

Original article

Effectiveness of occlusive bedding in the treatment of atopic dermatitis – a placebo-controlled trial of 12 months' duration

Background: Several studies on avoidance of house-dust-mite (HDM) and cat allergens have been carried out, most of them in asthmatic patients and only a few in patients with atopic dermatitis (AD). No study so far has focused on which subgroup of AD patients benefits from avoidance measures.

Methods: Forty adult patients with AD completed the 12-month avoidance study. They were divided into an active treatment ($n=22$) and a placebo ($n=18$) group. Active treatment comprised use of polyurethane-coated cotton encasings for bedding, and placebo use of cotton covers. Patients came for regular checkups during the 12-month period, when eczema severity was assessed and blood samples were analyzed for total IgE, HDM- and cat-specific IgE and soluble CD30 (sCD30) in serum. Dust samples were collected from mattresses before treatment and after 3, 6, and 12 months, and analyzed for content of HDM and cat allergen.

Results: Eczema severity decreased significantly in both groups ($P<0.001$), with a more pronounced decrease in patients with active covers. The HDM exposure decreased significantly in the active treatment group ($P<0.001$), and the levels of HDM-specific IgE were reduced ($P<0.05$). Exposure to cat allergens was unchanged in the active treatment group but decreased, albeit not significantly ($P=0.19$), in the placebo group. sCD30 levels were significantly reduced in both groups ($P<0.001$). Patients not sensitized to HDM allergens benefited from the bedcovers as much as sensitized patients.

Conclusions: Occlusive bedding significantly reduced HDM exposure in bed ($P<0.001$) and eczema severity, and sCD30 levels decreased significantly ($P<0.001$). Patients not sensitized to HDM and not exposed to HDM allergens benefited equally from use of the bedcovers, a result which could be due to a reduction of other important allergens, superantigens, or irritants in bed. We therefore recommend the use of bedcovers as part of treatment for AD.

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Atopic dermatitis (AD) is a chronic relapsing skin disease that in the West affects 10–20% of all children (1). Although the disease in most cases remits spontaneously during childhood or adolescence, it sometimes persists into adult life. The pathogenesis of this common disease is probably multifactorial. Recent data suggest an IgE-mediated contact reaction to airborne allergens as one of the mechanisms involved and indicate that house-dust mite (HDM) and cat might be two of the common allergens involved. Epicutaneously applied HDM allergen, in the atopy patch test (APT), provoked an eczema reaction in about 20–85% of patients with AD (2–7). About 60–90% of patients with AD have IgE to HDM in serum (8), and the level correlates to the severity of the dermatitis, which in turn positively correlates to the HDM exposure (9, 10).

Several studies have been done on avoidance of

HDM and cat allergens, most of them on asthmatic patients (11). Only a few have included patients with AD (11–14). Different kinds of avoidance procedures have been used, most of them complicated and hard for the patient to manage. For example, Sanda et al. (14) showed that efficient avoidance of HDM allergen through a complicated “clean room therapy” resulted in clinical improvement. Among measures to reduce mite allergen, including acaricides and various cleaning procedures, encasement of bedding materials in allergen-impermeable covers has been shown to be the most effective measure, in both reducing mite allergens (15–18) and ameliorating asthmatic symptoms (16, 19, 20), and in reducing eczema severity (13, 21, 22). However, most studies have been uncontrolled and thus hard to evaluate. The treatment periods have often been short, and the natural seasonal fluctuation of the

dermatitis has probably influenced the results. It is also possible that allergens other than those under examination contributed to the effects observed. Cat allergen is proposed to be an important indoor allergen in Sweden (23–25), and previous avoidance studies using encasement of bedding indicate a reduction of this allergen (15, 18). No study so far has focused on which subgroup of patients with AD benefits most from avoidance measures. We therefore constructed a placebo-controlled trial of long duration with easily performed avoidance measures and with different subgroups of patients with AD.

