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The need for personalized diet plans in the treatment of atopic skin diseases

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In patients with atopic dermatitis, relevant markers such as circulating immune complexes, specific IgE, IgG4, acute phase proteins and histamine levels increase significantly after allergen-rich test meals *[1-4]*. The wrong food can also aggravate the clinical condition of many skin patients by promoting the growth of pathogenic microorganisms in the gut.
Intolerance reactions to certain foods and food additives play a central role in the pathogenesis of atopic dermatitis. These intolerances are caused either by allergic or pseudo-allergic, i.e. immunologically or non-immunologically mediated reactions.

Allergies and pseudo-allergies

In the case of allergic reactions, a distinction must be made between

- the immediate type (type I) with the production of specific IgE antibodies,
- cytotoxic reactions (type II) with involvement of specific IgG antibodies and activation of the complement system,
- Immune complex-mediated reactions of a delayed type (type III),
- the cellular type (type IV) with sensitization of T lymphocytes, measurable with the lymphocyte transformation test (LTT) and with the epicutaneous test against individual substances.

Although immunological mechanisms do not play a role in pseudo-allergic reactions of the toxic-irritant type, inflammatory mediators such as histamine, prostaglandins and leukotrienes are also released.
These intolerances are often to sugars such as lactose, maltose, fructose, food additives (preservatives, colorants and flavorings, binding agents, emulsifiers, flavor enhancers), biogenic amines or heavy metals from food, dishes, cutlery and dental alloys. First and foremost, the weakened activities of disaccharidases (lactase, maltase) or beta-aldolase in fructose intolerance and detoxification enzymes such as monoamine and dia- minoxidases, glutathione-S-, N-acetyl- and glucuronyl transferases are responsible for the toxic-irritative reactions.

Many neurodermatitis sufferers are of their food allergies. In an earlier study, 45 patients with confirmed atopic dermatitis and 34 healthy control subjects were given two test meals six hours apart after eight days on a reduction diet (potatoes and tea) in order to determine the food allergy via the specific IgE *[1, 2]*.
These meals consisted of precisely measured quantities of various common foods with an antigen structure corresponding to the 25 RAST food allergens tested. Only 20 of the 45 atopic dermatitis sufferers were aware of their positive reactions to one, two or three foods.
The total serum IgE level was elevated in all 45 atopic dermatitis patients, with values above 1,000 U/ml recorded in 33 cases (73.3 %). In contrast, only six (17.6 %) of the 34 control subjects showed values between 100 and 400 U/ml, all others remained within the normal range (below 100 U/ml) *[1]*. The examination of specific IgE antibodies showed a total of 100 positive RAST results against the 25 food allergens used in 18 of 26 atopic dermatitis patients before the test meal (with one to eight positive results per patient). After two test meals, this increased to 22 patients with a total of 158 positive RAST results (with two to 21 positive results per patient). A 26% increase in the number of specific antibodies against mycotic allergens was also recorded. In contrast, only one of the 26 control subjects tested (3.8%) showed positive results against food allergens after test meals *[1]*.
Key contributors to this result were
The first is the (repeated) intake of a standardized test meal with a large number of foods and the second is the repeated RAST tests with a correspondingly wide range of food antigens.
With this method, a significantly higher number of positive RAST results can be recorded just 15 hours after a repeated test meal - a fact that can be attributed to either a "boosting effect"

in IgE synthesis or to a dissolution of pre-existing IgE complexes due to excess antigen. Furthermore, this test system significantly reduces the number of false-negative results that occur when blood samples are taken on an empty stomach.

The increased number of positive results with microbial allergens (Saccharomyces, Aspergillus, Candida and Staphylococcus aureus) underpins the observed susceptibility of atopic dermatitis patients to various bacterial and mycotic pathogens. The fact that the consumption of flour products, sweets, hazelnuts, etc. (in test meals) increases the risk of atopic dermatitis. (in test meals) promotes microbial growth can be assumed from the recorded increase in positive RAST results after test meal times *[1]*.

