy subjects, the peak flow rate is usually between 400 and 700 l/min. In this study, the subjects were instructed to perform a peak flow measurement three times a day with the nose clamp attached while standing. The peak flow measurement was carried out three times at each measuring point and the best results were documented.

2.2.6.2 Rhinomanometry

In all subjects rhinomanometric function parameters were determined with a spirometer (Flowscreen Pro, Jaeger GmbH, Hoechberg, Germany). The measurement method was used to determine the airway resistance when inhaling through the nose. During inhalation and exhalation, a special respiratory mask was used to measure the differential pressure between the space in front of the nostril and the oral cavity. With the aid of nasal olives, the choke pressure and flow were determined and the measured value was graphically recorded in a nasal resistance curve. The value of the nostril was selected as the reference point showing the least resistance before exposure.

In the nasal provocation test, after adaptation to room temperature, the provocation was applied with NaCl 0.9% to the lower nasal concha on the mucous membrane and the flow was recorded. The usual provocation with pollen was avoided due to the risk of an asthma attack.

2.2.6.3 Extraction of nasal secretion

To obtain nasal secretion, we used the absorption method with small cotton wool pieces: These small cotton wool pieces were inserted into the middle nasal passage on both sides under anterior rhinoscopy with a bayonet forceps for 15 minutes. Subsequently, they were centrifuged at +8 °C and 3000 R for 20 min and the nasal secretion obtained was stored at –70 °C until further processing. In all samples the eosinophilic cationic protein (ECP) was analyzed (CAP ECP FEIA, Pharmacia, Uppsala, Sweden).

2.2.6.4 Pulmonary function parameters

In all subjects pulmonary function parameters were determined with a spirometer (Flowscreen Pro, Jaeger GmbH, Hoechberg, Germany). The pulmonary function test measured parameters for the characterisation of lung size, certain partial volumes and flow resistance. The measured values were assessed in relation to standard values, so that a normal or limited lung function could be detected in the individuals. The lung function, but especially the intensity of change over time, is currently the most significant non-invasive parameter for measuring the co-reaction of the lungs and bronchi.

The routine parameters VC max, FEV1, FEV1/VC max, ITGV, R tot, SR tot and the flow-volume curve were evaluated using bodyplethysmography (Master Screen Body, Jaeger GmbH, VIASYS Healthcare, Höchberg, Germany). (Fig. 4)

Under resting conditions and/or slow breathing conditions the vital capacity as well as its partial volumes (VCin, ERV, IRC) were determined and the forced expiratory volume in one second (FEV1) and other parameters (FVC, FEV1 % VC, PEF, MEF75, MEF50, MEF25, MMEF) were determined by forcing expiratory volume in one second from the flow-volume curve. Bodyplethysmographically, the airway resistances and the intrathoracic gas volume at the end of normal exhalation (FRC) were determined by means of short term occlusion at the mouthpiece (18).

Fig. 4: Bodyplethysmography

2.2.6.5 Methacholine provocation

The methacholine provocation (for subjects with normal lung function) is one of the pharmacological bronchial provocation tests that have a firm place in patient care as well as in scientific and expert questions. This challenge test was performed with a bodyplethysmograph (Master Screen Body, Jaeger GmbH, VIASYS Healthcare, Hoechberg, Germany). After inhalation of a control solution (physiological saline solution) the inhalative provocation with methacholine was carried out in different dose levels. Inhaled methacholine does not cause any reaction at all in healthy airways. If the airways are inflamed and therefore hypersensitive, there is a brief airway constriction, which can be detected very well and early in the lung function. Lung function examinations were performed prior to provocation and after control and individual dose levels.

2.2.6.6 Measurement of nitrogen oxide (NO) in the exhaled air (Fig. 5)

The measurement of nitric oxide in exhaled air serves as an objective and simple marker of respiratory inflammation. For NO measurement, the patient exhaled in a seated position, then NO-free air was inhaled via a mouthpiece. Finally, the patient breathed out slowly into the mouthpiece, with the results being visible directly on a screen. After 3 measurements the correct value was displayed. FE_{NO} measurements (NIOX MINO; Aerocrine, Solna, Sweden) were performed at the different time points (19).

Fig. 5: Measurement of nitrogen oxide (NO) in the exhaled air

2.2.6.7 Conjunctival provocation test

Five serial dilutions (1:10) of grass pollen extracts were created. The test was carried out gradually up to a clinical reaction with a score of at least 2+ for itching and redness. Conjunctival symptoms (itching, burning, foreign body sensation, tears, redness, chemosis, eyelid swelling) were evaluated according to a score of 0 (none) to 3 (heavy) for each eye prior to allergen provocation and 5, 10, 15, 20 minutes after challenge. A single drop (20 µl) of the lowest concentration was placed in the conjunctival sac followed by the next concentration at 10-min intervals switching from one eye to the other until symptoms appeared. 0.1 % saline was used as negative control.

2.2.7 Questionnaires

2.2.7.1 SF-36 Health Survey Test

The Short Form Health Survey is a 36-item, patient-reported survey of patient health. The SF-36 covers 8 different dimensions that can be classified in the areas of "physical health" and "mental health": Physical functioning, physical role functioning, physical pain, general health perception, vitality, social function, emotional role functioning and mental health (20).