Material and methods

Subjects and study design

Forty-three patients aged ≥ 18 years with AD according to the criteria of Haifin and Rajka (26), attending the outpatient clinic of Dermatology, Stockholm Söder Hospital, Sweden, were included. Exclusion criteria were ongoing immunotherapy, pregnancy, the use of potent topical steroids, UV light treatment within 2 weeks before the start of the study, change of mattress or moving house after the first dust sampling, or clinical score of < 20 on the SCORAD index (27). During the trial, the only treatment allowed was mild topical steroids and emollients. Occasional short-term antibiotic treatment was allowed when secondary infection occurred.

The study was a double-blind, placebo-controlled trial of 12 months' duration. All patients started during the same month. Before starting the study, the patients were evaluated according to various parameters: total serum IgE; IgE to HDM, cat, and the opportunistic yeast *Pityrosporum orbiculare*; SPT and APT with HDM allergens; and the SCORAD index. The patients were divided into two groups, one active treatment group of 22 patients, and one placebo group of 21 patients. The groups were matched according to sex, eczema severity, and sensitization to HDM (according to specific IgE in serum, SPT, and APT). In the placebo group, three patients were excluded, two patients because they moved and one because of pregnancy. Thus, 22 patients in the active treatment group and 18 patients in the placebo group remained for analysis. The characteristics of the patients are given in Table 1.

On day 1, a blood sample was collected from each patient and analyzed for soluble CD30 (sCD30), total IgE, and IgE to HDM and cat allergens. A dust sample was collected from each patient's mattress and analyzed for HDM and cat allergens. The eczema severity was scored on the SCORAD index, and photo-documented. In the active treatment group, water-vapor-permeable cotton encasings were put on the mattresses and pillows of the patient's and the patient's partner's bed. The Allergy Control Covers (Medeca, Sweden) were coated on one side with polyurethane, with the ability to reduce HDM exposure in bed up to 98% (17). The covers were particle proof for sizes bigger than $1 \mu\text{m}$ (Swedish Institute for Fibre and Polymer Research). The duvets were washed in hot water ($> 60^\circ\text{C}$). The bedroom carpets were removed or vacuumed. The carpets and the surface of the mattresses were then vacuumed monthly, and the duvets were washed monthly during the study. In the placebo group, the patients were instructed not to take any avoidance measures, except putting on the placebo covers, made of cotton without the polyurethane layer. These covers allowed particles of $< 62 \mu\text{m}$ to penetrate (Swedish Institute for Fibre and Polymer Research). The patients kept a weekly diary of itch intensity. After 1, 2, 3, 6, and 12 months, the patients came for checkups. The eczema severity score was assessed and photo-documented. Blood samples were collected for the analyses of total IgE and IgE to HDM at each checkup and for IgE to cat at 6 and 12

months and sCD30 at 3, 6, and 12 months. New dust samples were collected at 3, 6, and 12 months and analyzed for HDM and content of cat allergen. The study was approved by the local ethics committee, and the patients gave their informed consent.

Dust sampling and assessment of exposure to HDM and cat

Dust samples from mattresses were collected for 2 min/m^2 with a filter bag (Medeca AB, Uppsala, Sweden) fitted into the inlet tube of the vacuum cleaner, as previously described (28). Subjects were requested not to vacuum-clean their mattresses for 14 days before collection of dust samples. All dust samples were stored at -18°C until extracted. Allergen extraction and analysis of Der p 1, Der f 1, and Fel d 1 (Indoor Biotechnologies, Chester, UK) were performed with monoclonal antibody-based ELISA, as reported earlier (28, 29). The lower detection limit for the allergens was 55 ng/g of dust.

Skin prick test (SPT)

The SPT was performed with commercially available extracts from ALK (Copenhagen, Denmark) with the potency of 10 HEP, which, according to the manufacturer, is equal to $20\,000 \text{ BU/ml}$. The allergens tested were *Dermatophagoides pteronyssinus* (Dpt) and *D. farinae* (Df). Test procedures were performed, according to Aas & Belin (30), on the volar part of the forearm. The skin reactions were read after 15 min and the wheal sizes were compared with positive histamine (histamine chloride 10 mg/ml) and negative control. A wheal size equal to the histamine reaction was scored 3+ on a scale of 1–5. A SPT reaction of $\geq 2+$ was considered positive. The same trained nurse performed all the tests.