Specific IgG detect delayed reactions

In the serum of atopic dermatitis patients, after two weeks of repeated administration of certain near-food causes a gradual increase in specific

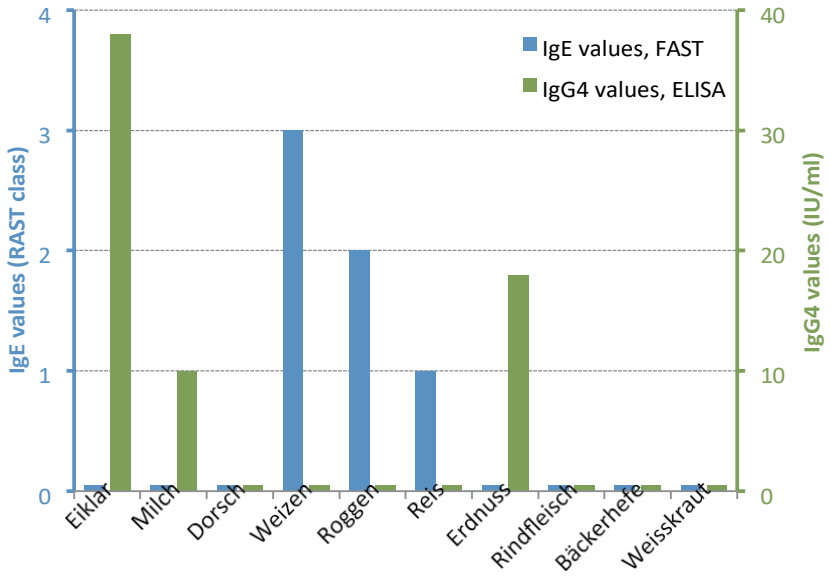


Fig. 1 *Food-specific IgE and IgG4 reactions in an atopic dermatitis patient*

Spezialklinik Neukirchen

Allergiediagnostik *Phadia IDM*

[redacted]