2.2.7.2 Eppendorf Itch Questionnaire (EIQ)

The Eppendorf itch questionnaire (21) is a validated instrument for qualitative and quantitative assessment of pruritus. It contains 80 items on itch sensation in blocks of ten. Each item is rated with regard to the itch sensation on a five-point scale from 0 (not applicable) to 4 (very applicable).

German Instrument for Measuring the Quality of Life in Skin Diseases – Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen (DIELH)

This questionnaire examines the quality of life for skin diseases in the areas of physical ailments, mental health, everyday life, leisure, job/school, personal environment and treatment on the basis of 36 questions (22).

2.2.7.3 Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) measures the functional problems (physical, emotional, social and occupational) that are most troublesome to adults (17–70 years) with either seasonal or perennial rhinoconjunctivitis of either allergic or non-allergic origin. The RQLQ has 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function). There are 3 'patient-specific' questions in the activity domain which allow patients to select 3 activities in which they are most limited by their rhinoconjunctivitis. Patients recall how bothered they have been by their rhinoconjunctivitis during the previous week and respond to each question on a 7-point scale (0 = not impaired at all –6 = severely impaired). The overall RQLQ score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains (22).

2.2.7.4 Blood parameters

The following blood parameters were determined: complete blood count (Sysmex XT-2000 i/XT-1800i; Sysmex Corpotation, Japan), eosinophil cationic protein (CAP ECP FEIA, Pharmacia, Uppsala, Sweden), human IL-16 (DuoSet ELISA Development System, R&D Systems Europe, Abingdon, United Kingdom) and IL-33 (Human IL-33 ELISA Quantitation Kit, Gentaur, Brussels, Belgium).

2.2.7.5 Statistical analysis

Data were analyzed using SPSS. For statistical analysis the Friedman's one-way analysis for variance by ranks was used for paired samples and the Wilcoxon test for unpaired samples. For the disease-related analysis the univariate analysis of Variance (ANOVA) was used. The critical value for significance was set at $P < 0.05$ for all analyses. Data are presented as mean (± SD).

2.3 Results

2.3.1 Patients

Out of the 18 patients 13 had rhinoconjunctivitis, 10 had asthma and 7 patients suffered from atopic eczema. 11 patients had positive prick tests to house dust mites, 14 to grass pollen and 12 to early flowering species (hazel, alder, birch). 14 patients had specific IgE antibodies to house dust mites, 16 to grass pollen and 10 to early flowering species. (Tab. 1)

Tab. 2: Significant results of skin, nasal, conjunctival and lung parameters, questionnaires and blood parameters at the beginning (t1) in Munich, at time point 2 (t2) and 3 (t3) in the UFS and time point 4 (T4) in Munich in the different groups: data are means ± SD (41)

Parameter	t1 (pat.)	t1 (contr.)	t2 (pat.)	t2 (contr.)	t3 (pat.)	t3 (contr.)	t4 (pat.)	t4 (contr.)	Wilcoxon	ANOVA
Skin parameters										
Str. corneum hydration (arb. units)	46 ± 10	48 ± 7	36 ± 8	39 ± 6	38 ± 7	39 ± 5	44 ± 14	47 ± 4	**t1/t2 **t3/t4	
PH	4.9 ± 1.3	5.2 ± 1.2	5.9 ± 1.3	5.4 ± 1.2	5.9 ± 1.3	5.4 ± 1.2	5.2 ± 1.3	4.5 ± 1.2	**t1/t2 **t3/t4	
Skin roughness (arb. units)	0.6 ± 0.3	0.5 ± 0.2	1.0 ± 0.3	0.6 ± 0.2	0.6 ± 0.4	0.5 ± 0.2	0.6 ± 0.4	0.5 ± 0.2	*t1/t2 **t3/t2	
Skin scaliness (arb. units)	0.3 ± 0.2	0.3 ± 0.2	0.7 ± 0.3	0.7 ± 0.4	0.8 ± 0.3	0.6 ± 0.3	0.6 ± 0.3	0.5 ± 0.2	**t1/t2 **t3/t4	
Skin smoothness (arb. units)	18.2 ± 2.0	18.2 ± 3.8	21.0 ± 3.8	18.8. ± 4.4	22.3 ± 4.3	18.5 ± 4.3	19.0 ± 2.9	15.1 ± 0.5	**t1/t2 **t3/t4	↓AE t1/t2
TEWL (g/(hm^2))	8.0 ± 5.0	6.0 ± 1.4	6.2 ± 2.5	5.9 ± 1.2	7.1 ± 3.8	7.0 ± 1.8	9.8 ± 9.2	7.5 ± 2.2		↑AE t3/t4
Blood flow (right) (arb. units)	109 ± 23	96 ± 16	n.d.		121 ± 49	97 ± 19	108 ± 15	98 ± 16		↑AE t1/t3
Blood flow (left) (arb. units)	115 ± 28	98 ± 15	n.d.		124 ± 60	96 ± 23	113 ± 28	101 ± 20		↑AE t1/t3 ↓AE t3/t4
Wheal diluted 1:10 (mm)	6.2 ± 2.9	n.d.	5.7 ± 2.3	n.d.	6.1 ± 2.6	n.d.	4.9 ± 1.6	n.d.		
Wheal diluted 1:100 (mm)	2.9 ± 1.1	n.d.	2.9 ± 1.1	n.d.	3.6 ± 1.2	n.d.	2.8 ± 1.0	n.d.	*t2/t3	
Flare diluted 1:10 (mm)	31.3 ± 10.1	n.d.	25.1 ± 10.8	n.d.	23.4 ± 8.5	n.d.	25.0 ± 9.6	n.d	**t1/t2	
Nasal and conjunctival parameters										
Resistance (after prov.) (ml/s)	1.1 ± 1.8	1.3 ± 2.1	0.7 ± 0.6	0.6 ± 0.6	0.5 ± 0.3	0.6 ± 0.5	0.5 ± 0.5	0.7 ± 0.6		↑Asthma t2/t3
Conjunctival provocation (score) Allergen 1/100 (5 min)	0.7 ± 0.5	n.d.	0.4 ± 0.5	n.d.	0.5 ± 0.5	n.d.	0.6 ± 0.5	n.d.		↑Asthma t1/t2 ↓Asthma t2/t3
Lung parameters										
FVC (l)	5.1 ± 1.7	4.6 ± 1.0	5.2 ± 2.0	5.0 ± 1.3	4.6 ± 1.2	4.7 ± 1.2	4.7 ± 1.5	5.0 ± 1.0	*t2/t3	
FEV1/VC (%)	78 ± 15	88 ± 12	80 ± 17	89 ± 8	85 ± 11	90 ± 7	81 ± 14	89 ± 9	*t1/t3	
PEF (l/s)	9.1 ± 2.9	10.0 ± 2.63	10.1 ± 2.5	11.2 ± 3.0	9.6 ± 2.5	10.9 ± 2.9	9.9 ± 2.7	10.2 ± 2.4	**t1/t2 **t2/t3 *t3/t4	