Total and specific IgE

Total IgE and specific IgE concentrations in serum were determined by the Pharmacia CAP System, IgE and RAST, FEIA (Pharmacia and Upjohn AB Diagnostics, Uppsala, Sweden). IgE was measured against *D. pteronyssinus* and *D. farinae*, as well as cat and the yeast *Pityrosporum orbiculare* (also denoted *Pityrosporum ovale* or *Malassezia furfur*). The cutoff for total serum IgE was 2 kU/l and for RAST 0.35 kU/l . The RAST values were expressed in classes of 0–6. RAST classes of ≥ 1 were considered positive.

Atopy patch test (APT)

Freeze-dried extract of *D. pteronyssinus* from ALK, Aquagen SQ, normally used for immunotherapy, was mixed in two different vehicles: phosphate-buffered saline solution (the dilution fluid used in immunotherapy) and white petrolatum, and in two concentrations: $20\,000 \text{ BU}$ and $100\,000 \text{ BU}$ per ml of solution or gram of petrolatum. Volumes of 0.03 ml of solution preparations and 0.03 g of petrolatum preparations were applied in Finn chambers (8 mm) on tape-stripped skin (stripped 15 times with tape having an adhesive capacity = 8 N/25 mm) and on clinically normal skin on the back for 24 or 48 h. Two control patches with the vehicles alone were added on both tape-stripped and intact skin. The series were read at 48 and 72 h. Scoring was performed by the standard reading procedure; –: no reaction, +: erythema, ++: erythema and induration/papules, +++: vesicles/exsudation. An APT reaction of $\geq ++$ was considered positive. The same physician evaluated all tests.

Severity scoring of AD

The patient's clinical score was estimated according to the consensus report of European Task Force on AD – the SCORAD index (27). This index is based on a mathematical formula whereby extent ("rule of nine") and subjective symptom account for 20% each of the total score, and intensity items (erythema, edema/papules, oozing/crusts, excoriations, lichenification, and dryness) represent 60%.

Table 1. Characteristics of AD patients in active treatment and placebo groups

	Patients with active covers <i>n</i> = 22	Patients with placebo covers <i>n</i> = 18
Male/female	9/13	6/12
Age, years, median (range)	31 (18–65)	30 (22–53)
AD duration, years, median (range)	28 (1–64)	28 (10–52)
Respiratory symptoms*	19 (86%)	13 (72%)
SCORAD**, median (range)	47 (22–79)	40 (15–75)
Total s-IgE (kU/l), median (range)	437 (2–13 900)	1000 (26–6900)
Allergen-specific IgE (RAST class $\geq$ 1)		
HDM***	12 (54%)	10 (55%)
Cat	12/19 (63%)	13/16 (81%)
<i>Pityrosporum orbiculare</i>	11 (50%)	7 (39%)
Skin prick test, HDM ($\geq$ 2)****	6 (27%)	5 (28%)
Atopy patch test, HDM ($\geq$ 2)*****	11 (50%)	6 (33%)
Unsensitized to HDM*****	6 (27%)	5 (27%)
Allergen exposure (ng/g)		
HDM*****:		
$\leq$ 55	14 (63.5%)	16 (89%)
> 55 < 2000, median (range)	5 (23%), 107 (59–1800)	2 (11%), 262 (57–468)
$\geq$ 2000, median (range)	3 (13.5%), 59 640 (12 832–325 392)	0 (0%)
Cat*****	<i>n</i> = 19	<i>n</i> = 16
$\leq$ 55	5 (26.5%)	3 (19%)
> 55 < 2000, median (range)	13 (68.5%), 200 (100–330)	9 (56%), 200 (61–610)
$\geq$ 2000, median (range)	1 (5%), 6800	4 (25%), 23 000 (5500–84 800)

* Rhinitis and/or asthma.

