

Anti-food-antibodies in obese and underweight children

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Fragestellungen :

Vorkommen von Immunreaktionen auf Nahrungsmittel des IgG Types bei Kindern mit und ohne Übergewicht und Einfluss von Nahrungsmittel-Allergenabstinenz auf die Gesundheit von Kindern.

Ergebnis:

In der Gruppe der übergewichtigen Kinder wurden signifikant erhöhte Insulin- und Leptinwerte gefunden, sowie signifikant erhöhte Immunreaktionen auf Nahrungsmittel. Das ultra-sensitive CRP war in der Gruppe der Übergewichtigen im Vergleich zu den Normalgewichtigen signifikant erhöht und korrelierte mit den Spiegeln der IgG-Antikörper gegen Nahrungsmittel. Diese Gesamtkonstellation charakterisiert den Beginn eines Metabolischen Syndroms. Die stark erhöhten Werte des ultrasensitiven CRP bei Übergewichtigen Kindern korreliert stark mit dem Maß des Übergewichtes und der Insulinresistenz.

Relevanz für ImuPro 300:

Übergewichte haben gegenüber Normalgewichtigen mehr und höhere IgG-Titer. Gleichzeitig korrelieren die IgG-Titer mit den CRP-Werten, die ein Entzündungsgeschehen im Körper anzeigen.

Dies untermauert die These, dass der Verzehr von Nahrungsmittel, gegen die IgG-Antikörper vorliegen, ein Entzündungsgeschehen auslöst. Dabei entsteht eine Insulinresistenz, die bewirkt, dass Betroffene immer dicker werden bzw. Schwierigkeiten haben, Gewicht zu reduzieren.

Eine Ernährungsumstellung auf Basis von ImuPro 300 stoppt dieses Entzündungsgeschehen, den Patienten gelingt es, erfolgreich Gewicht zu reduzieren.

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In a study for atherosclerosis in juveniles we examined obese, normal weight and underweight children. We found significantly raised levels of ultra sensitive CRP. To explore the cause for this finding we performed Elisa tests for IgG to food components in 30 children per group. Obese children had significantly raised levels of antibodies against food components, as well as raised insulin and leptin levels, indicating a beginning metabolic syndrome. Underweight children showed the highest levels of anti-food-antibodies, but had normal CRP and insulin levels. Avoidance of the intolerable food substances might seize the inflammatory state and normalize the metabolic state.

Childhood obesity with its associated conditions, represents an epidemic phenomenon with substantial effects on public health. Chronic low grade inflammation favours the development of atherosclerosis and cardiovascular disease. Obese subjects, adults as well as children, were found to have elevated plasma levels of inflammatory markers, which correlate with the degree of obesity and insulin resistance (1), and which decrease after weight reduction. In a study for the prevalence of atherosclerosis in children (2), we examined serum levels of ultra-sensitive CRP in 30 normal weight, 30 obese and 30 underweight children (age: mean 13 y, range 7-18 y). We found significant higher levels of ultra sensitive CRP in the obese group compared to the normal group and highly significant increases of averaged intima-media thickness of both common carotid arteries. A possible cause for this subclinical sign of inflammation might be food intolerance. Although the mechanisms to induce tolerance to food antigens are not fully understood, it is known that the existence of antibodies to food components causes a state of chronic inflammation. Several reports described a raised production of cytokines in children with food allergy. Serum IgG-antibodies against food antigen can be detected by Elisa (3). We tested IgG₁₋₄ in serum, directed against 270 food antigens, by a commercially available,

certified and standardized Elisa test (Evomed, Germany). The mean antibody level in the normal weight group was $\leq 0,5\mu\text{g/ml}$, which was set as 100%. Obese children appeared to have significant higher antibody levels against food antigens compared to normal weight children. Underweight children had the highest levels (Figure 1). Furthermore, obese children had significantly higher insulin and leptin levels compared to normal and underweight children (Table 1). This situation in the obese group might indicate a certain degree of insulin resistance, representing the beginning of a metabolic syndrome.

We hypothesize that locally active cytokines, most of all TNF- α , e.g. produced by mononuclear lamina propria cells in the gut, might represent the connecting link between chronic low-grade inflammation, insulin resistance and obesity. It is known that chronic low doses of TNF- α lead to obesity-linked insulin resistance by interfering with the signalling of insulin through its receptor and by action on insulin receptor substrate 1 (4); the insulin production is then raised to compensate for reduced sensitivity. This, in turn, leads to obesity since the lipogenic effects of insulin only demands low insulin levels. The existence of altered indices of chronic inflammation in obese children was reported before (1). On the other hand, high levels of anti-food-antibodies, as seen in the group of underweight children, could be accompanied by high levels of TNF- α , which then might induce cachexia, which is the more classic effect of TNF- α , formerly known as cachectin. These dose-dependent differences in biological effects were found to demonstrate at least two receptor systems that have different affinities for TNF (5).

These findings might have important implications for the management of children with problems in maintaining a normal body weight. It is known that an elimination diet for the antibody inducing food substances leads to improvement of the immune reactions and therefore to normalization of the metabolic state. Preliminary data on the effect of an elimination diet on body weight of obese subjects show an intensive weight reduction, which might also have implications on the

ongoing pre-atherosclerotic state accompanying obesity. In underweight children it is, although for other reasons, important too, to detect eventual food intolerances, since the reduced utilization of food will induce malnutrition with all its consequences. We therefore advise to test for food intolerance in both situations by a standardized method. Testing for IgG induced food intolerance might represent an effective strategy to prevent the long term effects of metabolic disarrangements.

obesity and type I diabetes associated with early signs of atherosclerosis. *Experimental and Clinical Endocrinology & Diabetes* 2004, 112:378-82

3. Isolauri E, Rautava S, Kalliomäki M. Food allergy in irritable bowel syndrome: new facts and old fallacies. *Gut* 2004; 53: 1391-3

4. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF- α - and obesity-induced insulin resistance. *Science* 1996; 271(5249): 665-8

5. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose Expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance: *Science* 1993; 259:87-91

1. Invitti C. Obesity and low-grade systemic inflammation. *Minerva Endocrinol* 2002; 27(3): 209-14

2. Mangge H, Schauenstein K, Stroedter L, Griesl A, Erwa W, Borkenstein M. Low grade inflammation in juvenile

This study was approved by the Ethical Committee of the Medical University of Graz. We obtained written informed consent from patients or their guardians.

Table 1:

		group 1: normal	group 2: obese	group 3: underweight
BMI	mean	21	30	16
	range	18,1-24	24,1-42	13-18
food antibodies (%)	mean	100	149	213
	range	33-225	38-366	38-625
us-CRP (mg/l)	mean	1,2	3,6	0,3
	range	0,01-6,72	0,17-12,52	0,1-2,4
insulin (μU/ml)	mean	13,1	30,2	7,8
	range	3,9-39	4,1-96,2	0,3-19,6
leptin (ng/ml)	mean	10,9	33,3	2,9
	range	1,2-19,4	7,9-55,6	1,9-3,7

Levels of significance by student t-test:

IgG-anti-food-antibodies: group 1 – 2: $p < 0,004$; 1 – 3: $p < 0,0001$; 2 – 3: $p < 0,02$

Ultra-sensitive-CRP: group 1 – 2: $p < 0,001$; 1 – 3: $p < 0,009$; 2 – 3: $p < 0,0001$

Insulin: group 1 – 2: $p < 0,05$; 1 – 3: ns; 2 – 3: $p < 0,12$

Leptin: group 1 – 2: $p < 0,001$; 1 – 3: ns; 2 – 3: $p < 0,003$

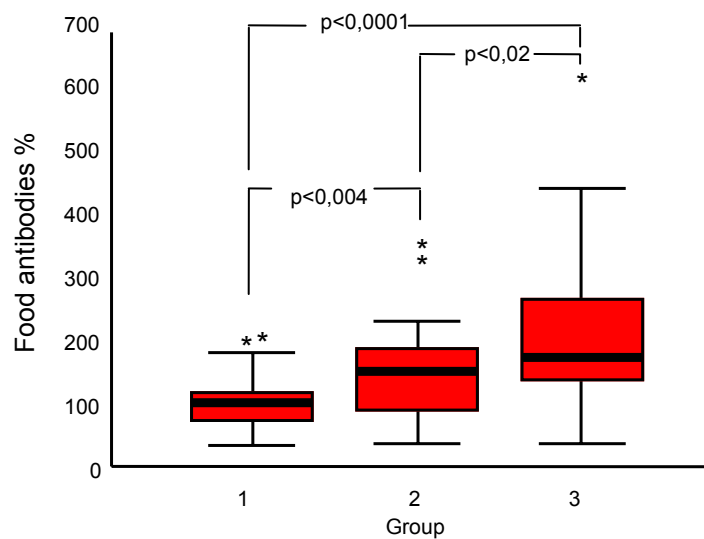


Figure 1: Group 1: normal weight; group 2: obese; group 3: underweight

Food intolerance in Crohn's disease

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Fragestellung :

Gibt es Unterschiede bei nahrungsmittelspezifischen, IgG-vermittelten Immunreaktionen (Typ III) zwischen Morbus Crohn Patienten und einem gesunden Patientenkollektiv?

Ergebnis:

Bei Morbus Crohn Patienten sind die Immunreaktionen auf Nahrungsmittel im Vergleich zum gesunden Patientenkollektiv signifikant erhöht. Die Stärke der Immunreaktion korreliert mit den Krankheitsstadien des Morbus Crohn Patienten. Es gibt spezifische Reaktionsmuster für verschiedene Nahrungsmittel.

Schlussfolgerung:

Die Ergebnisse lassen ein spezifisches Reaktionsmuster für einzelne Nahrungsmittel bei Morbus Crohn erkennen. Das zeigt, dass ein Nachweis von nahrungsmittelspezifischen IgG-Antikörpern kein Zeichen für eine normale Auseinandersetzung des Immunsystems mit der Nahrung darstellt, sondern verschiedene Nahrungsmittel für spezifische Erkrankungen und Symptome verantwortlich sein können.

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Introduction: Crohn's disease (CD) is an inflammatory bowel disease (IBD) with unknown etiology. Different genetic mutations and environmental factors are thought to play an important role in the development of CD. Immune responses against autoantigens or harmless food antigens are thought to be one reason for the perpetuation of the inflammation. The aim of this study was to determine if there are differences in food intolerance in CD patients compared to healthy volunteers.

Methods: Blood samples from 80 MC patients with different disease status (active: 47, chronically active: 24, remission: 8) and 20 healthy volunteers without history of allergy from the German IBD competence network serum bank were examined for food intolerance by the ImuPro 300 test (R-Biopharm AG, Darmstadt, Germany). The ImuPro 300 test is an ELISA for the detection of IgG-antibodies directed against about 300 different food components. Statistical analysis was performed using SigmaStat software.

Results: In CD patients a statistically significant higher number of "intolerance reactions" (elevated circulating specific IgG levels) could be detected compared to healthy controls (MC active: 70 positive reactions; control: 32 positive reactions, $p < 0.0001$, t-test). There was no difference between acute CD flare (73 reactions) versus chronically active CD (70 reactions). In CD in remission there was a trend towards reduced intolerance reactions (CD in remission: 55 reactions) without statistical significance. Whereas only minor differences between CD patients and healthy controls were found for fungi, milk products, fat and eggs, reactions to all other tested food groups were clearly increased in CD patients.

Conclusion: In CD patients "food intolerance" as measured by circulating IgG-antibodies against food components is increased compared to healthy controls. The number of intolerance reactions associates with disease activity. Further studies need to be performed to test whether a specific diet based on these results is helpful for disease management.

Supportet by the BMBF (Competence network IBD)

Inflammation Modifies the Effects of a Reduced-Fat Low-Cholesterol Diet on Lipids

Results From the DASH-Sodium Trial

Thomas P. Erlinger, MD, MPH; Edgar R. Miller III, MD, PhD;

Jeanne Charleston, RN; Lawrence J. Appel, MD, MPH

Studie mit 100 Teilnehmern mit durchschnittlichem BMI von 29,6 kg/m² ; Veröff. In „Circulation“ 2003; 108:150-154 und 126-128

Fragestellungen :

Hat eine systemische inflammatorische Aktivität bei Patienten Einfluss auf den Erfolg einer fettreduzierten cholesterinarmen Diät (DASH: Dietary Approaches to Stop Hypertension)?
Zu Beginn der Studie sowie nach vier, acht und zwölf Wochen wurden Blutfettwerte und die CRP-Konzentration bestimmt.

Ergebnis:

Die DASH-Diät zeigte keine Auswirkungen auf das CRP, führten jedoch zu einer signifikanten Abnahme der Gesamtcholesterinwerte. Probanden mit niedrigen CRP-Ausgangswerten sprachen deutlich besser auf die Diät an als Patienten mit hohem CRP.

Relevanz für ImuPro 300:

Patienten mit niedrigem CRP haben größeren Erfolg bei der Gewichtsreduktion, als Patienten mit hohem Entzündungsparameter. Das bedeutet, im Körper ablaufende Entzündungen erschweren das Abnehmen bzw. machen es ganz unmöglich. Dies erklärt die Erfolge mit ImuPro 300 beim Abnehmen. Durch die Ernährungsumstellung wird Entzündungsgeschehen gestoppt, die Blockade löst sich und den Patienten gelingt es, erfolgreich Gewicht zu reduzieren.

Bestätigt werden diese Ergebnisse durch eine andere Studie („Anti-food-antibodies in obese and underweight children“) bei der eine Korrelation zwischen CRP-Werten und der Anzahl und Höhe der IgG-Titer nachgewiesen wurde.

Diäterfolg vorher abschätzen

Hemmt hohes CRP den Fettabbau?

BALTIMORE/DALLAS – Bei manchen Patienten lassen sich die Blutfette mit einer Diät gut senken, bei anderen kaum. Kann man potenzielle Nonresponder an Entzündungsparametern im Blut erkennen?