Parameter	t1 (pat.)	t1 (contr.)	t2 (pat.)	t2 (contr.)	t3 (pat.)	t3 (contr.)	t4 (pat.)	t4 (contr.)	Wilcoxon	ANOVA
MEF50 (l/s)	4.26 ± 1.7	5.35 ± 2.0	4.76 ± 2.0	5.84 ± 2.1	4.85 ± 1.9	5.60 ± 1.8	4.67 ± 1.5	5.5 ± 1.4	*t1/t2	
MMEF 25/75 (l/s)	3.75 ± 1.5	4.73 ± 1.6	4.23 ± 1.8	5.19 ± 1.8	4.22 ± 1.6	5.02 ± 1.6	4.25 ± 1.1	5.02 ± 1.1	**t1/t2	
Resistance after 0.1 % methacholine (kPA*s/l)	0.33 ± 0.1	0.23 ± 0.02	0.42 ± 0.2	0.31 ± 0.2	0.52 ± 0.2	0.24 ± 0.1	n.d.		**t1/t2 **t1/t3	↓Asthma t1/t2 ↑AE t1/t2
FeNO (ppb)	41.6 ± 34.6	17.6 ± 7.9	32.0 ± 24.9	12.8 ± 10.2	38.2 ± 34.3	20.0 ± 15.4	33.2 ± 26.5	16.2 ± 9.3		
Questionnaires										
DIELH (score)	30 ± 30	1 ± 1	27 ± 30	1 ± 1	29 ± 29	1 ± 2	24 ± 28	0 ± 1		↑AE t1/t2
RQLQ (score)	5.6 ± 0.9	6.6 ± 0.3	5.6 ± 1.0	6.8 ± 0.2	5.8 ± 0.9	6.8. ± 0.2	5.7 ± 0.9	6.6 ± 0.3	*t1/t3	↓Asthma t2/t3 ↑AE t2/t3
SF-36 (score)	2.2 ± 0.4	2.0 ± 0.4	2.2 ± 0.4	2.0 ± 0.5	2.2 ± 0.4	2.0 ± 0.5	2.4 ± 0.2	2.2 ± 0.2		↓AR t2/t3
Blood parameters										
Erythrocytes (10^6/ml)	4.85 ± 0.4	4.85 ± 0.6	5.27 ± 0.5	5.09 ± 0.92	4.92 ± 0.42	4.86 ± 0.57	5.01 ± 0.37	4.79 ± 0.4	**t1/t2 **t2/t3	↓AR t2/t3
Hemoglobin (g/dl)	14.2 ± 1.5	14.1 ± 1.7	15.3 ± 1.8	14.9 ± 2.6	14.4 ± 1.5	14.0 ± 1.6	14.5 ± 1.4	13.8 ± 1.20	**t1/t2 *t2/t3 *t3/t4	
Hematocrit (%)	42.9 ± 3.7	42.3 ± 4.5	46.6 ± 4.6	44.3 ± 6.7	43.4 ± 3.6	42.6.0 ± 4.0	44.8 ± 3.2	43.0 ± 2.90	**t1/t2 *t2/t3	↓AR t2/t3
Eosinophils (%)	4.0 ± 3.1	1.9 ± 1.3	4.3 ± 2.9	2.0 ± 1.2	4.9 ± 3.1	3.1 ± 1.8	4.2 ± 3.1	2.3 ± 1.1	**t1/t3	
Basophils (%)	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.3 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.3 ± 0.20	**t1/t3	
ECP (mg/ml)	16.0 ± 11.0	6.0 ± 4.0	5.0 ± 5.0	2.0 ± 2.0	11.0 ± 11.0	6.0 ± 6.0	14.0 ± 9.0	5.0 ± 3.0	**t1/t2 **t2/t3 **t3/t4	
IL-33 (ng/ml)	2.96 ± 4.04	4.16 ± 5.98	2.81 ± 4.1	4.0 ± 5.92	2.72 ± 3.91	3.72 ± 5.97	1.85 ± 2.45	5.16 ± .6.94	*t1/t2	↑Asthma t3/t4