Geburtsdatum: 09.01.2010

Proben Datum: 07.07.2016
Patienten Id: 00015388
Proben Id: 00015388

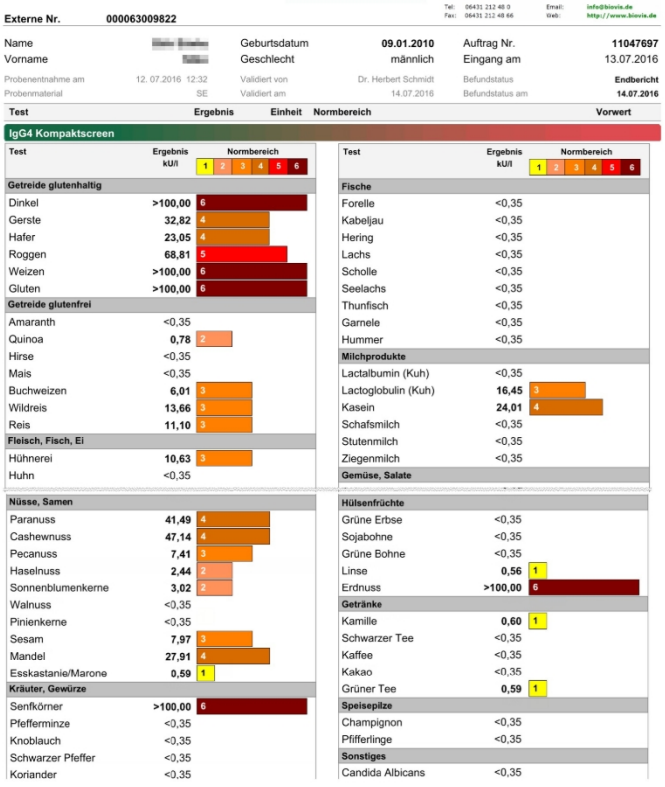
Ergebnisse

ImmunoCAP Total IgE

Test	Test Name	Konz.	Klasse	Cut-off
a-IgE	Gesamt-IgE	57,8 kU/l		

ImmunoCAP Specific IgE 0-100

Test	Test Name	Konz.	Klasse	Cut-off
ex1	Epithelienm.(e1 3-5)	0,80 kUA/l	2	Positiv
gx1	Gräser/Frühblüher(g3-6 8)	11,2 kUA/l	3	Positiv
gx4	Gräser/Spätbl.(g1 5 7 12 13)	9,33 kUA/l	3	Positiv
tx5	Bäume5/Frühbl.(t2 4 8 12 14)	0,02 kUA/l	0	Negativ
tx6	Bäumemischung 6(t1 3 5 7 10)	0,06 kUA/l	0	Negativ
hx2	Hausstaubm.(h2 d1-2 i6)	15,2 kUA/l	3	Positiv
mx2	Schimmelpilzm.(m1-3 5-6 8)	2,45 kUA/l	2	Positiv
ex71	Federmischung(e70 85-86 89)	0,01 kUA/l	0	Negativ
fx1	Nussmischung(f13 17-18 20 36)	0,11 kUA/l	0	Negativ
fx22	Nußm. 2 (f201 202 203 256)	1,17 kUA/l	2	Positiv
fx2	Meeresfrüchte(f3 24 37 40-41)	0,01 kUA/l	0	Negativ
fx13	Gemüsem.1(f12 15 31 35)	0,00 kUA/l	0	Negativ
fx15	Obstmischung 1(f33 49 92 95)	0,07 kUA/l	0	Negativ
fx20	Getreidemischung(f4 5 6 9)	0,04 kUA/l	0	Negativ
fx23	Fleischm. 1(f26 27 83 284)	0,01 kUA/l	0	Negativ
f1	Eiklar (Hühnereiweiss)	0,15 kUA/l	0	
f14	Sojabohne	0,01 kUA/l	0	
f2	Kuhmilch	0,06 kUA/l	0	
f286	Stutenmilch	0,03 kUA/l	0	
f300	Ziegenmilch	0,04 kUA/l	0	
f45	Bäckerhefe	0,05 kUA/l	0	
f85	Sellerie	0,02 kUA/l	0	
f25	Tomate	0,02 kUA/l	0	
f11	Buchweizenmehl	0,03 kUA/l	0	
f7	Hafermehl	0,03 kUA/l	0	
f8	Maismehl	0,04 kUA/l	0	
w6	Beifuss	0,08 kUA/l	0	
k82	Latex	0,01 kUA/l	0	
e1	Katzenschuppen	1,58 kUA/l	2	
e3	Pferdeepithelien	0,02 kUA/l	0	
e4	Rinderepithelien	0,03 kUA/l	0	
e5	Hundeschuppen	0,24 kUA/l	0	
e82	Kaninchenepithelien	0,01 kUA/l	0	
m5	Candida albicans	0,29 kUA/l	0	
m3	Aspergillus fumigatus	0,14 kUA/l	0	
m1	Penicillium chrysogenum	0,16 kUA/l	0	
f202	Cashewnuß	1,30 kUA/l	2	
f203	Pistazie	1,51 kUA/l	2	
f256	Walnuß	0,13 kUA/l	0	



Externe Nr. 000063009822

Name [redacted] Geburtsdatum 09.01.2010 Auftrag Nr. 11047697
Vorname [redacted] Geschlecht männlich Eingang am 13.07.2016
Probenentnahme am 12. 07.2016 12:32 Validiert von Dr. Herbert Schmidt Befundstatus Endbericht
Probenmaterial SE Validiert am 14.07.2016 Befundstatus am 14.07.2016