Um herauszufinden, ob Entzündungsvorgänge die cholesterinsenkende Wirkung einer fettreduzierten, cholesterinarmen Diät mindern, führten der Epidemiologe Dr. THOMAS P. ERLINGER und seine Kollegen von den Johns Hopkins Institutions in Baltimore folgende Studie mit 100 Teilnehmern durch: Zunächst erhielten alle Probanden (durchschnittlicher BMI: 29,6 kg/m²) zwei Wochen lang eine Kontrolldiät mit einem Gesamtfettanteil von 37 % und 16 % gesättigten Fettsäuren. Während der folgenden zwölf Wochen ernährten sich 50 Probanden weiterhin mit der Kontrolldiät, während die übrigen 50 Teilnehmer die so genannte DASH*-Diät erhielten (27 % Gesamtfettanteil, 6 % gesättigte Fettsäuren). Zu Beginn der Studie sowie nach vier, acht und zwölf Wochen wurden Blutfettwerte sowie CRP-Konzentration bestimmt.

Der CRP-Ausgangswert lag bei 2,37 mg/l. Die DASH-Diät zeigte keine Auswirkungen auf das CRP, führte jedoch zur signifikanten Abnahme der Gesamtcholesterinwerte sowie des LDL- und HDL-Cholesterins, während sich die Triglyzerid-

konzentrationen kaum änderten. Interessanterweise sprachen die Probanden mit niedrigem CRP-Ausgangswert in puncto Gesamtcholesterin- und LDL-Cholesterin-Reduktion deutlich besser auf die DASH-Diät an als jene mit hohem.

Entzündungsvorgänge könnten stören

Die Ergebnisse deuten darauf hin, dass Entzündungsvorgänge den lipidsenkenden Effekt der DASH-Diät auf die Blutfettwerte modifizieren, so die Autoren in der Zeitschrift „Circulation“. Vielleicht ließen sich in Zukunft mittels Bestimmung des CRP jene Patienten herausfiltern, die von einer fettreduzierten und cholesterinarmen Diät besonders profitieren.

Dr. SCOTT M. GRUNDY, Ernährungswissenschaftler an der Universität von Texas, ist weniger optimistisch: Auf Grund dieser Studie könne man noch nicht darauf schließen, dass ein subklinischer Entzündungszustand unmittelbar die Reaktionsfähigkeit der Blutfettwerte auf eine Ernährungsumstellung mindert, schreibt er in einem Editorial. Angesichts des erheblichen Übergewichts der Teilnehmer müssten weitere Studien untersuchen, wie die verschiedenen Komponenten des metabolischen Syndroms zum Erfolg oder Misserfolg einer fettreduzierten Diät beitragen. AW

*Dietary Approaches to Stop Hypertension
I. T. P. Erlinger et al., S. M. Grundy, Circulation 2003; 108: 150 – 154 und 126 – 128



Inflammation Modifies the Effects of a Reduced-Fat Low-Cholesterol Diet on Lipids

Results From the DASH-Sodium Trial

Thomas P. Erlinger, MD, MPH; Edgar R. Miller III, MD, PhD;
Jeanne Charleston, RN; Lawrence J. Appel, MD, MPH

Background—Inflammatory mediators regulate key aspects of lipid metabolism. We hypothesized that inflammation could diminish the cholesterol-lowering effect of a reduced-fat/low-cholesterol diet.

Methods and Results—After a 2-week run-in period on a control diet (37% total fat, 16% saturated fat), 100 participants were randomized to the control or DASH diet (27% total fat, 6% saturated fat) for 12 weeks. Median C-reactive protein (CRP) at baseline was 2.37 mg/L (interquartile range, 1.20, 3.79). The DASH diet, net of control, had no effect on CRP. Overall, there were significant net reductions in total (−0.34 mmol/L), LDL (−0.29 mmol/L), and HDL (−0.12 mmol/L) cholesterol from the DASH diet (each, $P < 0.001$) and little change in triglycerides (+0.05 mmol/L, $P = 0.21$). Baseline CRP was strongly associated with lipid responsiveness to the DASH diet. Total and LDL cholesterol were reduced to a greater degree in those with a “low” (below median) compared with a “high” (above median) baseline CRP (total, −9.8% versus −3%; P for interaction = 0.006; LDL cholesterol, −11.8% versus −3%; P for interaction = 0.009). Reductions in HDL cholesterol (−8.8%) were similar in persons with low versus high CRP. Triglycerides were increased in those with a high CRP but not in those with a low CRP (19.8% versus +0%; P for interaction = 0.019).

Conclusions—In this study, the presence of increased CRP was associated with less total and LDL cholesterol reduction and a greater increase in triglycerides from a reduced-fat/low-cholesterol diet. These findings document an additional mechanism by which inflammation might increase cardiovascular disease risk. (*Circulation*. 2003;108:150-154.)

Key Words: inflammation ■ lipids ■ cholesterol ■ diet

Chronic inflammation has been hypothesized to promote the development and progression of atherosclerosis.¹ Several markers of inflammation, including high-sensitivity C-reactive protein (CRP), have been shown to predict future cardiovascular disease events.^{2–4} These studies suggest a direct adverse effect of inflammation on cardiovascular risk. However, inflammation is also associated with several traditional cardiovascular risk factors,⁵ eg, hypertension, smoking, diabetes, and elevated cholesterol and triglycerides; therefore, it is reasonable to hypothesize that inflammation might have indirect adverse effects mediated through traditional cardiovascular risk factors.

See p 126

There is a long-recognized association between inflammation and lipids.⁶ Both cholesterol and triglyceride metabolism are affected by inflammatory pathways.^{7,8} Reductions in cholesterol during acute inflammation may be a result of decreased hepatic production of lipoproteins or increased catabolism with conversion to small dense particles.^{9,10} Increased triglyceride levels as a result of increased synthesis

and secretion is a more consistent feature of inflammation-induced lipid changes.^{6,11} These observations raise the possibility that the impact of diet on plasma lipids could be modified by the degree of underlying inflammation.

In this setting, we hypothesized that inflammation could modify the lipid responsiveness to a reduced-fat/low-cholesterol diet, such that there would be a reduced cholesterol-lowering effect of the diet in the presence of inflammation. Conversely, because triglyceride levels are increased in the presence of inflammation, a diet relatively higher in carbohydrates could lead to greater increases in triglycerides in the presence of inflammation. If true, these findings could help explain the considerable interindividual variation seen in response to a lipid-lowering diet.¹²

Methods

Study Design and Participants

This study was conducted as an ancillary study to the Dietary Approaches to Stop Hypertension- Sodium (DASH-Sodium) trial, a clinical trial. This ancillary study was conducted at the Johns

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Hopkins clinical center. As an ancillary study, it was designed and analyzed only by the coauthors. Detailed descriptions of the design of the DASH-Sodium trial and of its main results have been published.¹³ The protocol was approved by a local Institutional Review Board. All participants provided written informed consent.

Study participants were healthy adults (age ≥ 22 years) who were not receiving antihypertensive medications and who had a systolic blood pressure of 120 to 159 mm Hg and diastolic blood pressure of 80 to 95 mm Hg (average of 3 screening visits). Persons with total cholesterol >260 mg/dL were excluded from the study. In addition, persons were excluded if their LDL cholesterol (LDL-C) warranted pharmacological therapy according to the National Cholesterol Education Program Adult Treatment Program II guidelines,¹⁴ that is, LDL-C >220 mg/dL for young adults (men <35 years old and premenopausal women) without 2 or more cardiovascular disease risk factors, LDL-C >190 mg/dL for older individuals without 2 or more cardiovascular disease risk factors, and LDL-C >160 mg/dL for individuals with 2 or more cardiovascular risk factors. Persons were also excluded if they were taking cholestyramine, colestipol, or an unstable dose of a statin or any other lipid-lowering agents not already excluded. Six participants (5 control, 1 DASH) were taking a lipid-lowering agent at baseline. No participants reported starting or stopping lipid-lowering therapy during the trial. Participants were excluded if they reported drinking more than 14 alcoholic drinks per week. Of those who reported drinking (19 control, 17 DASH), the average number of drinks consumed was 3.9 per week (control) and 3.4 per week (DASH). Baseline CRP values were missing for 3 participants and they were excluded from this analysis.

The DASH-Sodium trial tested the effects of 2 dietary patterns (DASH versus control) using a parallel design and 3 dietary sodium levels (150, 100, and 50 mmol/d for a 2100-kcal diet) using a crossover design within each diet.¹³ The 2 dietary patterns in the present study corresponded to the "control" and "combination" diets in the first DASH trial.¹⁵ The combination, or DASH, diet emphasizes fruits and vegetables (total of ≈ 9 servings per day), low-fat dairy products, and other reduced-fat foods. The DASH diet provided 27% of calories from total fat: 6% from saturated fat, 13% monounsaturated fat, and 8% polyunsaturated fat. In contrast, the control diet provided 37% of calories from total fat: 16% saturated fat, 13% monounsaturated fat, and 8% polyunsaturated fat. In addition, the DASH diet provided 151 mg/d of cholesterol, compared with 300 mg/d in the control diet.

Meals were prepared in a metabolic kitchen and served in an outpatient dining facility. Throughout the 14 weeks of feeding, participants agreed to eat only the food provided to them and nothing else. Caloric intake was adjusted to maintain a stable weight.

After attending a series of 3 screening visits to determine eligibility and to collect baseline data, participants began a 2-week run-in feeding period using the control diet at the higher sodium level. Participants were then randomized to the DASH or control diet and also randomized to the sequence of sodium intake. After randomization, there were three 30-day feeding periods, 1 at each of the 3 sodium levels provided in a random order. Sampling of blood occurred at baseline (before randomization) and at the end of each 30-day period.

Measurements

Personnel involved in collection of outcome data were unaware of participants' diet assignment. Adherence to the diet was assessed by reviewing participants' food diaries and by measuring 24-hour urinary excretion of electrolytes and urea nitrogen.

Blood was drawn from the antecubital vein into a Vacutainer tube after an overnight fast and allowed to clot for 15 minutes before being centrifuged at $2000\times g$ for 15 minutes at room temperature. Plasma and serum were placed into 2-mL polyethylene storage containers and quickly frozen in a -70°C freezer until analysis.

CRP was measured from serum by high-sensitivity colorimetric competitive ELISA. In this assay, biotinylated CRP competes with CRP in the sample for coated antibody. Detection is via horseradish peroxidase conjugated in an avidin-biotin complex followed by the color reagent substrate, orthophenylene diamine. Standardization

TABLE 1. Baseline Characteristics of Participants by Diet Assignment

Characteristic	Control Diet (n=50)	DASH Diet (n=50)
Age, y	53 \pm 1.3	50 \pm 1.4
Female, n (%)	21 (42)	31 (62)
Black, n (%)	34 (68)	41 (82)
Smoking, n (%)	6 (12)	6 (12)
Cholesterol, mmol/L*		
Total	5.18 \pm 0.83	5.28 \pm 0.13
LDL	3.28 \pm 0.81	3.39 \pm 0.09
HDL	1.32 \pm 0.40	1.26 \pm 0.04
Triglycerides, mmol/L (IQR)	1.09 (0.87, 1.56)	1.01 (0.78, 1.51)
BMI, kg/m ²	30.1 \pm 0.6	29.3 \pm 0.5
CRP, ng/mL (IQR)	2.78 (1.46, 3.87)	1.74 (1.07, 3.40)

Values are mean \pm SD except for triglycerides and CRP, which are presented as medians (IQR).

*Multiply cholesterol values by 38.7 and triglyceride values by 88.6 to convert to mg/dL.

was done according to the World Health Organization CRP reference standard. The analytical CV for this assay is 5.14%. Total cholesterol, HDL cholesterol (HDL-C), and triglycerides were measured by enzymatic colorimetric methods. LDL-C was calculated.

Analysis

Because the distribution of CRP was right skewed, we present medians and interquartile ranges. Baseline characteristics were compared by Student's *t* test for normally distributed continuous variables (age, cholesterol, body mass index [BMI]), Wilcoxon rank-sum test for non-normally distributed data (CRP, triglycerides), and χ^2 tests for categorical variables (sex, race, smoking status).

Lipids were measured at the end of each sodium treatment period. However, we observed no effect of sodium intake on serum lipids or CRP levels. Hence, the effect of the DASH diet on lipids was assessed independently of sodium intake. Change in lipids was calculated as the difference between baseline and the mean of the 3 end-of-period lipid levels. Changes in lipids were calculated for the entire group and according to baseline levels of CRP (above or below median at baseline). To test for the presence of inflammation-related differences in lipid responsiveness to diet, interaction terms for diet group and CRP were entered into robust multivariate regression

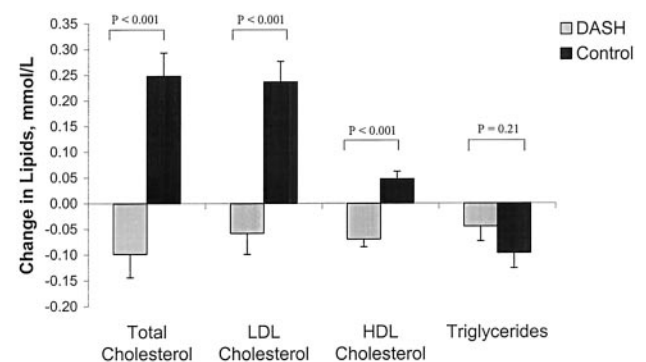


Figure 1. Change from baseline in serum lipids (mmol/L) by randomized diet assignment. Change is difference between baseline and mean of 3 end-of-period values. Gray bars (DASH diet) and black bars (control diet) reflect within-diet change. *P* values correspond to between-diet differences. Multiply cholesterol values by 38.7 and triglycerides by 88.6 to convert to mg/dL.