Abbreviations: AE: atopic eczema; AR: allergic rhinitis; arb. units: arbitrary units; contr.: controls; DIELH: Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen; ECP: eosinophil cationic protein; FeNO: fractional exhaled nitric oxide; FEV1/VC: forced expiratory volume in one second/volume capacity; FVC: forced volume capacity; MEF50: maximum expiratory flow at 50 % of vital capacity; MMEF 25/75: maximal mid-expiratory flow between 25 % and 75 % of vital capacity; n.d.: not done; pat.: patients; PEF: peak expiratory flow; ppb: parts per billion; RQLQ: Rhinitis Quality of Life Questionnaire; prov.: provocation; Str.: stratum;TEWL: transepidermal water loss; *$p < 0.05$; **$p < 0.01$

2

2.3.2 Dermatological examination and skin function measurements (Tab. 2)

The severity of eczema as measured by SCORAD showed no significant changes (Fig. 6). Also the sebum concentrations did not change significantly over the study period. Stratum corneum hydration decreased significantly during the stay at the UFS (Fig. 7). Skin surface pH showed a significant increase at the UFS between time point 1 and time point 2 as well as between time point 3 and time point 4 (Fig. 8).

Skin roughness showed a significant increase ($p < 0.05$) at time point 2 (controls: 0.6 ± 0.2; patients: 1.0 ± 0.3) vs. 1 (controls: 0.5 ± 0.2; patients: 0.6 ± 0.3) as well as a significant decrease ($p < 0.01$) at time point 3 (controls: 0.5 ± 0.2; patients: 0.6 ± 0.4) vs. time point 2 (controls: 0.6 ± 0.2; patients: 1.0 ± 0.3). Skin scaliness and skin smoothness increased significantly during the stay at the UFS with significant differences ($p < 0.01$) between time point 1 (controls: 0.3 ± 0.2; patients: 0.3 ± 0.2/controls: 18.2 ± 3.8; patients: 18.2 ± 2.0) vs. time point 2 (controls: 0.7 ± 0.4; patients: 0.7 ± 0.3/controls: 18.8 ± 4.4; patients: 21.0 ± 3.8) and time point 3 (controls: 0.6 ± 0.3; patients: 0.8 ± 0.3/controls: 18.5 ± 4.3; patients: 22.3 ± 4.3) to time point 4 (controls: 0.5 ± 0.2; patients: 0.6 ± 0.3/(controls: 15.1 ± 0.5; patients: 19.0 ± 2.9).

Transepidermal water loss (TEWL) did not show significant changes over the study period. Also TEWL measured during the alkali resistance test showed no significant change during the study period. The dermal blood flow did not show significant changes over the study period, but in patients with atopic eczema this parameter increased significantly ($p < 0.01$) between time point 3 vs. 1.

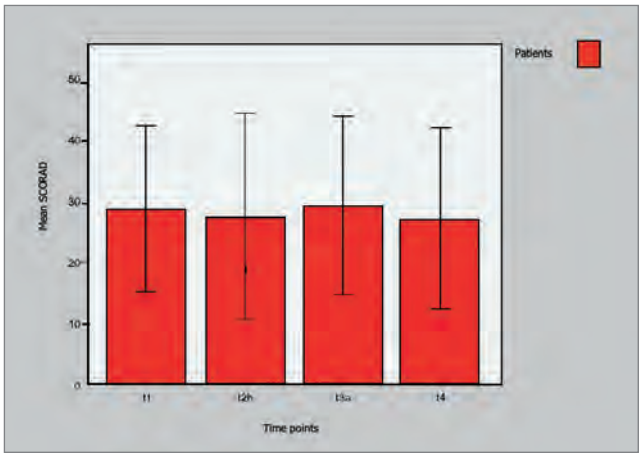

Fig. 6: SCORAD of patients with atopic eczema at the different time points (t1 and t4: Munich; t2 and t3: UFS)

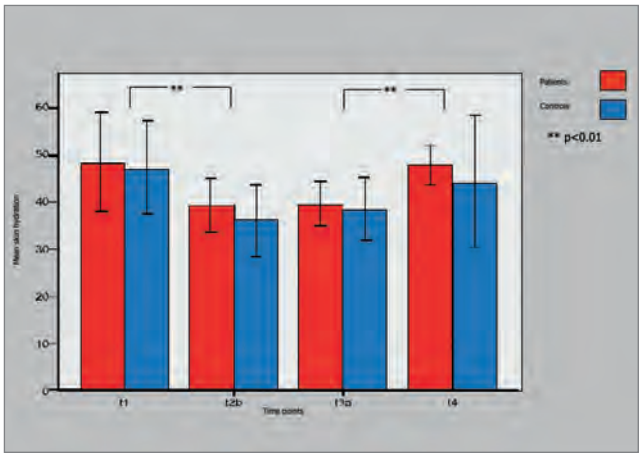

Fig. 7: Skin hydration of patients and controls at the different time points (t1 and t4: Munich; t2 and t3: UFS)