Test	Ergebnis	Einheit	Normbereich	Vorwert
IgG4 Kompaktscreen				

Test	Ergebnis kU/l	Normbereich 1 2 3 4 5 6
Getreide glutenhaltig		
Dinkel	>100,00	6
Gerste	32,82	4
Hafer	23,05	4
Roggen	68,81	5
Weizen	>100,00	6
Gluten	>100,00	6
Getreide glutenfrei		
Amaranth	<0,35	
Quinoa	0,78	2
Hirse	<0,35	
Mais	<0,35	
Buchweizen	6,01	3
Wildreis	13,66	3
Reis	11,10	3
Fleisch, Fisch, Ei		
Hühnerei	10,63	3
Huhn	<0,35	
Nüsse, Samen		
Paranuss	41,49	4
Cashewnuss	47,14	4
Pecanuss	7,41	3
Haselnuss	2,44	2
Sonnenblumenkerne	3,02	2
Walnuss	<0,35	
Pinienkerne	<0,35	
Sesam	7,97	3
Mandel	27,91	4
Esskastanie/Marone	0,59	1
Kräuter, Gewürze		
Senfkörner	>100,00	6
Pfefferminze	<0,35	
Knoblauch	<0,35	
Schwarzer Pfeffer	<0,35	
Koriander	<0,35	

Test	Ergebnis kU/l	Normbereich 1 2 3 4 5 6
Fische		
Forelle	<0,35	
Kabeljau	<0,35	
Hering	<0,35	
Lachs	<0,35	
Scholle	<0,35	
Seelachs	<0,35	
Thunfisch	<0,35	
Garnele	<0,35	
Hummer	<0,35	
Milchprodukte		
Lactalbumin (Kuh)	<0,35	
Lactoglobulin (Kuh)	16,45	3
Kasein	24,01	4
Schafsmilch	<0,35	
Stutenmilch	<0,35	
Ziegenmilch	<0,35	
Gemüse, Salate		
Hülsenfrüchte		
Grüne Erbse	<0,35	
Sojabohne	<0,35	
Grüne Bohne	<0,35	
Linse	0,56	1
Erdnuss	>100,00	6
Getränke		
Kamille	0,60	1
Schwarzer Tee	<0,35	
Kaffee	<0,35	
Kakao	<0,35	
Grüner Tee	0,59	1
Speisepilze		
Champignon	<0,35	
Pfifferlinge	<0,35	
Sonstiges		
Candida Albicans	<0,35	

IgG4 values. However, most patients high levels from the outset, such as against egg white, milk and nuts *[3, 5]*.

Interestingly, the patients who were treated by IgG4 values in the ELISA test from the beginning did not show positive IgE antibodies against the same foods in the RAST test, and vice versa (Fig. 1 and 2). It is possible that there is an age-related shift in the formation of these two categories of antibodies, whereby we have been observing an age-dependent reduction in specific IgEs with a simultaneous increase in specific IgG4 against foods for years.

In contrast, the 76 positive polyclonal IgG results were accompanied by specific IgE antibodies against the same food allergens in 33 cases. None of the control subjects titres of food-specific IgG4 and IgE antibodies above the detection limit at that time, and only two of them showed positive polyclonal IgG results *[3, 5]*.

Delayed IgG reaction in food allergies

The significance of food-specific IgG as a causative factor of food intolerances is still a matter of controversy. On the one hand, food-specific IgG is not only found in allergy sufferers, but also in healthy individuals.

On the other hand, there is increasing evidence that at least a large proportion of non-IgE-mediated food allergies are due to delayed IgG reactions. Not every patient who shows a positive prick test also IgE in their serum. Instead, allergy sufferers often have elevated food-specific IgG titres. 6 to 48 hours after Consumption of the food causes a delayed reaction. Generalized symptoms include diarrhea, flatulence, cramps, nausea, migraines, itching and skin rashes.