** Consensus report of European Task Force on AD (27).

*** RAST value of *Dermatophagoides pteronyssinus* (Dpt) and/or *D. farinae* (Df).

**** Dpt and/or Df.

***** HDM extract in APT: freeze-dried HDM extract of Dpt, from ALK, normally used for immunotherapy.

***** RAST < 1, SPT < 1 and APT $\leq$ 1.

***** Allergen content for group 1 *Dermatophagoides* allergens, Der p 1 and Der f 1.

***** Allergen content for Fel d 1.

sCD30 assay

The concentration of sCD30 in the serum samples was determined in duplicate by a sandwich enzyme-linked immunosorbent assay (CD30, Ki-1 antigen, ELISA; Dako, Glostrup, Denmark), as previously described (31) in which the mouse monoclonal antibodies (mAbs) used for coating and conjugate are noncompetitive and react with different epitopes on the CD30 molecule. According to the manufacturer's description, the detection limit of the assay was estimated to be 1 U/ml. In the present study, sera from different time points in the study were analyzed randomly on the same plates to avoid bias due to technical errors. Interassay variation was determined by assessing one sample in duplicates in seven assays run on different days. The coefficient of variation (CV) was estimated to be < 8%. Intra-assay variation was analyzed by assessing five identical duplicate samples in one assay, and here the CV was found to be < 6%. The serum samples were kept frozen at -20°C until analysis.

Statistical analysis

Overall, the data were analyzed in ANOVA repeated measurements design with time as the dependent factor with a various number of levels (six levels for SCORAD, itch, and total- and HDM-specific IgE in serum; four levels for exposure to HDM and cat allergen; and three levels for sCD30 and cat-specific IgE) and type of bedcover as an independent factor with two levels. We were also testing whether sensitization to HDM (according to RAST and APT), cat, or *P. orbiculare* (according to RAST), or exposure to HDM or cat allergens interacted with the results. They were added as independent factors in the ANOVA repeated measurements design. Some of the

outcome variables were log-transformed to get a more symmetric distribution. *P* values of < 0.05 were considered statistically significant.

Results

The severity score

The severity of the dermatitis, according to the SCORAD index, was significantly reduced by 45% in the group with active covers and by 39% in the group with placebo covers after 12 months ($P < 0.001$) (Fig. 1, Table 2). The patients' own perception of itch was also significantly reduced ($P < 0.001$), and followed the severity score in both groups.

Exposure to allergens

Exposure to HDM allergens was not particularly common. In the active treatment group, 8/22 (36.5%) patients and in the placebo group 2/18 (11%) patients had detectable levels of HDM allergens in dust samples from their mattresses at the beginning of the study (Table 1). The exposure decreased significantly during the study period in the active treatment group ($P < 0.005$) (Fig. 2, Table 2). Since nearly all patients in the placebo group (16/18) had levels of HDM allergens of < 55 ng/g in dust samples from their

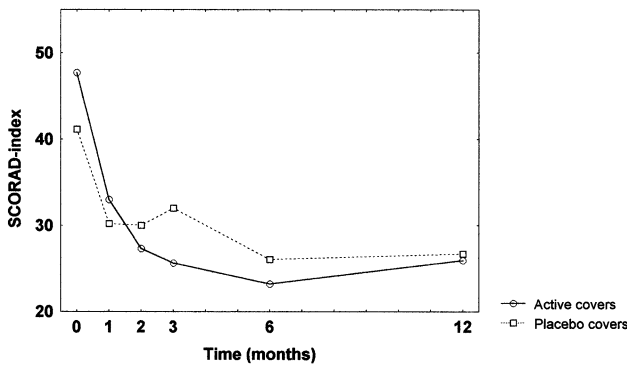


Figure 1. Mean values of SCORAD index (27) before treatment and follow-up visits at 1, 2, 3, 6, and 12 months for active treatment (○) ($n=22$) and placebo (□) groups ($n=18$). In both groups, SCORAD index was significantly reduced over time ($P<0.001$).

mattresses, it was not possible to perform any statistical analysis in this group. The two patients who had 57 and 468 ng/g from the start had levels below the detection limit at 3, 6, or 12 months.

Exposure to cat allergens in bed was more common than to HDM allergens, even though only one patient had a cat at home. In the active treatment group, 14/19 (73.5%) patients and in the placebo group 13/16 (81%) patients had levels of cat allergens over 55 ng/g in dust samples from the start (Table 1). The levels of cat allergen decreased during the study in the group with placebo covers, but it was not statistically significant because of a large intraindividual variation ($P=0.19$). The levels of cat allergen were unchanged in the group with active covers (Fig. 3, Table 2).