TABLE 2. Net Change in Serum Lipids (DASH Minus Control) Over the Entire Treatment Period by Baseline Level of CRP

	CRP <Median			CRP >Median			<i>P</i> for Interaction	Adjusted <i>P</i> for Interaction†
	Baseline*	Mean Between Diet Change (% Change)	<i>P</i>	Baseline*	Mean Between Diet Change (% Change)	<i>P</i>		
Cholesterol, mmol/L§								
Total	5.06±0.80	-0.50 (-9.8%)	<0.0001	5.37±0.85	-0.16 (-3.0%)	0.10	0.006	0.016
LDL	3.23±0.65	-0.38 (-11.8%)	<0.0001	3.46±0.80	-0.10 (-3.0%)	0.20	0.009	0.011
HDL	1.29±0.36	-0.11 (-8.8%)	<0.0001	1.29±0.36	-0.09 (-8.8%)	0.01	0.54	0.52
Triglycerides, mmol/L‡								
	1.01 (0.78, 1.53)	+0.01 (+0.001%)	0.95	1.04 (0.88, 1.42)	+0.21 (+19.8%)	<0.0001	0.019	<0.003

Change is the difference between baseline and the mean of the 3 end-of-period values.

*Baseline values are mean±SD except for triglycerides, which are medians (interquartile range).

†Adjusted for baseline lipid level, age, race, sex, smoking, and BMI.

‡Changes are medians (median % change).

§To convert to mg/dL, multiply cholesterol values by 38.7 and triglyceride values by 88.6.

analyses. Additional adjustment was made for age, sex, race (African-American versus non-African-American), smoking status (current, ever, never), and BMI. The continuous relationship between change in lipids and baseline CRP was examined by entering log-transformed CRP as a continuous interaction term with diet in multivariate models. Because of sample size considerations, we could not reliably assess higher order interactions.

Linear regression analysis was used to assess change in serum lipid levels, except for triglycerides, for which median regression was used because of its right-skewed distribution. Change in CRP was also assessed by median regression. All models were adjusted simultaneously for baseline values of each outcome variable. All analyses were conducted according to the principle of intention to treat. All tests were 2-sided and were performed with STATA 7.0 statistical software.

Results

The mean age of participants was 52±9.9 years. Participants included 52 women and 75 African-Americans, with a mean BMI of 29.6 kg/m². There were no significant differences between diet groups at baseline (Table 1).

The DASH diet resulted in significant ($P<0.001$) reductions in total cholesterol (-0.34 mmol/L), LDL-C (-0.29 mmol/L), and HDL-C (-0.12 mmol/L) levels (Figure 1). Triglyceride levels were not changed significantly with the DASH diet (+0.05 mmol/L, $P=0.21$). These findings are consistent with results from the initial DASH trial.¹⁶ Median changes in CRP were similar in the control and DASH diets (-0.12 versus +0.02 mg/L, $P=0.50$).

Table 2 illustrates changes in lipids from the DASH diet, net of control, stratified by baseline level of CRP (below versus above median). In persons with baseline CRP levels below the median (<2.37 mg/L), the DASH diet significantly reduced total cholesterol (0.5 mmol/L [9.8%], $P<0.0001$) and LDL-C (0.38 mmol/L [11.8%], $P<0.0001$) levels. In persons with a baseline CRP above median, reductions in total cholesterol and LDL-C were modest and not significant (0.16 mmol/L [3%] and 0.10 mmol/L [3%], respectively, $P\geq 0.10$). Reductions in HDL-C from the DASH diet, net of control, were similar in persons with low and high baseline CRP levels (0.11 mmol/L [8.8%] and 0.09 mmol/L [8.8%], respectively, $P\leq 0.01$). In persons with low baseline CRP, the DASH diet had no significant effect on triglycerides (+0.01 mmol/L, $P=0.95$). However, a significant increase in

triglycerides associated with the DASH diet (0.21 mmol/L [19.8%], $P<0.0001$) was observed among persons with a high baseline CRP. Tests for interaction between diet and baseline CRP were significant for total cholesterol ($P=0.006$), LDL-C ($P=0.009$), and triglycerides ($P=0.019$) but not HDL-C ($P=0.54$). These tests for interaction remained significant after adjustment for age, race, sex, smoking, and BMI ($P=0.016$, $P=0.011$, and $P<0.003$, respectively). Evidence of a statistical interaction between diet and baseline CRP on lipid responsiveness persisted after entering log CRP as a continuous variable in fully adjusted multivariate regression models (P for interaction=0.001 for total cholesterol, 0.002 for LDL-C, and 0.056 for triglycerides).

In persons with low CRP, differences in lipid responses to the DASH diet by baseline CRP were evident by 4 weeks and persisted over time (Figure 2). Median triglyceride levels tended to increase; however, triglyceride measurements were less precise than corresponding cholesterol measurements.

Discussion

Our findings suggest that inflammation significantly and substantially affects the lipid response to a reduced-fat/low-cholesterol diet. In this study, the greatest degree of lipid reduction was seen in persons with low CRP. Conversely, the increase in triglycerides that was expected with greater consumption of carbohydrates occurred only in persons with elevated CRP.

Most circulating cholesterol is the result of endogenous hepatic synthesis. In animal studies, interleukin 6, a potent stimulator of CRP production, inhibits lipoprotein lipase activity in adipocytes¹⁷ and induces hepatic triglyceride secretion.¹⁸ In humans, interleukin 6 may be responsible for the lipid abnormalities found in the insulin-resistance syndrome.¹⁹

Despite substantial differences in nutrient composition, the DASH diet, net of control, had no significant effect on CRP levels. This finding is in contrast with epidemiological studies showing that diets higher in fiber or the consumption of foods with a lower glycemic index could reduce CRP levels.^{20,21} Our findings suggest that previous associations of diet and CRP could be confounded by other unmeasured factors or could be the result of residual confounding from other

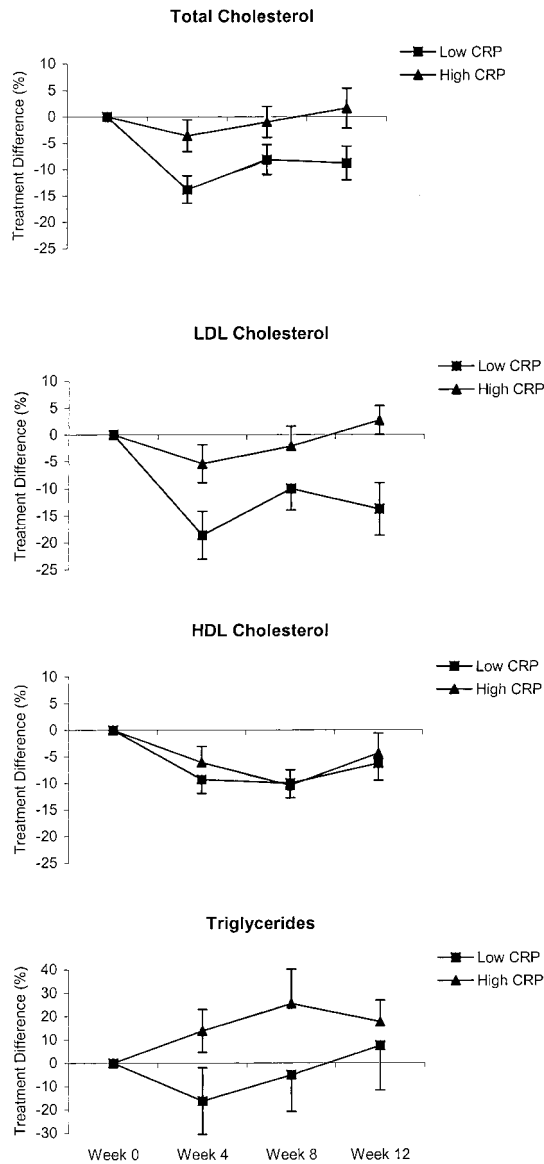


Figure 2. Change from baseline at weeks 4, 8, and 12 in blood lipids in persons with low and high baseline CRP level.

potential determinants of CRP, such as weight change.^{22,23} However, we cannot rule out the possibility that our study was underpowered to detect a small effect of diet on CRP. Overall, we had 80% power to detect a 25% change in CRP.

These findings have both clinical and scientific implications. Specifically, a reduced-fat/low-cholesterol diet that is relatively higher in carbohydrates may be extremely beneficial for persons with low levels of inflammation and could thereby mitigate the need for pharmacological therapy. In contrast, among persons with higher levels of inflammation, such diet changes might increase triglycerides and reduce HDL-C. This apparently adverse pattern of changes in triglycerides and HDL-C commonly occurs in the setting of a reduced-fat/high-carbohydrate diet. Our data suggest that inflammation is at least a marker, if not potentially a determinant, of this adverse response. Perhaps the most important implication of our findings is the use of CRP as a

means to distinguish those individuals who are likely to experience a favorable response to reduced-fat/low-cholesterol diet from those who are likely to experience an unfavorable response. In addition, these findings have important implications for the analysis and interpretation of studies examining the relationship between diet and lipids and could partially account for the considerable variability in lipid responsiveness in the literature. For example, previous studies have demonstrated less cholesterol reduction from a low-fat diet among women¹⁶ and overweight individuals.^{24–26} Additional studies are needed to determine whether inflammation could account for these observed subgroup differences.

Although we observed highly significant lipid changes in subgroups and significant interactions between subgroups, we cannot rule out the possibility of a spurious finding, ie, type I error. However, as discussed previously, there is a reasonable biological basis for postulating an interaction between diet and inflammation. Clearly, additional studies would be useful both to confirm the interaction and to better assess the point at which inflammation attenuates the beneficial effects of dietary change. Because of sample size considerations, we used median CRP as the cut point in this study.

In summary, our study suggests that inflammation modifies the effects of the DASH diet on serum lipid levels. These findings could have important implications for targeting individuals who are most likely to respond favorably to dietary changes.

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References

- Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med*. 1999; 340:115–126.
- Danesh J, Collins R, Appleby P, et al. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA*. 1998;279: 1477–1482.
- Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973–979.
- Ridker PM, Rifai N, Stampfer MJ, et al. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000;101:1767–1772.
- Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol*. 1999;84:1018–1022.
- Gallin JI, Kaye D, O'Leary WM. Serum lipids in infection. *N Engl J Med*. 1969;281:1081–1086.
- Cabana VG, Siegel JN, Sabesin SM. Effects of the acute phase response on the concentration and density distribution of plasma lipids and apolipoproteins. *J Lipid Res*. 1989;30:39–49.
- Khovidhunkit W, Memon RA, Feingold KR, et al. Infection and inflammation-induced proatherogenic changes of lipoproteins. *J Infect Dis*. 2000;181(suppl 3):S462–S472.
- Ettinger WH Jr, Sun WH, Binkley N, et al. Interleukin-6 causes hypocholesterolemia in middle-aged and old rhesus monkeys. *J Gerontol A Biol Sci Med Sci*. 1995;50:M137–M140.
- Feingold KR, Krauss RM, Pang M, et al. The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased

- prevalence of low density lipoprotein subclass pattern B. *J Clin Endocrinol Metab.* 1993;76:1423–1427.
11. Grunfeld C, Pang M, Doerrler W, et al. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab.* 1992;74:1045–1052.
 12. Jacobs DR Jr, Anderson JT, Hannan P, et al. Variability in individual serum cholesterol response to change in diet. *Arteriosclerosis.* 1983;3:349–356.
 13. Svetkey LP, Sacks FM, Obarzanek E, et al. The DASH Diet, Sodium Intake and Blood Pressure Trial (DASH-Sodium): rationale and design. DASH-Sodium Collaborative Research Group. *J Am Diet Assoc.* 1999;99:S96–104.
 14. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA.* 1993;269:3015–3023.
 15. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med.* 1997;336:1117–1124.
 16. Obarzanek E, Sacks FM, Vollmer WM, et al. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr.* 2001;74:80–89.
 17. Greenberg AS, Nordan RP, McIntosh J, et al. Interleukin 6 reduces lipoprotein lipase activity in adipose tissue of mice in vivo and in 3T3-L1 adipocytes: a possible role for interleukin 6 in cancer cachexia. *Cancer Res.* 1992;52:4113–4116.
 18. Nonogaki K, Fuller GM, Fuentes NL, et al. Interleukin-6 stimulates hepatic triglyceride secretion in rats. *Endocrinology.* 1995;136:2143–2149.
 19. Pickup JC, Mattock MB, Chusney GD, et al. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia.* 1997;40:1286–1292.
 20. Ludwig DS, Pereira MA, Kroenke CH, et al. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *JAMA.* 1999;282:1539–1546.
 21. Liu S, Manson JE, Buring JE, et al. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr.* 2002;75:492–498.
 22. Tchernof A, Nolan A, Sites CK, et al. Weight loss reduces C-reactive protein levels in obese postmenopausal women. *Circulation.* 2002;105:564–569.
 23. SoRelle R. Weight loss decreases C-reactive protein levels. *Circulation.* 2002;105:E9071–E9072.
 24. Hannah JS, Jablonski KA, Howard BV. The relationship between weight and response to cholesterol-lowering diets in women. *Int J Obes Relat Metab Disord.* 1997;21:445–450.
 25. Cole TG, Bowen PE, Schmeisser D, et al. Differential reduction of plasma cholesterol by the American Heart Association Phase 3 diet in moderately hypercholesterolemic, premenopausal women with different body mass indexes. *Am J Clin Nutr.* 1992;55:385–394.
 26. Denke MA, Adams-Huet B, Nguyen AT. Individual cholesterol variation in response to a margarine- or butter-based diet: a study in families. *JAMA.* 2000;284:2740–2747.

Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial

Atkinson et al. 2003

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Fragestellung

Doppelblindstudie mit 150 Patienten zum Einfluss von IgG-Test-gestützten Eliminationsdiäten beim Reizdarmsyndrom

D.h., die Hälfte der Reizdarm-Patienten erhielt eine Auslassdiät, die die individuellen Nahrungsmittel-Unverträglichkeiten berücksichtigte (durch Test auf nahrungsmittel-spezifische IgG-Antikörper nachweisbar). Die restlichen Reizdarm-Patienten erhielten eine Scheindiät, die keine Unverträglichkeiten berücksichtigte.

Erfasst wurden folgende Symptome:

Verschlechterung und Verbesserung der Symptome, Darm-unspezifische Symptome, Lebensqualität, Angstzustände und Depressionen

Ergebnisse:

Bei Patienten, die sich mit der IgG-Test-gestützten Auslassdiät ernährten, verbesserte sich der Gesundheitszustand und das Reizdarmsyndrom signifikant. Die Autoren kalkultierten daraufhin, dass von 4 Patienten jeder 3. auf diese Weise behandelt werden sollte.

Relevanz für ImuPro 300:

Erstmals konnte damit in einer Doppel-blind-Studie gezeigt werden, dass durch eine Ernährungsumstellung auf Basis einer IgG-Diagnostik signifikante Erfolge zu erzielen sind. Damit ist der Zusammenhang zwischen IgG-Antikörpern und bestimmten chronischen Entzündungserkrankungen eindrucksvoll bewiesen. Der Verzehr von Nahrungsmitteln löst ein Entzündungsgeschehen aus, dass sich durch eine gezielte Ernährungsumstellung stoppen lässt, ähnlich wie es auch beim Heilfasten häufig beobachtet wird.

IRRITABLE BOWEL SYNDROM

Food Elimination Diets

A second novel study, also presented at the plenary session, evaluated a different treatment modality—namely, food elimination diets—in IBS. Arguably, the results of this study could change current management of IBS. Atkinson and associates⁴⁸ conducted a double-blind, randomized, controlled trial. They entered 150 outpatients with all bowel habit subtypes of IBS and randomized them to either a diet excluding all foods to which they had measurable IgG antibody titers ($\geq 3:1$) or, alternatively, a sham diet. In the sham diet, the same number of foods were excluded but not those to which the patients were sensitive, based on elevated IgG antibody titers. Appropriate outcomes were measured, including symptom severity, non-colonic symptoms, quality of life, and anxiety and depression. Patients were defined as responders if they were better or excellent on a 7-grade Global Outcome Likert scale

. The study was double-blind and appears have been very carefully conducted; an ITT analysis was performed, as is appropriate. The results were very interesting. Patients on the diet in which foods that had positive IgG antibody titers were excluded did significantly better than patients on the sham diet. Global symptoms, as well as symptom severity scores, improved. Moreover, adherence to the diet led to a higher response in patients on the correct rather than the sham diet intervention. Both diarrhea- and constipation- predominant IBS appeared to respond similarly, which was somewhat unexpected because, theoretically, one might expect patients with diarrhea to have food intolerance and to respond best to a dietary approach. The authors calculated the number needed to treat was an impressive three to four.

This study is important because, if correct, it would be relatively easy to apply the approach taken. It is of interest that the foods that appeared to be important in terms of sensitivity largely included lactose-containing products and wheat-containing foods. The authors stated in discussion that patients with celiac disease and lactose intolerance would, for the most part, have been excluded and should not have biased the results of this study. Further work is needed to test the place of food elimination diets in IBS. However, if these results are confirmed, they have the potential to change practice because, arguably, this approach should be cheaper and may be more effective than most other current therapies available.

Patients on the diet in which foods that had positive IgG antibody titers were excluded did significantly better than patients on the sham diet.

48. Atkinson W, Gurney R, Sheldon TA, Whorwell PJ. Do food elimination diets improve irritable bowel syndrome? A double blind trial based on IgG antibodies to food [abstract]. *Gastroenterology*. 2003;124:A-29.

IRRITABLE BOWEL SYNDROME

Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial

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Background: Patients with irritable bowel syndrome (IBS) often feel they have some form of dietary intolerance and frequently try exclusion diets. Tests attempting to predict food sensitivity in IBS have been disappointing but none has utilised IgG antibodies.

Aims: To assess the therapeutic potential of dietary elimination based on the presence of IgG antibodies to food.

Patients: A total of 150 outpatients with IBS were randomised to receive, for three months, either a diet excluding all foods to which they had raised IgG antibodies (enzyme linked immunosorbant assay test) or a sham diet excluding the same number of foods but not those to which they had antibodies.

Methods: Primary outcome measures were change in IBS symptom severity and global rating scores. Non-colonic symptomatology, quality of life, and anxiety/depression were secondary outcomes. Intention to treat analysis was undertaken using a generalised linear model.

Results: After 12 weeks, the true diet resulted in a 10% greater reduction in symptom score than the sham diet (mean difference 39 (95% confidence intervals (CI) 5–72); $p = 0.024$) with this value increasing to 26% in fully compliant patients (difference 98 (95% CI 52–144); $p < 0.001$). Global rating also significantly improved in the true diet group as a whole ($p = 0.048$, NNT = 9) and even more in compliant patients ($p = 0.006$, NNT = 2.5). All other outcomes showed trends favouring the true diet. Relaxing the diet led to a 24% greater deterioration in symptoms in those on the true diet (difference 52 (95% CI 18–88); $p = 0.003$).

Conclusion: Food elimination based on IgG antibodies may be effective in reducing IBS symptoms and is worthy of further biomedical research.

Irritable bowel syndrome (IBS) is a common disorder which causes abdominal pain, abdominal distension, and bowel dysfunction, characterised by loose bowels, constipation, or a fluctuation between these two extremes.¹ This condition significantly impairs quality of life and places a large burden on health care resources.² Treatment of IBS is largely based on the use of antispasmodics, antidepressants, and medications that modify bowel habit, depending on whether constipation or diarrhoea is the predominant problem.¹ The notorious inadequacies of current drug therapy lead to much patient dissatisfaction and a tendency for patients to seek a variety of alternative remedies, especially of a dietary nature.

IBS is likely to be a multifactorial condition involving a number of different mechanisms although the prominence of any particular factor may vary from patient to patient.^{1–3} However, patients often strongly believe that dietary intolerance significantly contributes to their symptomatology and some sufferers seem to benefit from eliminating certain foods from their diet. Detection of food intolerance is often difficult due to its uncertain aetiology, non-specific symptomatology, and relative inaccessibility of the affected organ. Thus most previous studies have relied on the use of exclusion diets, which are extremely labour intensive and time consuming.^{4–5} Attempts to “test” for food intolerance in IBS have largely focused on “classic” food allergy based on the presence of IgE mediated antibody responses, although it appears that these “immediate type” reactions are probably quite rare in this condition.^{6–10} It is therefore possible that adverse reactions to food in patients with IBS might be due to some other form of immunological mechanism, rather than dietary allergy. Such reactions could be mediated by IgG antibodies, which characteristically give a more delayed response following exposure to a particular antigen¹¹ and have been implicated in some cases of food hypersensitivity.^{12–14} However, this mechanism is controversial and is considered by some to be

physiological^{15–17} especially as IgG food antibodies can be present in apparently healthy individuals.^{18–20} It has previously been suggested that IgG food antibodies may have a role in IBS²¹ and it was therefore the purpose of this study to formally evaluate, in a randomised controlled trial, the therapeutic potential of an elimination diet based on the presence of IgG antibodies to food in patients with IBS.

PATIENTS AND METHODS

Patients

All patients with uncomplicated IBS (all bowel habit subtypes) attending the Gastroenterology Department at the University Hospital of South Manchester were considered eligible for the study, and those aged between 18 and 75 years, who satisfied the Rome II criteria,²² were invited to participate. Tertiary care patients were excluded from the study. All patients had normal haematology, biochemistry, and endoscopic examination when indicated. Coeliac disease was excluded using the tissue transglutaminase test and a hydrogen breath test was used for excluding lactose intolerance. Patients were also excluded from participating in the study if they had any significant coexisting disease or a history of gastrointestinal surgery, excluding appendicectomy, cholecystectomy, and hiatus hernia repair. The study was approved by the local ethics committee and all patients provided written informed consent.

Methods

The study used a double blind, randomised, controlled, parallel design in which patients were randomised to either a “true” diet or a “sham” diet control group. At screening,

Abbreviations: IBS, irritable bowel syndrome; ELISA, enzyme linked immunosorbant assay; AU, arbitrary unit; HAD, hospital anxiety and depression scale; QOL, quality of life; NNT, number needed to treat

blood was taken and sent, with only a numerical identifier, to YorkTest Laboratories Ltd (York, UK) where an enzyme linked immunosorbant assay (ELISA) test was performed to detect the presence of IgG antibodies specific to a panel of 29 different food antigens. This test has been described in detail elsewhere²³ and involves specimens being diluted 1/50, 1/150, and 1/450 with each dilution applied to an allergen panel. Each test was calibrated using 0 arbitrary unit (AU) and 25 AU standards prepared from a serum with a high IgG titre to a cow's milk allergen extract. A positive control serum at 45 AU was applied to each test. The test results were obtained from the 1/150 dilution of the specimen. Where a high specimen background was observed, the test results were obtained from the 1/450 dilution. The threshold for a positive (reactive) result was selected as three times the background signal obtained by the same sample against a no food allergen coated control well equivalent to 3 AU. Test results were scored as positive or negative only, relative to this cut off.

Staff based at the YorkTest Laboratories produced a true and sham diet sheet for each patient. The sham diet eliminated the same number of foods to which a patient exhibited IgG antibodies but not those particular foods. The goal was to try and include in the sham diet an equally difficult to eliminate staple food for every staple food in the true diet. Thus cow's milk was (generally) replaced with potato, wheat with rice, and yeast with whole egg, where this was possible. Nut reactivities were replaced with other nuts in the sham diet, and legumes with other legumes, but this was not systematised.

The true and sham diet sheets for each patient were sent to the University of York, again with only a number for identification. Patients were allocated to one of the two diet sheets based on a randomisation schedule developed using a random computer number generator. Thus patients would receive either an elimination diet based on their true sensitivity results (true diet) or a sham diet. All patients and clinical staff in the Gastroenterology Research Department and YorkTest Laboratory were blinded to the group assignment of all patients for the duration of the study.

Patients were given their allocated diet sheet by staff at the Gastroenterology Research Department and asked to eliminate the indicated foods from their diet for a period of 12 weeks. They also received a booklet with advice on eliminating the different foods and the telephone contact details of a free nutritional advisor whom they were able to contact for further advice if necessary.

Symptoms were assessed using a questionnaire scoring system validated for use in IBS, including the IBS symptom severity score (range 0–500).²⁴ This is a system for scoring pain, distension, bowel dysfunction, and general well being, with mild, moderate, and severe cases indicated by scores of 75–175, 175–300, and >300, respectively. A reduction in score of 50 or over is regarded as a clinically significant improvement.²⁴ Non-colonic symptomatology,²⁵ such as lethargy, backache, nausea, and urinary symptoms, was assessed and scored using visual analogue scales (range 0–500). Quality of life (QOL) was measured using an instrument proven to be sensitive to change in IBS (range 0–500).^{26–28} Anxiety and depression were evaluated using the hospital anxiety and depression scale (HAD).²⁹ This instrument scores anxiety and depression up to a maximum score of 21 for each parameter, with a score above 9 indicating significant psychopathology. Data on these measures were recorded at baseline and after 4, 8, and 12 weeks of the dietary intervention period. In addition, at 4, 8, and 12 weeks, patients were asked to give a global rating of their IBS using the question, "Compared with your IBS before you started the food elimination diet, are you now: terrible, worse,

slightly worse, no change, slightly better, better, or excellent?" The atopic status of all patients entering the study was also assessed.

During the treatment phase, patients were allowed to take concomitant medication provided it had been constant for six months prior to the start of the study. They were encouraged not to alter medication use during the course of the trial but any changes were recorded. Any patient withdrawing from the study was encouraged to complete a final symptom questionnaire at week 12 and their reasons for withdrawal were recorded. At the end of 12 weeks, patients were asked to resume consumption of the foods they had been advised to eliminate in order to assess the effect of their reintroduction. Patients were then reassessed after four weeks using the same measures and the result compared with their scores at the end of the elimination phase.

Data analysis

Questionnaires were scored by an assessor blinded to the randomisation. The primary outcome measures were changes in IBS symptom severity score and global impact score at 12 weeks. Changes in non-colonic symptoms, QOL, and HAD scores were regarded as secondary outcome measures. Two sample *t* tests were used to establish whether there was an overall difference in the change in continuous outcome measures between the two groups of patients. Patients were analysed according to the group to which they were randomised, independent of their adherence to the diet. The global impact score, an ordered categorical variable, was analysed using a Wilcoxon Mann-Whitney test to compare the numbers in the active and sham groups showing significant improvement ("better" or "excellent"), no significant change ("slightly worse", "no change", or "slightly better"), and significant deterioration ("worse" or "terrible"). The number needed to treat (NNT) was calculated from the global impact score by calculating the reciprocal of the difference in probability of a significant improvement between the treatment and control groups. General linear modelling in SPSS was used to explore whether there was a

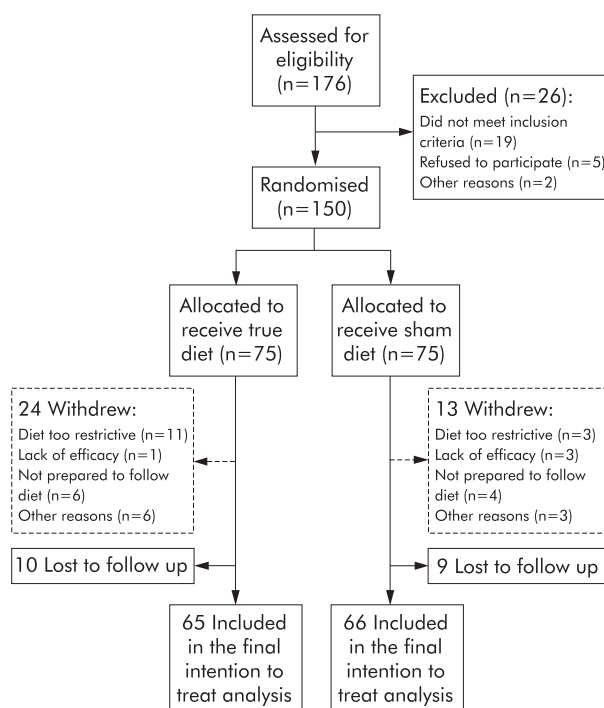


Figure 1 Study flow diagram.