In a subsequent study (2007-2010), we found significantly elevated IgG4 levels against food in more 70 % of neurodermitis cases in adults. In contrast, less than 30 % of the controls had levels above 0.25 mg/L *[6]*. In the meantime, the clinical relevance of IgG4-based sensitization in allergy sufferers has been confirmed by further studies *[7-10]*.

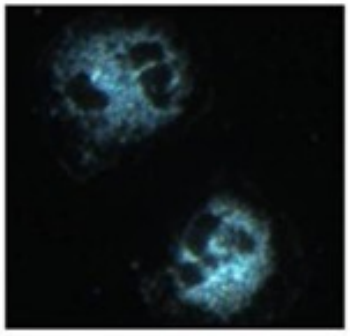
Circulating immune complexes in the pathogenesis of atopic dermatitis

Increased concentrations of circulating immune complexes with IgE and IgG have many side effects. Among other things, they activate the aggregation of thrombocytes (explains the chronically cold extremities of many patients) and the complement system with the release of mediators and lysosomal enzymes *[2]*.

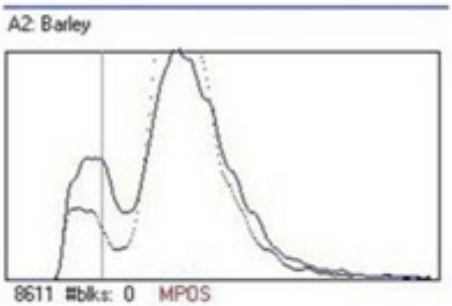
They also inhibit cellular immune function *[11, 12]*. In atopic dermatitis patients, the concentration of circulating IgE and IgG immune complexes was about 10,000% and 300% higher, respectively, than in healthy controls *[1]*, a fact explains the delayed, type III, reactions associated with itching, redness or asthma attacks many hours after meals.

Involvement of cellular reactions against food

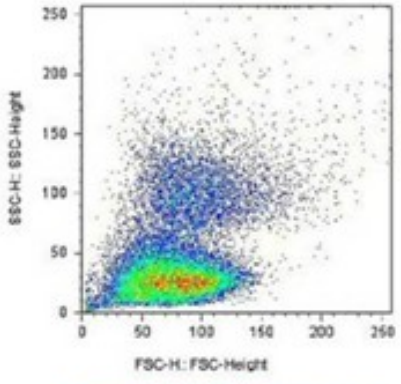
Not only antibodies but also cellular sensitization play an important role in the release of inflammatory mediators. In addition to the



PMN Cells observed in the Barley Well using CytoViva microscopy



BARLEY RX GRAPH (Analyzed with the Robocat II) plotted against the CONTROL GRAPH



PMN Cells in the Barley Well analyzed by FACSCalibur flow cytometry

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Fig. 3 *Circulating neutrophils after contact with barley extract significantly increase their volumes, which is the basis for the ALCAT test.®*
Source: Study Comparing Alcat Test Results With Flow Cytometry and Microscope, Dr. Gitte Jensen, NIS Labs (Natural Immune System) Oregon, USA, 2009

Normalwerte Keimzahl/g feuchten Stuhl	Lactobazillen $>10^6$	Bifido-bakterien $>10^8$	Haemolyt. Coliformen $<10^4$	Klebsiella $<10^4$	Proteus $<10^4$	Pathogene Clostridien $<10^5$	Candida/ Geotrichum $<10^3$
AE Patienten	abwesend oder $<10^4$	$<10^7$	$>10^6$	$>10^6$	$>10^5$	$>10^6$	10^4—10^7
n = 110 (p%)	76 (69 %)	31 (28,2 %)	52 (47,3 %)	36 (32,7 %)	22 (20 %)	40 (36,3 %)	48 (43,6 %)
Kontrollen	2×10^4	$>10^8$	3×10^5	$<10^4$	$<10^4$	$<10^5$	$2,5 \times 10^4$
n = 30 (p%)	3 (10 %)	30 (100 %)	2 (6,6 %)	30 (100 %)	30 (100 %)	30 (100 %)	3 (10 %)

Tab. 1 *Intestinal microflora in 110 atopic dermatitis patients and 30 controls. Data from [19]*

classic lymphocyte transfomation test (LTT) and the basophil degranulation test (BDT), the Alcat Test® also provides considerable help in identifying provocation factors.