Serology

Total IgE remained unchanged in both groups during the study period, while HDM-specific IgE decreased significantly ($P<0.05$) (Table 2). The levels of HDM-specific IgE were unchanged for the first 6 months, and

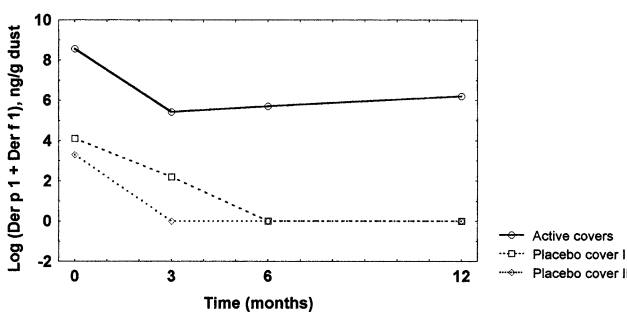


Figure 2. Log-transformed mean values of HDM content (Der p 1 plus Der f 1) in dust samples from bed mattresses before and after 3, 6, 12 months of trial in active treatment (○) group ($n=6$) and log-transformed values for two patients in placebo (□) group. From mattresses encased with active covers, HDM content was significantly reduced over time ($P<0.005$). Statistical analysis could not be performed in placebo group because of too few samples.

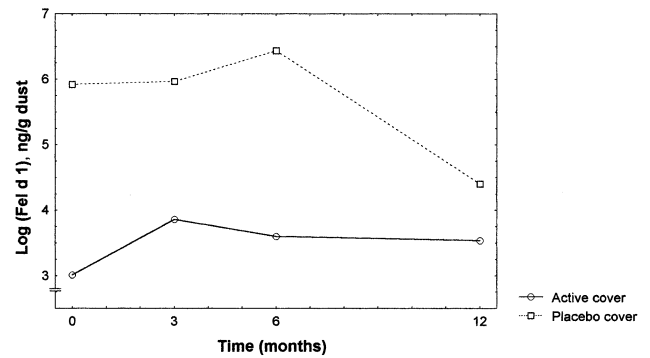


Figure 3. Log-transformed mean values of content of cat allergen (Fel d 1) in dust samples from bed mattresses before and after 3, 6, 12 months of trial, in active treatment (○) ($n=10$) and placebo (□) group ($n=11$). From mattresses encased with placebo covers, allergen levels were reduced over time, but because of intraindividual variation, reduction was not statistically significant ($P=0.19$).

the decrease came during the last 6 months of the study (Fig. 4). The levels of cat-specific IgE remained unchanged during the whole period. sCD30 followed the severity score in both groups, with a significant reduction after 12 months ($P<0.001$) (Fig. 5, Table 2).

Interaction of sensitization and exposure to allergens and correlation to use of covers

In the different subgroups of AD patients – i.e. sensitized, according to RAST ($n=22$), SPT ($n=11$), and/or APT ($n=17$), or unsensitized to HDM allergens ($n=11$), HDM-exposed ($n=10$), or unexposed ($n=30$) – the eczema severity, according to the SCORAD index, was similarly decreased. This was also true for patients sensitized ($n=25$) or unsensitized to cat ($n=10$), as well as exposed ($n=27$) or unexposed ($n=8$) to cat allergens. In patients with IgE to HDM in serum ($n=22$), the itch was significantly reduced over time, compared to those lacking specific IgE ($n=18$) ($P<0.05$). Patients with positive patch test reaction to HDM, had a more pronounced reduction of HDM-specific IgE in serum

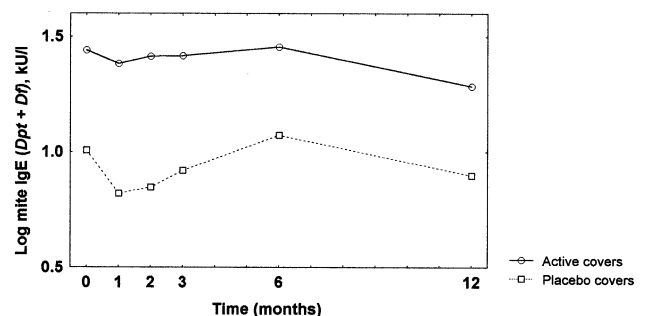


Figure 4. Log-transformed mean values of HDM-specific IgE (*Dermatophagoides pteronyssinus* and *D. farinae*) in serum at beginning and after 1, 2, 3, 6, and 12 months of trial in active treatment (○) ($n=22$) and placebo (□) group ($n=18$). During last 6 months of study, levels were significantly reduced in both groups ($P<0.05$).