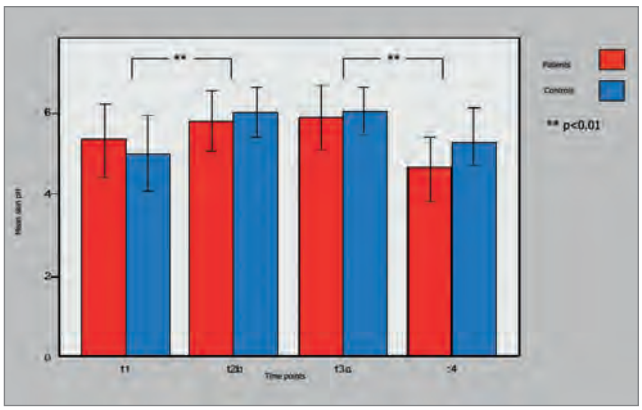

Fig. 8: PH-values of patients and controls at the different time points (t1 and t4: Munich; t2 and t3: UFS)

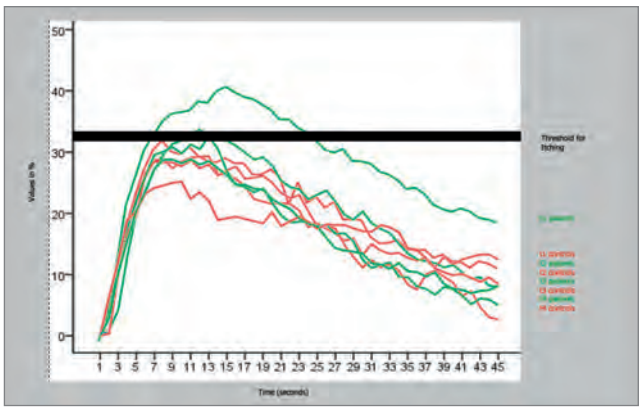

Fig. 9: Itch intensity after skin prick test with histamine of patients and controls at the different time points (t1 and t4: Munich; t2 and t3: UFS) (41)

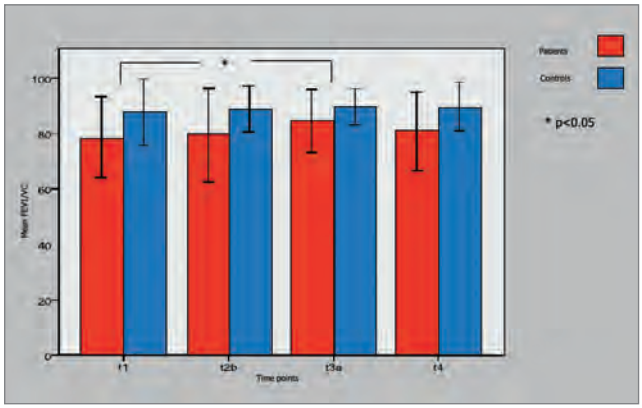

Fig. 10: FEV1/VC of patients and controls at the different time points (t1 and t4: Munich; t2 and t3: UFS)

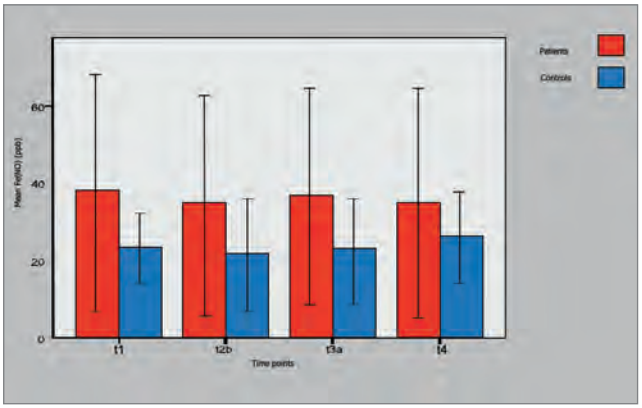

Fig. 11: FE(NO) of patients and controls at the different time points (t1 and t4: Munich; t2 and t3: UFS)

The size of the wheals and flares after a prick test with different concentrations of the grass pollen showed minor changes, namely an increase of the wheal size after prick test of the 1:100 solution at time point 3 vs. 2 and the decrease of the flare size of the 1:10 solution at time point 1 vs. 2 (data not shown). In patients with rhinoconjunctivitis the wheal size of the 1:10 solution increased significantly ($p < 0.05$) between time point 1 vs. 2.

Itch intensity after prick testing of histamine rated on a computerized visual analogue scale (VAS) decreased significantly between time point 2 vs. 1 and between time point 3 vs. 2 (Fig. 9). In patients with rhinoconjunctivitis itch intensity decreased significantly ($p < 0.05$) between time point 1 vs. time point 2.

2.3.2.1 Respiratory parameters (Tab. 2)

No significant changes in the rhinomanometric parameters (nasal flow and nasal resistance) were found before and after application of NaCl during the study.