Alcat Test® is a biological immune stimulation test in which the patient's leukocytes exposed to food, food additives or other chemicals. In the case of existing sensitization, the cells measurably change their volume (Fig. 3). Several double-blind, placebo-controlled studies document a good correlation (over 85 % correlation) between the clinical reactions to food and the Alcat Test® results *[13-15]*.

Acute phase proteins after test meals If the initial values of acute phase proteins (α1-antitrypsin, α2-macroglobulin, haptoglobin and caeruloplasmin) are already higher in neurodermatitis patients than in control subjects, the differences two hours after the first allergen-rich test meal are significant for α1-antitrypsin, haptoglobin and caeruloplasmin ($p< 0.05$). The increases in α1-antitrypsin α2-macroglobulin may interpreted as an anti-plasminic activity reaction, which can occur in the course of an increased coagulation or fibrinolytic process *[2]*. The compensatory increase in the two fibrinolysis inhibitors (α1-antitrypsin and α2-macroglobulin) can, however, also have undesirable side effects. On the one hand, they inhibit various digestive enzymes (trypsin, chemotrypsin, pepsin), which can result in incompletely degraded protein cleavage products with an increased allergic potential.

On the other hand, there is a relative increase in blood viscosity due to increased α2-macroglobulin levels. This favors the erythrocyte gel roll formation in the small blood vessels and can also lead to reduced peripheral blood flow or cold extremities.

The increase in haptoglobin levels can be interpreted as a protective mechanism against the free radicals and hydrogen peroxide released by leukocytes due to the peroxidase-like activity of the haptoglobin-hemoglobin complex. This can take place in the intestine (after a test meal) or in the damaged skin areas.

The increase in caeruloplasmin could an antioxidant and thus protective effect against damaged lipoprotein structures in the intestine or skin. The rapid upward fluctuations in caeruloplasmin may also be due to its phenol oxidase activity against various toxic aromatic substances that enter the bloodstream with food *[2]*.

The disruption of the intestinal mycrobiome as a cause of food intolerance After lactose exposure, atopic dermatitis patients show significantly less galactose and glucose in blood and urine compared to healthy controls. This lactose malabsorption is caused by an inhibition of lactase activity, which explains the widespread intolerance reaction of neurodermatitis patients to lactose and other carbohydrates (with simultaneous inhibition of lactase, sucrase, maltase, etc.).

The undigested and unsplit sugar products are used by pathogenic bacteria and especially fungi to multiply in the intestine and form high concentrations of carbohydrate fermentation products such as alcohols, methane and hydrogen (which serves as the basis for the H_2 breath test) *[16, 17]*. These bacteria can also act as disaccharidase inhibitors *[4, 18]*.

In a summarizing study with 110 neurodermitis patients, we were able to prove for the first time that in almost 70 percent of the cases examined, there was an intestinal dysbiosis with significantly reduced levels of lactobacilli and bifidobacteria as well as a massive increase in pathogenic germs such as haemolytic Escherichia coli, Klebsiella, Proteus, Clostridia and yeast and mould fungi such as Can- dida and Geotrichum (Table 1) *[19]*. Candida albi-

cans and hemolytic E. coli are the most important inhibitors of lactase activity in the small intestine *[20, 21]*.

Intestinal dysbiosis overloads the immune system

IgE-mediated histamine release in the intestine after contact with food allergens could not explain the chronically increased intestinal permeability in neurodermatitis sufferers. The cause of this permeability is intestinal dysbiosis, which is present in almost all atopic dermatitis patients and is associated with an excess of pathogenic bacteria and fungi and a reduction in healthy lactic acid-producing bacteria *[4, 18]*.