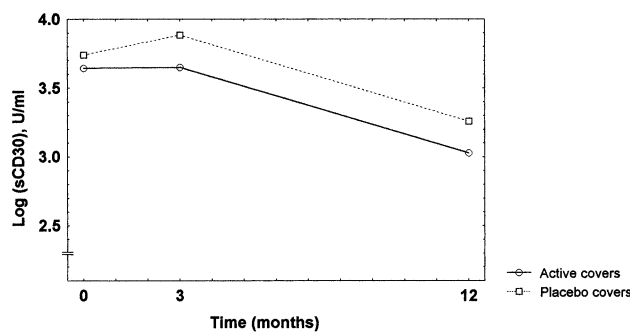


Figure 5. Log-transformed mean values of soluble CD30 levels at three different time points (0, 3, and 12 months) in patients with active treatment (○) ($n=22$) and in placebo group (□) ($n=18$). sCD30 levels were significantly reduced in both groups over time ($P<0.001$).

when using active covers ($n=11$) compared to placebo covers ($n=6$) ($P<0.05$). Among patients sensitized to *P. orbiculare*, according to RAST ($n=18$), the eczema severity was significantly more reduced in patients with active covers ($n=11$) than in those with placebo covers ($n=7$) ($P<0.05$).

Discussion

Because of the cool and dry climate of northern Scandinavia, domestic mite infestation has been rare (32). However, recent studies, including our own study from the Stockholm region, indicate an increasing prevalence of mite sensitization in Sweden, probably reflecting an increase in mite infestation (28, 33–35). Wickman et al. found levels of HDM allergen in mattress dust samples from central and northern Sweden sometimes exceeding those of subtropical regions. One reason may be the new building techniques, with residences carefully insulated to conserve energy. These sparingly ventilated buildings accumulate humidity that promotes HDM growth (36). In a temperate climate like Sweden's, the main source of HDM allergens is mattresses, in which the temperature and humidity are optimal for HDM growth. Cat allergen is thought to be an important indoor allergen in Sweden (25); therefore, we also measured this allergen in bedding.

The first objective of our study was to determine whether allergen avoidance through use of the bed covering system gave clinical improvement in patients with AD. The second objective was to determine which subgroup, if any, of patients with AD benefits most from allergen avoidance through use of the bed covering system: patients with positive APT, SPT, and/or RAST to HDM or even unsensitized and/or unexposed AD patients whose condition might improve as a result of reduction of other possible contact allergens in bed.

We found a significant reduction of eczema severity

Table 2. Changes in eczema severity (SCORAD index), HDM (Der p 1 plus Der f 1) and cat (Fel d 1) exposure, HDM IgE levels (Dpt plus Df), and sCD30 in serum during the 12-month study

	Means (standard deviations)		
	At baseline	At 12 months	P value
SCORAD index			
Active treatment group	48 (17)	26 (17)	<0.001
Placebo group	41 (17)	27 (17)	<0.001
Log (Der p 1 plus Der f 1), ng/g			
Active treatment group	8.56 (3.75)	6.19 (4.32)	<0.005
Log (Fel d 1), ng/g			
Active treatment group	3.01 (2.61)	3.53 (3.09)	NS
Placebo group	5.92 (3.77)	4.40 (4.44)	=0.19
Log HDM IgE (Dpt plus Df), kU/l			
Active treatment group	1.44 (1.78)	1.28 (1.68)	<0.05
Placebo group	1.01 (1.00)	0.90 (0.95)	<0.05
Log sCD30, U/ml			
Active treatment group	3.64 (1.09)	3.03 (1.55)	<0.001
Placebo group	3.74 (1.26)	3.26 (1.31)	<0.001