The forced vital capacity (FVC) showed a significant decrease ($p < 0.05$) at time point 3 (controls: 4.7 ± 1.2 l; patients: 4.6 ± 1.2 l) vs. time point 2 (controls: 5.0 ± 1.3 l; patients: 5.2 ± 2.0 l). FEV1/VC (Fig. 10), PEF, MEF 50 and MMEF25/75 (data not shown) increased significantly ($p < 0.05$) at time point 3 or 2 vs. 1. The resistance during provocations tests with different concentrations of methacholinchloride, peak-flow values and values of the measurement of exhalative nitric oxide (NO) did not differ significantly at the different time points (Fig. 11).

2.3.2.2 Conjunctival provocation test (Tab. 2)

Conjunctival provocation with allergen solution in different concentrations did not differ significantly at the different time points. In patients with asthma there was a significant increase ($p < 0.05$) of this parameter at a concentration of 1:100 after 5 minutes at time point 1 vs. 2 and a significant decrease ($p < 0.05$) at time point 2 vs. 3 (ANOVA).

2.3.1.3 Quality of life – questionnaires (Tab. 2)

Statistical analysis of several questionnaires (SF-36 Questionnaire, Eppendorf Itch questionnaire, Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen [DIELH]) revealed no significant differences of the scores at all time points. The score of the Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]) increased significantly ($p < 0.05$) between time point 1 (controls: 6.6 ± 0.3; patients: 5.6 ± 0.9) vs. 3 (controls: 6.8 ± 0.2; patients: 5.8 ± 0.9). This increase reflects an improvement of symptoms.

2.3.2.4 Blood parameters (Tab. 2)

Erythrocytes, hemoglobin and hematocrit increased significantly ($p < 0.01$) at time point 2 vs. time point 1. In the serum a significant decrease ($p < 0.01$/$p < 0.05$) of the eosinophil cationic protein (ECP) and of interleukin-33 was found at the beginning of the stay at the UFS versus the first assessment in Munich (t2 vs. t1) and again a significant increase for ECP ($p < 0.01$) at the

last assessment in Munich versus the end of the stay at the UFS (t4 vs. t3). Interleukin-16 in the serum and ECP in the nasal secretions did not differ significantly during the different time points.

For the influence of the different atopic diseases (rhinoconjunctivitis, atopic eczema, asthma) on the above mentioned parameters (ANOVA) see Tab. 2.

2.4 Discussion

It was shown in this study, that a 5-day-sojourn at the Environmental Research Station Schneefernerhaus (UFS Zugspitze) at an altitude of 2650 m alt. exerts different effects on atopic diseases with amelioration of itching and some respiratory parameters.

A clinical improvement of atopic eczema skin lesions using the severity score SCORAD was not found. This was in contrast to reported benefits of climate therapy in patients with atopic eczema during treatment in specialized in-patient facilities in the alpine mountain climate of Bavaria (24, 25) or in mountain altitude conditions like Davos (4, 7, 26). Moreover a worsening of some skin physiology parameters (e. g. stratum corneum hydration, pH, skin roughness) was observed. One reason of this phenomenon might be the fact that topical glucocorticosteroids were withdrawn 1 week before time point 1, another reason could be the low air humidity at this altitude with negative influences on the skin. Only histamine-induced itching improved significantly during the observation period at the UFS. It is known that in the Swiss mountain area of Davos itch intensity was found to be correlated with some meteorological variables, especially air temperature (27).

Several lung parameters (FEV1/VC, PEF, MEF 50 and MMEF25/75) improved, only the forced vital capacity decreased. This is in accordance to previous studies with children and adolescents in in-patient rehabilitation programs (28, 29, 30, 31) in moderate high mountain climate showing an improvement of lung function disturbances. Decrease of exhaled NO as a parameter of lung inflammation was also seen in asthmatic patients under mountain climate therapy (5), but not in our study.

The SF-36 questionnaire was constructed to survey health status and designed for use in clinical practice and research, health policy evaluations and general population surveys (20). In our study at the UFS there were no significant differences of the score at the different time points. Furthermore the scores of the skin specific questionnaires emphazising the pruritus (The Eppendorf Itch Questionnaire) and the quality of life (DIELH) did not differ significantly in our study. By contrast, in the AURA study we found a significant amelioration of the scores confirming the benefit of the therapy in Pfronten (25). Only the RQLQ showed a significant difference between time point 1 and time point 2 in our study with a negative influence of atopic eczema and a positive influence of asthma.

Exposure to the moderate altitude had significant effects on red blood cells (32) with an increase of eosinophils during the stay at the UFS. This is in contrast to other studies during hospital treatment of atopic eczema in the mountain climate (33) and the North Sea climate with decreased eosinophils (34).

Elevated ECP and IL-33 levels are regarded as markers of inflammation in asthma and atopic eczema (35, 36). In our patients with atopic diseases ECP together with IL-33 decreased significantly. Similar effects had been shown in the mountain climate of Davos for ECP (8).

It could be shown that circulating Il-16 levels are correlated with the SCORAD in adult patients with atopic eczema (37) and decreased significantly in these patients after successful treatment (38). We did not find a decrease in our patients with atopic diseases.