Table 1 Baseline characteristics of the patients

Group	True diet (n=75)	Sham diet (n=75)
Age (y) (range, SD)	44 (17–72; 12.9)	44 (19–74; 15.2)
No of males (%)	7 (9.3%)	13 (17.3%)
No of foods to which sensitive	6.65 (3.66)	6.63 (4.1)
Symptom duration (y)	11.5 (9.9)	10.1 (7.5)
IBS symptom severity score	331.9 (70.8)	309.0 (78.5)
Non-colonic features score	459.1 (160.7)	452.6 (170.1)
Quality of life score	640.1 (252.6)	639.3 (222.3)
HAD anxiety score	9.5 (4.6)	9.5 (4.5)
HAD depression score	5.3 (3.4)	6.0 (3.6)
No of diarrhoea predominant patients (%)	37 (52.1%)	41 (56.9%)
No of constipation predominant patients (%)	19 (26.8%)	16 (22.2%)
No of alternating predominant patients (%)	15 (21.1%)	15 (20.8%)

Results are expressed as mean (SD).
HAD, hospital anxiety and depression scale.

relationship between the change in symptoms from baseline and treatment group, patient characteristics (for example, IBS subtype, history of atopy, number of foods to which sensitive, and concomitant medication) and adherence to the diet.³⁰

Sample size calculation

It was estimated that approximately 40% of the placebo arm would report a significant improvement in symptoms. It was calculated that a sample size of 55 patients would be required in each group to detect, with 90% power, a difference of 30% points in the proportion reporting such an improvement (that is, 70% in the treatment arm) as statistically significant at the 5% level. Assuming a 20% dropout rate, a minimum of 138 patients would need to be entered into the trial. Thus we aimed to recruit a total of 150 patients into the study.

RESULTS

Recruitment of patients and their flow through each stage of the study is illustrated in fig 1, as recommended by the

CONSORT statement.³¹ In summary, between January 2001 and July 2002, 176 patients were eligible for the study, of which 26 (15%) were excluded from participation, leaving 150 patients who were all found to be sensitive to at least one food. Seventy five of these were randomised to receive an elimination diet based on their true food sensitivity results and 75 patients to a sham diet. Data from 131 (87%) patients who gave 12 week data were available for the intention to treat analysis: 65 and 66 patients from the true and sham groups, respectively.

Patient characteristics

The patients were typical of those with IBS in secondary care practice, the majority being women. Patients, on average, had experienced symptoms of IBS for over a decade and were found to be sensitive to approximately 6–7 foods (range 1–19). Baseline demographic and clinical characteristics of the two groups, including the use of concomitant medication, were found to be similar with the exception of the IBS symptom severity score which was slightly higher in the treatment group (table 1). Thirty per cent of patients were found to be atopic.

The frequency of foods excluded from the diet is shown in table 2. Adherence was lower in those on the true diet although no specific adverse events were recorded in either group. Twenty four patients withdrew from the study in the true diet group (mainly because of difficulty in following the diet) and 13 from the sham diet group (for a variety of reasons). However, 12 week data were obtained from 14 of those who withdrew in the true diet group and four in the sham diet group. There were no significant differences

Table 2 Frequency of foods excluded from the diet (% of patients)

Food	Treatment group	Sham group
Barley	26.7	9.3
Corn	22.7	14.7
Rice	8	54.7
Rye	8	25.3
Wheat	49.3	8
Milk	84.3	1.3
Beef	24	9.3
Chicken	21.3	13.3
Pork	5.3	36
Cabbage	12	24
Celery	5.3	21.3
Haricot bean	17.3	14.7
Pea	38.6	1.3
Potato	9.3	61.3
Soy bean	22.7	10.7
Tomato	4	44
Apple	1.3	33
Orange	6.7	29.3
Strawberry	0	20
Almond	28	12
Brazil nut	22.7	17.3
Cashew nut	49.3	8
Peanut	10.7	20
Walnut	2.7	29.3
Cocoa bean	1.3	21.3
Shellfish	21.3	10.7
Fish mix	17.3	28
Whole egg	57.3	26.7
Yeast	86.7	0

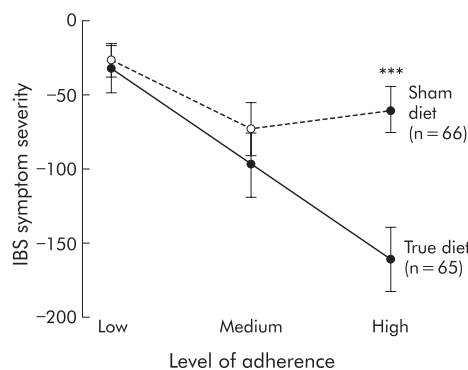


Figure 2 Mean change in symptom severity scores at 12 weeks according to degree of adherence. Difference between the groups with high adherence: 101 (95% confidence interval 54, 147); ***p<0.001.

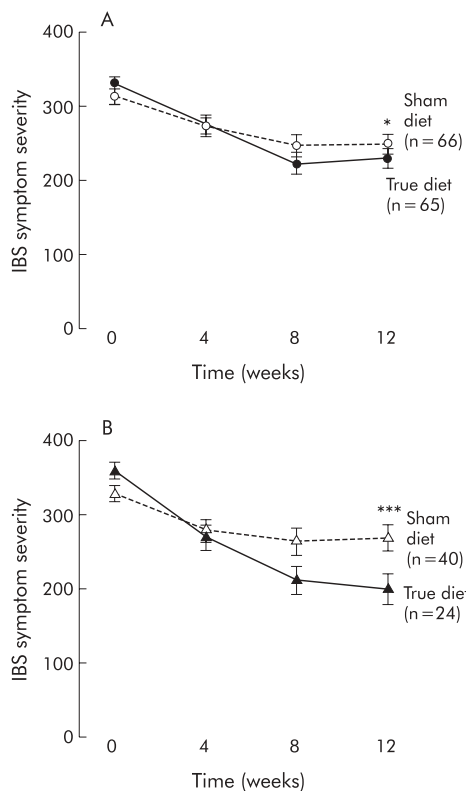


Figure 3 (A) Average symptom severity scores over time for the group as a whole. Difference in mean change from baseline at 12 weeks: true versus sham 39 (95% confidence interval 5, 72); *p=0.024. (B) Average symptom severity scores over time for the full adherence group. Difference in mean change from baseline at 12 weeks: true versus sham 98 (95% confidence interval 52, 144); ***p<0.001.

between baseline characteristics of the 19 who were lost to follow up and those for whom 12 week data were obtained.

Primary outcomes

IBS symptom severity

Patients in the true diet group experienced a 10% greater reduction in symptom severity than those allocated to the sham diet, with change in scores of 100 and 61.5, respectively (mean difference 39 (95% confidence interval (CI) 5.2, 72.3); p=0.024): a standardised effect size of 0.52 (see fig 3A). There were no differences in the response to the diet in terms of age, sex, IBS bowel habit subtype, or IBS duration. In addition, there was no difference in response to the diet

between atopic and non-atopic patients. There was however a statistically significant interaction between treatment group and both adherence to the diet and number of foods to which patients were sensitive. For patients sensitive to the average number of foods who fully adhered to their allocated diet, a 26% difference in reduction in symptom severity score was observed in favour of the true diet (a difference in score of 98 (95% CI 52, 144), p<0.001: a standardised effect size of 1.3). This benefit increased by a further 39 points (12%) (95% CI 7, 70; p= 0.016) for each food to which they were sensitive over and above the average number. These results were not materially altered by carrying out an ANCOVA analysis (in which the final score is the dependent variable and the baseline score is included as a covariate) instead of modelling change in scores.³⁰ The interaction between treatment group and adherence is demonstrated in fig 2 which shows a greater reduction in symptoms with full adherence in the true diet but not in the sham diet group. Figure 3A and 3B show the average change in symptom severity score over 12 weeks for the group as a whole and for those who fully adhered, respectively. This reveals that most improvements in symptoms are fully achieved within two months.

Global impact score

The reported global rating of change by treatment group is shown in table 3. The difference in mean ranking (70.9 v 60.3) was statistically significant (p = 0.048). When this was repeated including only patients who fully adhered to their diets (table 3), a greater percentage difference favouring the true diet was found (p = 0.001). The NNT was 9 in the group as a whole and 2.5 in patients fully adherent to the diet.

Secondary outcome measures

As can be seen from fig 4A and 4B, all data show changes favouring the true diet group and are consistent with the results for the primary outcomes. These trends were further strengthened after adjustment for adherence and number of food sensitivities but only reached statistical significance for non-colonic symptomatology (p = 0.05). There were no significant changes in medication use during the course of the trial.

Reintroduction of eliminated foods

Of the 131 patients who gave 12 week data, 93 (41 in the true and 52 in the sham diet groups) agreed to attempt reintroduction of foods they had been asked to eliminate and provided further follow up data on the primary outcomes measures. Of these, 62% reported full adherence and 37% moderate adherence to the previous elimination diet. Mean IBS symptom severity score increased (that is, worsening of symptoms) by 83.3 in the true group and by 31 in the sham

Table 3 Global impact score at 12 weeks

	Treatment group		
	True diet (n (%))	Sham diet (n (%))	
All patients			
Significantly worse	3 (4.7)	8 (12.1)	
No significant change	44 (67.2)	47 (71.2)	
Significantly improved	18 (28.1)	11 (16.7)	
Total	65	66	NNT = 9
Patients fully adhering to the diet			
Significantly worse	1 (4.2)	5 (12.5)	
No significant change	10 (41.7)	29 (72.5)	
Significantly improved	13 (54.1)	6 (15)	
Total	24	40	NNT = 2.5

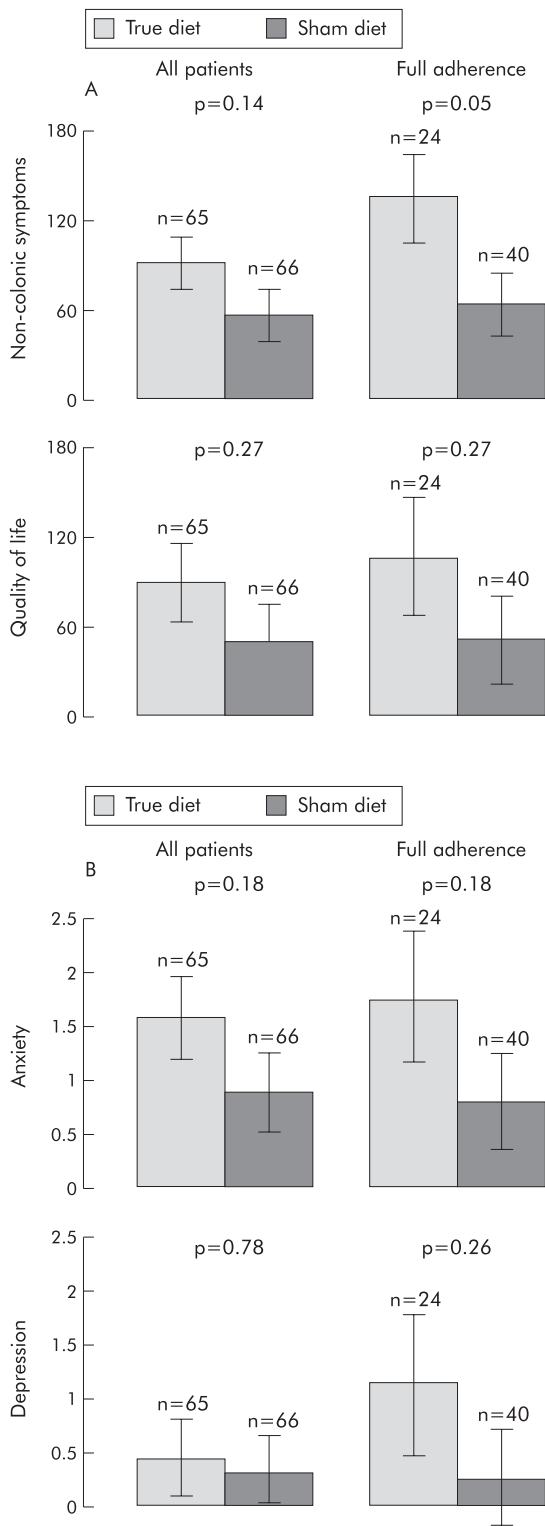


Figure 4 (A) Mean change in the secondary outcome measures of non-colonic symptoms and quality of life for the group as a whole and the full adherence group. (B) Mean change in the secondary outcome measures of anxiety and depression for the group as a whole and the full adherence group.

group, a statistically significant difference of 52 (24%) (95% CI 18, 86; $p = 0.003$). The change in global score following reintroduction of foods is shown in table 4. This indicates a reversal of the pattern observed during the active treatment phase, with more patients in the true diet group showing

Table 4 Global rating following reintroduction of foods relative to the end of the elimination phase

	Treatment group	
	True diet group (n (%))	Sham diet group (n (%))
Significantly worse	17 (41.5)	13 (25)
No significant change	23 (56.1)	35 (67.3)
Significantly improved	1 (2.4)	4 (7.7)
Total	41 (100)	52 (100)

worsening of health compared with the sham diet group ($p = 0.047$).