over a period of 1 year in patients who were using a semipermeable bed covering system ($P<0.001$). We found an almost equal reduction in patients using placebo cotton covers. The reason for this could be that these covers also had an allergen-reducing capacity. Previous avoidance studies, using cotton covers similar to those used as placebo in this study, have shown a decrease in mite allergens from bed mattresses (13). In our study, the two patients in the placebo group who had ≥ 55 ng/g HDM allergens in bed dust at the beginning of the study had levels below detection limit at the end of the study. Furthermore, there was a reduction, although not a statistically significant one ($P=0.19$), of levels of cat allergen in the placebo group, suggesting an allergen-reducing capacity of the placebo covers. Another reason could be that patients in the placebo group took avoidance measures not recommended in this group, such as changes in cleaning and airing habits. It appears that awareness of possible mite infestation leads to changes in cleaning habits. Wickman et al. (17) observed reduced levels of mite allergen in a reference group where no avoidance measures were to be taken. They related this to a reduced indoor humidity secondary to intensified airing.

As in previous studies, we could see a positive correlation between HDM-exposure and HDM-specific IgE levels in serum, as well as between specific IgE levels and eczema severity (9, 10). However, in our study, there was a delay of 6 months from the start of avoidance until the decline in specific IgE became obvious. Specific IgE can therefore not be recommended as an indicator of effectiveness of avoidance measures in studies of short duration.

Interestingly, we found a relationship between eczema severity and sCD30 in serum. CD30 is a surface antigen expressed by T helper (Th) cells. Allergen-

specific human CD4⁺ T-cell clones of Th1, Th0, and Th2 type have the ability to express CD30 after activation, although with a sustained expression only in Th2 cells (37). sCD30 has been studied previously in AD as a potential marker of disease activity, but the results have been conflicting (31, 38–41). In this study, however, we found a correlation between disease activity and sCD30, and after 12 months there was a significant decrease in sCD30 levels. We recommend that future clinical trials on AD assess sCD30 as a marker of eczema severity, since there still is need for a reliable laboratory marker of disease activity in AD.

Comparison of subgroups of AD patients did not show any specific group that seemed to benefit more than others from use of the bed covering system according to the eczema severity score. Patients not sensitized to HDM as well as patients not exposed to HDM benefited just as much from the bed covers as those who were sensitized and/or exposed to HDM. The reason for this could be the existence of other important allergens, superantigens, or irritants in bed. Miller et al. (18) reported a significant decrease in the release of cat allergen from mattresses, and Carswell et al. (15) a significant decrease in airborne cat allergen in homes with no pets when active bed covers were used. In our study, the proportion of the patients that had cat allergen in bed was surprisingly high, i.e., 27/35 (77%), considering that only one patient had a cat at home. This was probably due to a passive transfer of cat allergen either through direct contact or through deposition of allergen in public places where it is then picked up on the clothes of those who do not own cats. A passive transfer of animal dander from school to home has been reported by Almqvist et al. (42). Another possible explanation is earlier occasional visits of a cat that left behind cat allergens. When discussing trigger factors in AD patients, we therefore have to be aware that cat allergen is a possible trigger even in homes without a pet. Other possible sources of

contact allergens/superantigens are the microflora colonizing the patient's own skin. Both the bacterium *Staphylococcus aureus* and the yeast *P. orbiculare* have been proposed as possible allergens/superantigens in AD (43–48). Our study found that in patients sensitized to *P. orbiculare* the eczema severity was significantly more reduced in patients using active covers than in those using placebo covers ($P < 0.05$). This indicates that a reduction of this antigen/allergen in bed could be of importance. Future avoidance studies, including active bed covers, should therefore not only focus on the HDM allergen, but also include other possible contact allergens, superantigens, or irritants. For each of these, it is important to determine which kind of cover (permeability/pore size) is optimal.

The use of active bed covers, together with regular vacuum-cleaning of the mattress and airing of the bedroom, reduces the allergen/antigen load in bed, and thereby creates a sleeping environment that can reduce eczema severity in patients with AD. In conclusion, therefore, we recommend that patients with AD use bed covers as part of their treatment.

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