Despite the extensive and detailed measurements of characteristics of atopic diseases during a 5 day observation period in the mountain climate of the Zugspitze in Bavaria only a few parameters improved. The stay was helpful for patients with asthma, whereas patients with atopic eczema did not benefit from it and even their skin physiology parameters worsened. This might be due to the short duration of the sojourn and specific environmental factors at this altitude. It would be of interest assessing the skin parameters and characteristics of atopic eczema during observation periods lasting several weeks in the alps.

Since there is recently some criticism regarding validated data for the moderate altitude therapy for patients with allergic diseases (39, 40) the methodology presented can serve as a suitable template for qualified studies on the effect of climate therapy.

Acknowledgement

The statistical analysis was performed by the Institut für Medizinische Statistik und Epidemiologie, Technische Universität München (Bernhard Haller).

The authors also want to thank Free State of Bavaria (Bayerisches Staatsministerium für Umwelt und Gesundheit) for funding and the Christine Kühne Center for allergy research and education (CK – CARE) for support in data evaluation.

References

1. Ring J., Eberlein-König B., Behrendt H. Environmental pollution and allergy. Ann Allergy Asthma Immunol 2001; 87: 2–6
2. Behrendt H. Environmental factors as determinants of allergy development. MMW Fortschr Med 2006; 148: 32–33
3. Bärtsch P., Dvorak J., Saltin B. Football at high altitude. Scand J. Med Sports 2008; 28 Suppl I: iii–iv
4. Steiger T., Borelli S. Significance of climatic factors in the treatment of atopic eczema (Atopic Constitutional Neurodermitis). In: Handbook of atopic eczema. T. Ruzicka, J. Ring, B. Przybilla, eds. Springer, Berlin pp 1991; 420–428.
5. Schultze-Werninghaus G. Should asthma management include sojourns at high altitude. Chem. Immunol Allergy 2006; 91: 16–29.
6. Karagiannidis C., Hense G., Rueckert B., Mantel PY, Ichters B., Blaser K., Menz G., Schmidt-Weber C. B. High-altitude climate therapy reduces local airway inflammation and modulates lymphocyte activation. Scand J Immunol 2006; 63: 304–310.
7. Guhring H. Complex high altitude climate therapy for children and adolescents with neurodermitis constitutionalis atopica. Kinderärztl. Praxis 1992; 60:150–155.
8. Engst R., Vocks E. High-mountain climate therapy for skin diseases and allergy: Mode of action, therapeutic results, and immunologic effects. Rehabilitation (Stutg) 2000; 39: 215–222.
9. Simon S., Weigl L., Disch R. Influence of high-altitude climate therapy on atopic eczema. Allergologie 1999 Suppl 1; S26–S28.
10. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980; Suppl 92: 44–47.
11. Williams H. C., Burney P. G., Hay R. J., Archer C. B., Shipley M. J., Hunter J. J., Bingham F. A., Finlay A.Y., Pembroke A. C., Graham-Brown RA. The U. K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J. Dermatol 1994; 152: 735–741.
12. Ring J., Ruzicka T., Przybilla B. Handbook of atopic eczema. 2nd edition. 2006; Springer, Berlin, Germany
13. Global Strategy for Asthma Management and Prevention. updated December. Scientific information and recommendations for asthma programs. NIH Publication 2011; No. 02-3659
14. Kunz B., Oranje A. P., Labreze L., Stalder J. F., Ring J., Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1997; 195: 10–19.
15. Pfab F., Valet M., Sprenger T., Toelle T. R., Athanasiadis G. I., Behrendt H., Ring J., Darsow U. Short-term alternating temperature enhances histamine-induced itch: a biphasic stimulus model. J. Invest Dermatol 2006; 126: 2673–2678.
16. Eberlein-König B., Schäfer T., Huss-Marp J., Darsow U., Möhrenschlager M., Herbert O., Abeck D., Krämer U., Behrendt H., Ring J. Skin surface pH, stratum corneum hydration, trans-epidermal water loss and skin roughness related to atopic eczema and skin dryness in a population of primary school children. Acta Derm Venereol 2000; 80: 188–191.
17. Pinnagoda J., Tupker R. A., Agner T., Serup J. Guidelines for transepidermal water loss (TEWL) measurement. A report from the Standardization Group of the European Society of Contact Dermatitis. Contact Dermatitis 1990; 22: 164–178
18. Fischer R., Lang S. M., Bergner A., Huber R. M. Monitoring of expiratory flow rates and lung volume during a high altitude expedition. Eur J. Med Res 2005; 10: 469–474