DISCUSSION

A clinically significant improvement in IBS symptomatology was observed in patients eliminating foods to which they were found to exhibit sensitivity, as identified by an ELISA test for the presence of IgG antibodies to these foods. The number needed to treat of 9 for the group as a whole and 2.5 for patients closely adhering to the diet are both considerably better than the value of 17 achieved after three months of treatment with tegaserod,³² a drug that has been recently licensed in the USA for use in IBS. IBS symptom severity and global rating scores were chosen as primary outcome measures in this study as they represented the most direct measure of clinical improvement in this condition based on patient self assessment. Rather than using the traditional method of classifying global improvement as any value exceeding adequate relief of symptoms, we used a much stricter definition requiring patients to report symptoms as being either “better” or “excellent” compared with pretreatment levels. Despite this, the diet still achieved a significant improvement. However, as might be expected, the placebo response using this end point was somewhat lower than that usually reported in IBS treatment trials which have used less demanding criteria. The observation that patients on the sham diet also improved, although to a lesser extent, emphasises the importance of conducting double blind randomised controlled trials of such non-drug interventions in order to avoid overestimating their potential.

Most patients with IBS have attempted at least some form of dietary modification, which in some cases can be very extreme. Conflicting results have been reported using exclusion diets^{4 5 33-36} and this approach also suffers from the limitation that it has to be empirical. Thus potentially offending foods can only be identified after their elimination and subsequent reintroduction. This time consuming process would be much reduced if the offending foods could be identified beforehand. Attempts to do this using IgE antibodies have been disappointing⁸⁻¹⁰ but the results of this study suggest that measuring IgG antibodies may be much more rewarding. The response to the IgG based diet in our trial did not correlate with atopic status, the prevalence of which was found to be no greater than that occurring in the general population.³⁷

The observation that adherence to the diet is critical in determining a good outcome in the “true” diet group but not the “sham” group is indicative of the fact that the diet is an “active treatment” which if not adhered to, does not seem to have an effect. This notion is further supported by the observation that a significantly greater deterioration was observed in subjects in the true diet group compared with those in the sham group when they reintroduced eliminated foods at the end of the diet phase of the trial. Furthermore, the improvement of 98 in the symptom severity score in those fully adherent in the true diet group is well above the value of

50, which is regarded as being of clinical significance both in validation studies²⁴ and clinical practice.^{26–28} It was interesting to note that patients exhibiting a greater number of sensitivities, as determined by the IgG test, experienced a greater symptom reduction if they adhered to the true but not the sham diet.

There is currently considerable interest in the concept that at least in some patients, IBS may have an inflammatory component.^{38–42} Most of the work in this area has centred on post dysenteric IBS, with gut pathogens being viewed as the initiators of this process which can be identified by subtle changes on histology.³⁸ However, if, as indicated in this study, IgG antibodies to food are important in the pathogenesis of IBS in some patients, they too may be of relevance. Not all patients exhibiting histological features consistent with post dysenteric IBS give a history of a previous dysenteric illness. This is usually assumed to be due to the fact that this has been forgotten by the patient but our results may suggest an alternative mechanism for immune activation and inflammation without the need for prior infection.

It is now well recognised that up to 70% of patients with IBS have evidence of hypersensitivity of the rectum,⁴³ which probably extends to involve most of the gut in many individuals.⁴⁴ It is possible that this hypersensitivity renders patients more reactive to a low grade inflammatory process which would not necessarily cause symptoms in a normal individual. This would explain why excluding foods to which patients have IgG antibodies might be particularly beneficial in IBS despite the fact that these antibodies may also be present in the general population. Indeed, if this mechanism is particularly important in IBS, it might be anticipated that IgG food antibodies would be relatively common in this condition, as was the case in our study.

Many patients with IBS would prefer a dietary solution to their problem rather than having to take medication, and the economic benefits of this approach to health services are obvious. It is well known that patients expend large sums of money on a variety of unsubstantiated tests in a vain attempt to identify dietary intolerances. The results of this study suggest that assay of IgG antibodies to food may have a role in helping patients identify candidate foods for elimination and is an approach that is worthy of further biomedical and clinical research.

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REFERENCES

- Drossman DA, Camilleri M, Mayer EA, et al. American Gastroenterological Association Technical Review on Irritable Bowel Syndrome. *Gastroenterology* 2002;123:2108–31.
- Lea R, Whorwell PJ. Quality of life in irritable bowel syndrome. *Pharmacoeconomics* 2001;19:643–53.
- Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002;360:555–64.
- Jones VA, McLaughlan P, Shorhouse M, et al. Food intolerance: a major factor in pathogenesis of irritable bowel syndrome. *Lancet* 1982;2:1115–17.
- Nanda R, James R, Smith H, et al. Food intolerance and the irritable bowel syndrome. *Gut* 1989;30:1099–104.
- Zwetchkenbaum J, Burakoff, R. The irritable bowel syndrome and food hypersensitivity. *Ann Allergy* 1988;61:47–9.
- Zar S, Kumar D, Benson M. J. Review article: food hypersensitivity and irritable bowel syndrome. *Aliment Pharm Ther* 2001;15:439–43.
- Petitpierre M, Gumowski P, Girard JP. Irritable bowel syndrome and hypersensitivity to food. *Ann Allergy* 1985;54:538–40.
- Barau E, Dupont C. Modifications of intestinal permeability during food provocation procedures in pediatric irritable bowel syndrome. *J Pediatr Gastroenterol Nutr* 1990;11:72–7.
- Roussos A, Koursarakos P, Patsopoulos D, et al. Increased prevalence of irritable bowel syndrome in patients with bronchial asthma. *Respir Med* 2003;97:75–9.
- Crowe SE, Perdue MH. Gastrointestinal food hypersensitivity: basic mechanisms of pathophysiology. *Gastroenterol* 1992;103:1075–95.
- el Rafei A, Peters SM, Harris N, et al. Diagnostic value of IgG4 measurements in patients with food allergy. *Ann Allergy* 1989;62:94–9.
- Host A, Husby S, Gjesing B, et al. Prospective estimation of IgG, IgG subclass and IgE antibodies to dietary proteins in infants with cow's milk allergy. Levels of antibodies to whole milk protein, BLG and ovalbumin in relation to repeated milk challenge and clinical course of cow's milk allergy. *Allergy* 1992;47:218–29.
- Awazuhara H, Kawai H, Maruchi N. Major allergens in soybean and clinical significance of IgG4 antibodies investigated by IgE and IgG4 immunoblotting with sera from soybean-sensitive patients. *Clin Exp Allergy* 1997;27:325–32.
- Barnes RMR, Johnson PM, Harvey MM, et al. Human serum antibodies reactive with dietary proteins: IgG subclass distribution. *Int Arch Allergy Appl Immunol* 1988;87:184–8.
- Lessof MH, Kemeny DM, Price JF. IgG antibodies to food in health and disease. *Allergy Proc* 1991;12:305–7.
- Husby S, Mestecky J, Moldoveanu Z, et al. Oral tolerance in humans. T cell but not B cell tolerance after antigen feeding. *J Immunol* 1994;152:4663–70.
- Haddad ZH, Vetter M, Friedmann J, et al. Detection and kinetics of antigen-specific IgE and IgG immune complexes in food allergy. *Ann Allergy* 1983;51:255.
- Husby S, Oxelius VA, Teisner B, et al. Humoral immunity to dietary antigens in healthy adults. Occurrence, isotype and IgG subclass distribution of serum antibodies to protein antigens. *Int Arch Allergy Appl Immunol* 1985;77:416–22.
- Kruszewski J, Raczka A, Klos M, et al. High serum levels of allergen specific IgG-4 (asIgG-4) for common food allergens in healthy blood donors. *Arch Immunol Ther Exp* 1994;42:259–61.
- Finn R, Smith MA, Youngs GR, et al. Immunological hypersensitivity to environmental antigens in the irritable bowel syndrome. *Br J Clin Pract* 1987;41:1041–3.
- Drossman DA, Corazzari E, Talley NJ, et al. Rome II: a multinational consensus document on functional gastrointestinal disorders. *Gut* 1999;45:1–81.
- Foster AP, Knowles TG, Hotston Moore A, et al. Serum IgE and IgG responses to food antigens in normal and atopic dogs, and dogs with gastrointestinal disease. *Vet Immunol Immunopathol* 2003;92:113–24.
- Francis CY, Morris J, Whorwell PJ. The irritable bowel scoring system: A simple method of monitoring IBS and its progress. *Aliment Pharmacol Therap* 1997;11:395–402.
- Whorwell PJ, McCallum H, Creed FH, et al. Non-colonic features of irritable bowel syndrome. *Gut* 1986;27:452–6.
- Houghton LA, Heyman DJ, Whorwell PJ. Symptomatology, quality of life and economic features of irritable bowel syndrome—the effect of hypnotherapy. *Aliment Pharmacol Ther* 1996;10:91–5.
- Gonsalkorale WM, Toner BB, Whorwell PJ. Cognitive change in patients undergoing hypnotherapy for irritable bowel syndrome. *J Psychosom Res* 2004;56:271–8.
- Gonsalkorale WM, Houghton LA, Whorwell PJ. Hypnotherapy in irritable bowel syndrome: a large scale audit of a clinical service with examination of factors influencing responsiveness. *Am J Gastroenterol* 2002;97:954–61.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
- Everitt BS, Pickles A. *Statistical aspects of the design and analysis of clinical trials*. London: Imperial College Press Publishers, 2003:108–42.
- Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663–94.
- Novick J, Miner P, Krause R, et al. A randomised, double blind, placebo controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2002;16:1877–88.
- Niec AM, Frankum B, Talley NJ. Are adverse reactions to food linked to irritable bowel syndrome? *Am J Gastroenterol* 1998;93:2184–90.
- Burden S. Dietary treatment of irritable bowel syndrome: current evidence and guidelines for future practice. *J Hum Nutr Diet* 2001;14:231–41.
- Bentley SJ, Pearson DJ, Rix KJB. Food hypersensitivity in irritable bowel syndrome. *Lancet* 1983;2:295–7.
- McKee AM, Prior A, Whorwell PJ. Exclusion diets in irritable bowel syndrome: Are they worthwhile? *J Clin Gastroenterol* 1987;9:526–8.
- Durham SR, Church MK. Principles of allergy diagnosis. In: Holgate ST, Church MK, Lichtenstein LM, eds. *Allergy*, 2nd edn. London: Mosby, 2001:3–16.
- Spiller RC, Jenkins D, Thornley JP, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. *Gut* 2000;47:804–11.
- Gonsalkorale WM, Perrey C, Pravica V, et al. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? *Gut* 2003;52:91–3.
- Collins SM, Piche T, Rampal P. The putative role of inflammation in the irritable bowel syndrome. *Gut* 2001;49:743–5.
- Collins SM. A case for an immunological basis for irritable bowel syndrome. *Gastroenterology* 2002;122:2078–80.
- Chadwick VS, Chen W, Shu D, et al. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002;122:1778–83.
- Mertz H. Review article: visceral hypersensitivity. *Aliment Pharmacol Ther* 2003;17:623–33.
- Francis CY, Houghton LA, Whorwell PJ. Enhanced sensitivity of the whole gut in patients with irritable bowel syndrome. *Gastroenterology* 1995;108:601(abstract).

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Ist Adipositas eine entzündliche Erkrankung?

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Hintergrund: Der größte Teil der adipösen Patienten werden erhöhte Konzentrationen von Interleukon 6 (IL-6) und Tumor-Nekrose-Faktor-alpha (TNF- α) gemessen. Erhöht sind auch die Werte für Entzündungsmarker, die in enger Verbindung zu Diabetes, Bluthochdruck und Schlaganfall stehen. **Hypothese:** Adipositas/Fettsucht ist eine entzündliche Erkrankung. Die Roux-Operation (Magenresektion) führt zu einer Reduktion der Entzündungsmarker und schränkt die genetisch kontrollierte Biosynthese der Nahrungsmittelenergie-abhängigen Zellen des Hypothalamus ein und reduziert die Zellen des Unterhautfettgewebes.

Methoden: Die Fettleibigkeit wurde durch hochkalorische Kost bei 24 drei-wöchigen Sprague Dawley Welpen herbeigeführt. Die Untersuchung erfolgte in drei Gruppen (n = 8/Gruppe): Gruppe Roux-Operation, Gruppe Schein-Operation und **pair-fed**, Gruppe Schein-Operation und hochkalorische Kost ad libitum. Die Kontrollgruppe waren sechs nicht-adipöse Ratten. Die Ratten wurden zehn Tage nach der Operation getötet und Blutproben zur Untersuchung der Glukosteroide und des Unterhautfettgewebes entnommen und Mesenterialfettgewebe zur Untersuchung von IL-6, TNF- α und der Glukosteroide. Für das Genexpressionsprofil wurden die vollständige mRNA und das Unterhautfettgewebe aufbereitet. Mittels Analyse der Varianz, des Mann-Whitney Tests und des t-Tests wurden die Daten ausgewertet. **Ergebnisse:** Vor der Operation wogen die adipösen Gruppen 493 +/- 7g und die Kontrollgruppe 394 +/- 12g. Das postoperative Gewicht nach zehn Tagen betrug in der Gruppe Roux-Operation = 417 +/- 21g, in der Gruppe Schein-OP und pair-fed = 436 +/- 14g, und in der Gruppe Schein-OP und hochkalorischer Kost ad lib. = 484 +/- 15g. In der Gruppe Roux-OP sank das Gewicht des Mesenterial- und Unterfettgewebes. Im Verhältnis dazu sanken die Werte für Interleukin 6, TNF- α und Glukosteroide und das Genexpressionsprofil zeigte einen Rückgang des Entzündungsgeschehens nach der Operation. **Schlussfolgerungen:** Die erhöhten Werte von Entzündungsmarkern bei Adipositas sinken nach einer Magenresektion und der darauf folgenden Gewichtsreduktion stark ab. Man postuliert deshalb, dass die Fettsucht/Adipositas ein entzündlicher Zustand ist.