Increased absorption of food antigens in the gut, combined with a permanent release of microbial antigens and toxins, provides ideal conditions for overloading the immune system and maintaining elevated levels of circulating IgE, IgG and IgM immune complexes in atopic dermatitis patients *[1]*.

Personalized nutrition as a prerequisite for successful therapy

The most important approaches in the treatment of atopic dermatitis include a personalized, low-allergen diet plan in the form of a rotation diet, which takes into account the identified intolerances and reduces the risk of sensitization by offering the same permitted food only every fifth day.

To create such a diet plan, not only the immediate, IgE-mediated reactions, but also the delayed, IgG4-mediated and the cellular (Alcat Test® /LTT) reactions must be taken into account.

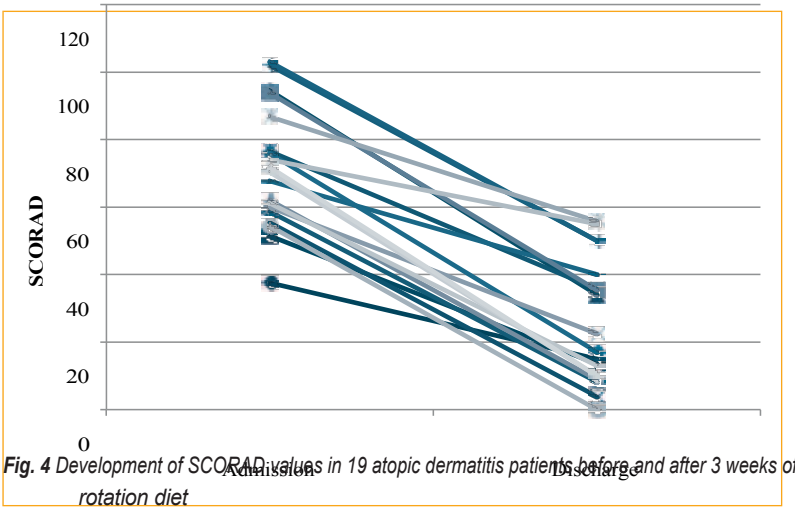

Fig. 4 *Development of SCORAD values in 19 atopic dermatitis patients before and after 3 weeks of rotation diet*

In addition, in the case of existing histamine intolerance due to low DAO levels, as we have already shown in the 1980s *[22, 23]*, foods rich in histamine or tyramine (such as frozen fish, matured cheese and sausage, wine, beer, sparkling wine, etc.) as well as histamine liberators (such as citrus fruits, onions, garlic, NAC) are avoided.

In the case of a documented intolerance to various types of sugar (lactose, fructose) or cereals containing gluten, foods rich in lactose, fructose or gluten should be removed from the diet. Such a concept is an integral part of the therapy concept of the Neukirchen Special Clinic.

In a controlled study, we showed that the SCORAD index, which quantifies the severity of atopic dermatitis, could be reduced by 66 % by following personalized diet plans supplemented by standard local treatment (Fig. 4) *[6]*.

For the support of patients after discharge

A computer program was developed (Food Allergy Control), which summarizes all sensitivities, intolerances and allergic reactions and creates an individualized cookbook for each patient (www.allergy-diet.com).

The patient is not only with information and tips on allergies and intolerances, but is also given recipes with precise quantities and preparation instructions.

It usually takes another six to nine months before patients are able to eat normally again after being discharged from hospital.

As part of our integrative therapy concept, microbial foci in the skin and intestines are also cleaned up, pseudoallergic reactions are eliminated and supportive immunomodulatory measures are taken. Psychogenic factors and the patient's neurohormonal abnormalities (increased noradrenaline levels) are also always taken into account in the therapy, as these can play an important role in maintaining the symptoms.

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