19. Huss-Marp J., Krämer U., Eberlein B., Pfab F., Ring J., Behrendt H., Gulyas A. F. Reduced exhaled oxide values in children with asthma after inpatient rehabilitation at high altitude. J. Allergy Clin Immunol 2007; 120: 471–472
20. Ware J. J., Snow K. K., Kosinski M., Gandek B. SF-36 Health Survey. Manual and interpretation guide. 1993; Boston, The Health Institute, New England Medical Center
21. Darsow U., Mautner V. F,. Bromm B., Scharein E., Ring J. The Eppendorf Pruritus Questionnaire. Hautarzt 1997; 48: 730–733.
22. Schäfer T., Staudt A., Ring J. German instrument for the assessment of quality of life in skin diseases (DIELH). Internal consistency, reliability, convergent and discriminant validity and responsiveness. Hautarzt 2001; 52: 624–628.
23. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991; 21: 77–83
24. Eberlein B., Gulyas A., Schultz K., Lecheler J., Flögel S., Wolfmeyer C., Thiessen K., Gass S., Kroiss M., Huss-Marp J., Darsow U., Hollweck R., Schuster T., Behrendt H., Ring J. Benefits of alpine mountain climate of Bavaria in patients with allergic diseases and chronic obstructive pulmonary disease: results from the AURA study. J. Investig Allergol Clin Immunol 2009; 19: 159–161.
25. Eberlein B., Gulyas A., Schultz K., Lecheler J., Flögel S., Wolfmeyer C., Thiessen K., Jakob T., Hollweck R., Ring J., Behrendt H. Domestic allergens and endotoxin in three hospitals offering in-patient rehabilitation for allergic diseases in the alpine mountain climate of Bavaria – the AURA study. Int J Environ Health 2009; 212: 21–26.
26. Autio P., Komulainen P., Larni H. M. Heliotherapy in atopic dermatitis: a prospective study on climatotherapy using the SCORAD index. Acta Derm Venereol 2002; 82: 436–440.
27. Vocks E., Busch R., Fröhlich C., Borelli S., Mayer H., Ring J. Influence of weather and climate on subjective symptom intensity in atopic eczema. Int J Biometeorol 2001; 45: 27–33.
28. Petermann F., Gulyas A., Niebank K., Stübing K., Warschburger P. Rehabilitationserfolge bei Kindern und Jugendlichen mit Asthma und Neurodermitis. Allergologie 2000; 23: 492–502.
29. Grootendorst D. C., Dahlen S. E., van den Bos J.W., Duiverman E. J., Veselic-Charvat M., Vrijlandt E. J. L. E., O'Sullivan S., Kumlin M., Sterk P. J., Roldaan A. C. Benefits of high altitude allergen avoidance in atopic adolescents with moderate to severe asthma, over and above treatment with high dose inhaled steroids. Clin Exp Allergy 2001; 31: 400–408.
30. van Velzen E., van den Bos J.W., Benckhuijsen J. A., van Essel T., de Bruijn R., Aalbers R. Effect of allergen avoidance at high altitude on direct and indirect bronchial hyperresponsiveness and markers of inflammation in children with allergic asthma. Thorac 1996; 51: 582–584.
31. Rijssenbeek-Nouwens LH, Bel EH. High-altitude treatment: a therapeutic option for patients with severe, refractory asthma? Clin Exp Allergy 2011; 41: 775–782
32. Schmidt W. Effects of intermittent exposure to high altitude on blood volume and erythropoietic activity. High Alt Med Biol 2002; 3: 167–176
33. Simon H. U., Grotzer M., Nikolaizik K., Blaser M., Schöni H. High altitude climate therapy reduces peripheral blood T-lymphocyte activation, eosinophilia and bronchial abstruction in children with house-dust mite allergic asthma. Pediatr Pulmonol 1994; 17: 302–311.
34. Pürschel W., Pahl O. Behaviour of eosinophilic granulocytes, total IgE and allergen specific IgE antibodies in atopic neurodermitis during hospital treatment of the North Sea climate. Z Hautkr 1985; 60: 661–670.
35. Remes S., Korppi M., Remes K., Savolainen K., Mononen I., Pekkanen J. Serum eosinophil cationic protein (ECP) and eosinophil protein X (EPX) in childhood asthma: the influence of atopy. Pediatr Pulmonol 1998; 25: 167–174.
36. Kurowska-Stolarska M., Hueber A., Stolarski B., McInnes I. B. Interleukin-33: a novel mediator with a role in distinct disease pathologies. J. Intern Med 2011; 269: 29–35
37. Angelova-Fischer I., Hipler U. C., Bauer A., Fluhr J.W., Tsankov N., Fischer T.W., Elsner P. Significance of interleukin-16, macrophage-derived chemokine, eosinophil cationic protein and soluble E-selectin in reflecting disease activity of atopic dermatitis – from laboratory parameters to clinical score. Br J Dermatol 2006; 154:1112–1117.
38. Masuda K., Katoh N., Okuda F., Kishimoto S. Increased levels of serum interleukin-16 in adult type atopic dermatitis. Acta Derm Venereol 2003; 83: 249–253.
39. Massimo T., Blank C., Strasser B., Schobersberger W. Does climate therapy at moderate altitudes improve pulmonary function in asthma patients? A systematic review. Sleep Breath 2014; 18: 195–206
40. Fieten K. B., Weststrate A. C., van Zuuren E. J., Bruijnzeel-Koomen C. A., Pasmans S. G. Alpine climate treatment of atopic dermatitis: a systematic review. Allergy 2015; 70: 12–2
41. Eberlein B., Huss-Marp J., Pfab F., Fischer R., Franz R., Schlich M., Leibl M., Allertseder V., Liptak J., Kriegisch M., Hennico R., Latotski J., Ebner von Eschenbach C., Darsow U., Buters J., Behrendt H., Huber R., Ring J. Influence of alpine mountain climate of Bavaria on patients with atopic diseases: studies at the Environmental Research station Schneefernerhaus (UFS- Zugspitze) – a pilot study. Clin Transl Allergy 2014; 4: 17