Is obesity an inflammatory disease?

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BACKGROUND: Most obese individuals have elevated concentrations of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), markers of inflammation closely associated with diabetes, hypertension, and stroke. **HYPOTHESIS:** Obesity is a low-grade inflammatory disease, and Roux-en-Y gastric bypass (RYGB) reduces biochemical markers of inflammation and modifies gene expression in hypothalamic food intake/energy-related nuclei and subcutaneous abdominal fat (SAF). **METHODS:** Obesity was induced in 24 3-week-old Sprague Dawley pups fed a high-energy diet (HED). Three groups (n = 8/group) were studied: RYGB, sham-operated pair-fed, and sham-operated ad libitum HED. Controls were nonobese rats fed chow (n = 6). Rats were killed 10 days after operation, and blood was collected to measure corticosterone and SAF and mesenteric fat to measure IL-6, TNF-alpha, and corticosterone. Total mRNA from arcuate nucleus and SAF purified for gene expression profiling. Data were analyzed with analysis of variance, Mann-Whitney test, and t test. **RESULTS:** Before operation, the body weight of the obese groups was 493 +/- 7 g and control = 394 +/- 12g. The 10-day postoperative weight was RYGB = 417 +/- 21 g, pair-fed = 436 +/- 14 g, and ad libitum HED = 484 +/- 15 g. Mesenteric and SAF weight decreased in RYGB. Mesenteric/SAF ratio of IL-6, TNF-alpha, corticosterone, and gene profiling showed decrease of inflammation after RYGB. **CONCLUSIONS:** Gastric bypass reduces biochemical markers of inflammation, suggesting that obesity is an inflammatory condition.

PMID: 12947337 [PubMed - indexed for MEDLINE]

Great Smokies Diagnostic Laboratory North Carolina, USA (www.gsdl.com)

Wer ist Great Smokies?

Weltweit führendes biochemisches Labor im Bereich Immunologie, Ernährung, Endokrinologie. In USA arbeiten mehr als 8000 Ärzte mit GSDL zusammen. Tochtergesellschaften und Vertretungen in Australien, Deutschland, Finnland, Frankreich, Griechenland, Großbritannien, Italien, Israel, Japan, Kanada, Korea, Neuseeland, Niederlande, Russland, Saudi Arabien, Schweiz, Spanien, Schweden, Taiwan, Ukraine.

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- Bastyr University
- International College of Integrative Medicine

Mary James, Toward an understanding of Allergy and In-Vitro Testing

Begriffserläuterungen S. 4f

“Hypersensitivität:

Obwohl der Begriff Hypersensitivität manchmal nur für IgG vermittelte Reaktionen des Typs III nach Gell und Coomb reserviert ist, wird der Ausdruck traditionell für alle 4 Typen der Gefäßschädigung angewandt. Typ 1 bis 4 hängen von der Interaktion eines Antigens mit einem Antikörper ab und resultieren aus einer exzessiven Reaktion auf ein Antigen, was eine starke Gewebeveränderung mit Symptomen bewirkt.

Typ I Reaktionen sind durch IgE Antikörper vermittelt und durch die Freisetzung von Histaminen und anderen chemischen Mediatoren aufgrund eines Kontakts mit einem Allergen charakterisiert. Typ I Reaktionen sind für das sofortige Entstehen von Allergien verantwortlich wie bspw. Heuschnupfen und anaphylaktische Reaktionen...

Typ II Immunreaktionen beinhalten antikörpervermittelte Gefäßzerstörungen nach Anhaften am Fremdgewebe. Der Reaktionstypus wird oft als zytotoxische Reaktion bezeichnet. Beispiel ist u.a. eine Penicillinreaktion, die rote Blutzellen oder Blutplättchen zerstört

Typ III Reaktionen sind durch verschiedene Immunglobuline vermittelt, hauptsächlich jedoch durch IgG. Komplexe aus Antigen und Antikörper aktivieren das Komplementsystem und Zytokine im Körper, was wiederum in einem Entzündungsprozeß mündet. Typ III Reaktionen bilden die Basis der verzögert einsetzenden Nahrungsmittelallergien. Die Symptome erscheinen verzögert, da die Bildung von (Immun-)komplexen Zeit benötigt...

Typ IV meint die zellvermittelte Immunreaktion, wobei T-Zellen eine Hauptrolle spielen. T-Zellen werden zytotoxisch indem sie durch ein Antigen aktiviert werden. Sie sind dadurch in der Lage, Viren, Bakterien, Tumorzellen und andere Zellen zu zerstören....

Allergie:

Die Begriffsdefinition der Allergie ist heftig umstritten. Obwohl viele traditionelle Allergologen den Begriff ausschließlich für die Typ I, IgE vermittelte Reaktion wie Heuschnupfen reservieren, beinhaltet eine allgemeinere Definition der Allergie jegliche erworbene Überempfindlichkeit für ein Antigen mit einer negativen immunologischen Konsequenz...“

S. 6f: „Verzögert einsetzende IgG Reaktionen

...IgG vermittelte Reaktionen resultieren typischerweise aus einer starken Einwirkung an Antigenen über einen längeren Zeitraum hinweg. Im Falle von Nahrungsmittelunverträglichkeiten, führt erhöhte Darmpermeabilität mit wiederholter Verdauung des speziellen Nahrungsmittels dazu, daß das Antigen in hohem Maße dem Immunsystem präsentiert wird. Die Bildung von Antigen-Antikörper-Komplexen aktiviert das Komplementsystem und im Anschluß zum Ausstoß von Neutrophilen, der Freisetzung von proteolytischen Enzymen, Mastzellenüberträger und vasoaktiven Peptiden und zur Thrombozytenaggregation... Das Einsetzen der Symptome ist typischerweise um Stunden oder Tage verzögert und variiert nicht nur in der Art der Immunkomplex sondern auch aufgrund des Gewebes, wo die Immunkomplexe sich ablagern. Kopfweh, Vaskulitiden oder Bluthochdruck kann durch Ablagerung im Gefäßsystem entstehen, Asthma, Alveolitis oder wiederkehrende Infektionen durch Ablagerung im Atemsystem, dermatologische Veränderungen durch Ablagerung in der Haut... Abhängig von der individuellen Prädisposition kann jegliches System betroffen sein.

S.8: Diagnose

Ein Allergietest sollte immer im Zusammenhang mit dem Krankheitsbild gesehen werden. Wenn immunologische **Clearance Mechanismen (?)** eines Individuums zur Abwehr von Symptomen aktiv sind, so besteht eine Allergie und ein Test kann helfen die Nahrungsmittel zu identifizieren, die das Immunsystem belasten. Wenn eine Person gegen mehrere Nahrungsmittel allergisch ist, kann der Test helfen, die Ausgangslage für eine Elimination zu klären.

In-vivo Hauttest

Typ I Allergien werden häufig diagnostiziert über einen Pricktest (Nadelstiche) oder einem intradermalen Test als Folgemaßnahme eines negativen Pricktests.... Da ein Hauttest nur IgE vermittelte Reaktionen belegt, können sie dem Arzt keine Informationen über mögliche verzögerte Hypersensitivitätsreaktionen geben, die für die so breitgefächerten klinischen Symptome verantwortlich sind.

In-vitro Antikörper Messung

Die Messung von antigenspezifischen Antikörpern ist ein hilfreiches Instrument um Allergien zu erfassen, besonders gegen Nahrungsmittel. Eine Studie an kleinen Kindern hat gezeigt, daß 62,5% der Kinder mit Symptomen spezifische IgG Antikörper hatte und 22,9% IgE Antikörper während Kinder ohne Symptome einer Nahrungsmittelallergie weder das eine noch das andere aufwiesen (Quelle: IgE and IgG antibodies in children with food allergy. Rocznik Akad Med Białymst. 1995;40(3):468-73, Hofman T. Allergy Center, Poznan)

Report British Allergy Foundation

Dieser Report beinhaltet die unabhängige Auswertung der Untersuchungen der York Nutritional Laboratorys, durchgeführt von der Abteilung für Gesundheits-Studien der University of York, im Auftrag der British Allergy Foundation.

Professor Trevor A Sheldon MSc MSc DSC FMedSci.

Department of Health Studies

University of York

November 2000

Fragestellungen :

Überprüfung von erhöhten lebensmittelspezifischen IgG-Antikörpern im Serum von Patienten mit chronischen Symptomen.

YNL hat eine umfassende Studie/Untersuchung mit insgesamt 4200 Patienten durchgeführt, die getestet wurden und auf der Grundlage dieser Resultate eine Ernährungsumstellung durchführten. Die Abteilung für Gesundheits-Studien der Universität von York hatte den Auftrag von der British Allergy Foundation, eine Überprüfung des York Nutritional Laboratory vorzunehmen, um sicher zu stellen, dass die Untersuchungsergebnisse eine ganz genaue Wiedergabe der Erfahrungen der Personen sind, die den IgG-Test durchgeführt haben

Ergebnis:

Die Richtigkeit der Resultate der YNL Studie wurden bestätigt. Allgemein (auch in Bezug auf die Angelegenheit der Non-Responder) gibt die YNL Studie genau die Berichte über die Erfahrungen der Patienten wieder. Etwa 40% der Patienten, die sich dem IgG-Test mit anschließender Ernährungsumstellung unterzogen, haben eine Verbesserung der Symptome erfahren. Es konnte eine signifikante Verbindung zwischen strikter Befolgung der Diät und einer Verbesserung der Symptome bestätigt werden.

Relevanz für ImuPro 300:

Nahrungsmittel-Unverträglichkeiten kommen häufig vor. Die British Allergy Foundation geht davon aus, dass 45 Prozent der Bevölkerung in Europa und in den USA an einer Nahrungsmittel-Unverträglichkeit leiden.

Die Patienten profitieren von der Ernährungsumstellung auf Basis eines IgG-Tests. Besonders diejenigen, die die Ernährungsumstellung konsequent umsetzen, erfahren eine deutliche Verbesserung. Dabei ist die Verbesserung bei etwa 70 Prozent der Patienten über einen Zeitraum von einem Jahr konstant.

Ein weiteres Argument für die Durchführung von Tests auf nahrungsmittelspezifische IgG-Antikörper ist die Einsparung von Kosten. Zusätzlich zu den individuellen Gesundheits-Verbesserungen, können auch wichtige soziale Vorteile und Kostenersparnisse erzielt werden. Notwendig ist eine einmalige Investition. Sowohl für Patienten als auch für die Krankenkassen ist diese günstig, wenn man sie mit den Kosten vergleicht, die durch chronische Erkrankungen verursacht werden.

**The content of this document is to be embargoed until
Monday 22nd January 2001.**

The report contains an independent audit of the York Nutritional Laboratory survey, conducted by the Department of Health Studies, University of York, on behalf of the British Allergy Foundation.

**A copy of this report can be found on our website
www.allergy-testing.com**

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Audit of the York Nutritional Laboratory Survey

Background

Adverse reactions to food can cause a range of symptoms throughout the body. Some of these reactions are mediated through the immune system either by IgE (food allergy) or, more controversially, by IgG (food sensitivity). Over the last few years the York Nutritional Laboratory (YNL) have been conducting enzyme-linked immunosorbent assay (ELISA) tests on blood samples to detect raised food-specific IgG in the serum of people with one or more, usually chronic, symptoms.

YNL has conducted an extensive survey of people who have been tested and given dietary advice based on the results. The survey was distributed to a random sample of 4,200 individuals in the UK who had taken a 'pin prick' food sensitivity test between February 1998 and August 1999. A 42% response rate resulted in a total of 1761 questionnaires returned for analysis. Approximately 50% of all responders reported an improvement in symptoms at point 4 or 5 (relatively high improvement).

Whilst these results are encouraging, survey results are susceptible to several forms of bias including:

- 1) *Mistakes in data entry or data analysis*: Errors in transcribing data from the form to the computer.
- 2) *Responder bias*: Respondents may overstate improvements in their health because it is a company questionnaire.
- 3) *Non - response bias*: Those who do not respond to questionnaires are not representative of the general population and may be reluctant to report lack of benefit or lack of compliance with the diet. As a result, survey results which are based solely on those who respond are likely to be biased in favour of the interventions.

The Department of Health Studies, University of York was commissioned by the British Allergy Foundation to carry out an audit of the York Nutritional Laboratory in order to be sure that the survey results are an accurate reflection of the views of food sensitivity test users.

Methods

The audit comprised 3 parts:

1) *Accuracy of data entry and analysis.*

A random sample of 100 cases was checked against the original questionnaires to verify the accuracy of data inputting and coding. An error rate of more than 5% would be regarded as significant.

2) *Validity of responses of responders and estimate of non-responders*

Two letters were developed inviting previous responders and non-responders to the YNL survey to participate in the audit. These were sent to a random sample of 150 responders and 450 non-responders, all of who had been sent the YNL survey within the last year. 70 people refused to participate in the audit, 9 responders and 61 non-responders. 3 people had moved, 1 had died, 4 had not included their name in the contact details, 2 had not yet started to eliminate the foods indicated.

The telephone interviews resulted in data for 46 responders (just under the 50 intended) and 90 non-responders. In order to increase the number of non-responders in the survey a second list of non-responders was obtained from YNL and letters were sent to a further random sample of 300 clients. (Unfortunately a YNL administrative error led to certain people being included on this list who had already been approached, 7 let us know). This second mailing resulted in data for a further 24 telephone interviews, resulting in data for 114 non-responders, less than the 150 intended. Due to shortage of time, we did not attempt to increase further the sample of non-responders.

As slips were returned agreeing or refusing to participate in the audit, names were checked against the YNL survey database to establish whether individuals were previous responders or non-responders to the original YNL survey.

Two phone questionnaires were devised, one for responders and one for non-responders. Responders were asked a subset of the same questions as in the original survey, to see if they would now respond in the same way. In addition interviewees were asked if the reported benefits (if any) were still present. Non-responders were asked the same subset of questions from the original survey but with a few changes. The question about benefit from the dietary changes was changed to include a 'no benefit' score, and the question on time taken to feel benefit was modified to allow an answer of 'no benefit'

The return slips were distributed to the telephone interviewers in order to ensure both had an equal number of responders and non-responders. Telephone interviews took place at a time specified on the contact slip. Previous responder responses were coded and entered into an SPSS file alongside each interviewee's original responses. Previous non-responder's responses were coded and entered as new cases in an SPSS file.

3) Statistical analysis

The results from the re-surveying of responders were compared with original responses and the percentage showing a reduction in symptoms of 4 and 5 (a lot or quite a lot) estimated. This part of the study will enable us to report the proportion reporting relatively high benefit with a precision (95.0% confidence level) of approximately plus/minus 12% points and will allow us to test whether the results are significantly different from the YNL survey.

Data on the non-responders were analysed in the same way as the responders. We estimated the difference in response with the responders and then extrapolated this in order to estimate average results for all YNL users.

Results

1) *Accuracy of data entry and analysis.*

A random sample of 100 completed client questionnaires was requested from YNL for comparison with data recorded on their database. Data were imported from the SNAP database to an SPSS file.

143 questionnaires were received and the first 100 were checked. 12 of the questionnaires were duplicates and were omitted from the total.

Nine minor entry errors were found: one incorrect entry of presenting condition, two instances of omission of a second condition, one instance of omission of offending food, one instance of incorrect entry of client's name and sex, one omission of action following receipt of results, one misrecording of ease of dealing with laboratory ('difficult' recorded as 'easy'), one instance of misrecording of perceived benefit following modification of diet ('no benefit' recorded as 'no reply') and one instance of mis-recording of duration of condition.

The data entry was over 95% accurate in the checked sample.

2) *Validity of responses of responders and estimate of non-responders*

The distribution of results for the responders in this survey and the previous survey are shown below. 61% of the respondents to our phone survey said that they experienced, quite a lot or a lot of benefit, after changing their diet. This is the same percentage as in the postal survey (although the distribution between quite a lot and a lot differs slightly). The 95% confidence interval around this estimate is 47% to 74%. Thus this includes the 50% overall estimate for people reporting benefit in these two categories found in the YNL survey. Thus there is no statistically significant difference between the results of this phone survey and the larger postal survey ($p= 0.2$).

BENEFIT AS RECORDED IN PHONE SURVEY

	Frequency	Percent	Cumulative Percent
no benefit	6	13.0	13.0
low	4	8.7	21.7
a little	1	2.2	23.9
moderate	7	15.2	39.1
quite a lot	9	19.6	58.7
A lot	19	41.3	100.0
Total	46	100.0	

BENEFIT AS REPORTED IN ORIGINAL POSTAL SURVEY

	Frequency	Percent	Cumulative Percent
low	6	13.0	13.0
a little	2	4.3	17.4
moderate	6	13.0	30.4
quite a lot	11	23.9	54.3
A lot	17	37.0	91.3
no reply	4	8.7	100.0
Total	46	100.0	

Just over 70% reported that the benefits had been maintained since the test, over the last year, whilst around 20% said that symptom change had not been maintained or only partly over this period.

On the other hand, the results from the previous non-responders (shown below) are different. 36% of the 116 people responding to our phone survey reported improvements in the top two categories (95% CI: 28% to 45%). This is statistically significantly lower than those of the original YNL main survey result of 50% ($p=0.004$). In addition, 31% reported little or no benefit. Thus non-responders who replied to our phone survey have a lower reported rate of benefit following the test. The rate of reduction of symptoms reported here may be a slight over-estimate given that only around 15% of previous non-responders contacted were included in the survey; most did not reply to the letter or declined to be interviewed. Thus these new respondents may not be a representative sample of all non-respondents.

**PREVIOUS NON-RESPONDERS:
BENEFIT REPORTED IN PHONE SURVEY**

	Frequency	Percent	Cumulative Percent
no benefit	33	28.4	28.4
low	3	2.6	31.0
some	8	6.9	37.9
moderate	23	19.8	57.8
quite a lot	21	18.1	75.9
A lot	21	18.1	94.0
N/A	7	6.0	100.0
Total	116	100.0	

The response rate in the YNL main survey was 42%. Therefore, we can get a better overall estimate of the proportion of clients likely to have experienced a reduction in symptoms by calculating a weighted average of those who responded and did not respond and the corresponding rates of improvement.

$$\text{Average proportion with a lot or quite a lot of improvement in symptoms} = 0.42 \times 50\% + 0.58 \times 36\% = 42\%$$

Thus we can estimate that optimistically, around 40% of those having the YNL test may have experienced a lot or quite a lot of reduction in symptoms following the test.

3) Association between reported benefit and adherence to diet

In the YNL survey they found that whilst the proportion of clients showing relatively high benefit (quite a lot and a lot) was 50%, the proportion of those who stated that they rigorously adhered to the diet reporting substantial benefit was 58%. Only 33% not rigorously adhering to the diet reported relatively high benefit. We checked to see if this association was also true in the sample of people who previously were non-responders.

Of the 116 new respondents, 34 rigorously altered their diet of whom 47% reported quite a lot or a lot of improvement. Only 19% of those not rigorously altering their diet reported this level of benefit. Thus there is an association between stated adherence and reported benefit ($p=0.008$).

As above, we can get a better overall estimate of the proportion of clients *who rigorously altered their diet* who were likely to have experienced a substantial reduction in symptoms by calculating a weighted average of those who responded and did not respond and the corresponding rates of improvement.

Average proportion of those who rigorously altered diet reporting a lot or quite a lot of improvement in symptoms = $0.42 \times 58\% + 0.58 \times 47\% = 52\%$

Thus we can estimate that around 52% of those having the YNL test who rigorously altered their diet may have experienced a lot or quite a lot of reduction in symptoms following the test.

Conclusions

This audit has shown that:

- 1) Data entry from the YNL original survey was carried out at a high level of accuracy and so their results reflect the data collected.
- 2) The responses by YNL clients given in the postal survey are supported by the results of an independent phone survey. In particular, that around 50% of clients report a lot or quite a lot of reduction in symptoms after dietary change following the test results.
- 3) Around 70% of clients reported in the phone survey that these improvements have been maintained subsequently.
- 4) Non-responders experienced a lower rate of reduction in symptoms with 36% (95% CI: 28% to 45%) reporting a lot or quite a lot of reduction.
- 5) A weighted average of the proportion experiencing a lot or quite a lot of reduction in symptoms is 42%. This may however, be a slight over-estimate.
- 6) A higher proportion of those stating that they rigorously altered their diet reported a lot or quite a lot of symptom reduction – 58% in the responders and 47% in the previous non-responders (a weighted average of 52%).
- 7) The YNL survey form is flawed by not including a 'no benefit' option. Though this does not appear to affect the proportion of clients reporting 'a lot' or 'quite a lot' of benefit, it does distort the results lower down the scale. This should be amended in future surveys by the company.

This study has validated the results of the YNL survey. In general (taking into account the issue of non-responders) the YNL survey accurately reflects the reported experience of their clients.

It is important to note, however, that this does not mean that the reported improvement in symptoms is the result of or can be directly attributed to either the ELISA test or the dietary modification. Chronic symptoms do fluctuate, often randomly, and it is likely that on average, if people sought the food sensitivity test during a period of severe symptoms, then this would be followed by a reduction in symptoms (regression to the mean). In addition, there is the well-known phenomenon of the placebo effect, which may also account for some or all of the symptom reduction reported.

The association between rigorous adherence to dietary changes and reported benefit in both samples is a necessary finding if there is any causal association between the intervention and symptom reduction. However, it is

not proof of causality since one would expect a higher placebo effect amongst compliers. In addition, the causality could be working in the reverse direction those experiencing a reduction in symptoms (for whatever reason, including regression to the mean) may be more motivated to adhere to a new diet.

On the other hand, over 70% of clients reported that the benefits had persisted and given that many of these people came to YNL with long histories of chronic symptoms, this is important. Thus whilst the survey results cannot be taken as proof of the benefit of the ELISA test and/or subsequent dietary modification, they are sufficiently suggestive to justify further evaluation by means of properly conducted randomised controlled trials (RCTs). These could be undertaken with patients reporting those symptoms for which people most commonly sought food sensitivity testing – gastrointestinal (e.g. irritable bowel syndrome), dermatological (e.g. eczema), and neurological (e.g. migraine).

A further argument for rigorous evaluation is the potential cost-effectiveness of this health technology if such symptom reductions are indeed the direct result of the dietary changes based on the test results. In addition to the potential individual health benefits, significant societal benefits and cost reductions could possibly be achieved if this is effective because the test is a one off intervention and cheap for the NHS (though not for individuals) relative to the costs of these chronic conditions. In order to estimate the potential cost savings to the NHS we carried out a brief review of studies of the economic impact of these three common conditions. (See appendix).

In all of these three common conditions, a test and food elimination diet which costs no more than £200 would be cost saving to society within one year and cost saving to the NHS within 2-3 years assuming a 40% effectiveness sustained for these periods (i.e. 40 % of patients had a significant reduction in symptoms which resulted in a pattern of doctor consultation and work absence similar to people of the same age and sex without these symptoms). The cost-effectiveness of the test, if effective at these levels, would of course be significantly greater if the price was lower. Studies of cost effectiveness would also need to take into account the cost of any specialist nutritionist support to help maintain dietary change in patients who, unlike many of the YNL clients, were not self referred and might need more motivation and support.

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Appendix

Studies on the direct and indirect costs of relevant chronic conditions

Migraine

The economic burden of migraine falls predominantly on patients and their employers in the form of bedridden days and lost productivity as the condition predominantly affects people during their working lives (Hu et al, 1999; Solomon and Price, 1997; Lipton et al, 1997)). People with migraine require around 4-6 bed rest days per year (Solomon and Price, 1997; Roijen et al 1995). Medical expenses in the USA came to about \$100 per year per patient, however, the productivity loss per patient was greater at between \$700 to \$1,100 per year on average given the proportion who are employed. European studies showed an annual direct cost of around £50 million (1993 costs) in the UK or around 0.1% of NHS costs. This is likely to increase with better disease recognition and new more expensive treatments. Indirect costs of around £500 million have been estimated (Ferrari, 1998).

Irritable Bowel Syndrome

It has been conservatively estimated that IBS is the cause of 850,000 consultations in the UK per year costing nearly £50 million (1995 prices), including GP prescribing (Camilleri & Willims, 2000). Wells et al (1997) using market research estimated that total prescribing costs in 1995 for IBS were about £12.5 million a year, which with costs of GP visits and hospital services rises to around £46 million a year. US studies have shown that patients with IBS symptoms have double the medical costs of age and sex matched people without these symptoms (Talley et al, 1995). The development of new drugs for treating IBS is likely to raise these costs considerably in the near future. In addition there are considerable indirect costs due to nearly double the rate of absence from work than people without IBS (Donker et al, 1999). The direct cost of IBS has been estimated to account for between 0.1% and 0.5% of NHS expenditure, the indirect costs are as least as great, resulting in estimates of a total societal cost of IBS of around £250 per year.

Eczema

Atopic dermatitis is a common disease which affects over 10% of children and over 2% of the whole population in Western communities. Treatment costs in Australia have been estimated at between \$A1,000 and \$A6,000 per child per year (Kemp, 1999) with personal costs at around \$A800 per year depending on severity. In the 1995 a British study reported that the annual costs to the NHS exceeded £125m and personal costs due to days of lost salary etc were around £300m (Herd et al, 1996).

References

- Camilleri M, Williams DE. Economic Burden of irritable bowel syndrome. *Pharmaco-economics*, 2000;17:331-338.
- Donker, Foets M, Spreeuwenberg P. Patients with irritable bowel syndrome: health status and use of health care services. *Br J Gen Practice* 1999;49:787-792.
- Ferrari M D.. The economic burden of migraine to society. *Pharmacoeconomics*, 1998, 13(6), pp.667-676.
- Herd RM, Tidman MJ, Prescott RJ, Hunter JAA. The cost of atopic eczema *British Journal of Dermatology*, 1996, 135(1), pp. 20-23.
- Hu X H, Markson L E, Lipton R B, Stewart W F, Berger M L. Burden of migraine in the United States: disability and economic costs. *Archives of Internal Medicine* 1999; 159: 813-818.
- Kemp A S. Atopic eczema: its social and financial costs. *Journal of Paediatrics & Child Health* 1999; 35(3): 229-231.
- Lipton R B, Stewart W F, Von Korff M.. Burden of migraine: societal costs and therapeutic opportunities. *Neurology*, 1997, 48(3 Suppl 3), pp. S 4-S 9
- Solomon G D, Price K L. Burden of migraine: a review of its socioeconomic impact *PharmacoEconomics*, 1997, 11(Suppl. 1), pp.1-10
- Su J C, Kemp A S, Varigos G A, Nolan T M.. Atopic eczema: its impact on the family and financial cost. *Archives of Disease in Childhood*, 1997, 76(2), pp. 159-162
- Talley NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome *Gastroenterology*, 1995, 109(6), pp. 1736-1741
- van Roijen L, Essink-Bot M-L, Koopmanschap M A, Michel B C, Rutten F F.. Societal perspective on the burden of migraine in the Netherlands. *PharmacoEconomics*, 1995, 7(2), pp. 170-179.
- Wells N E J, Hahn B A, Whorwell P J. Clinical economics review: irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics* 1997; 11(6): 1019-1030.

Ovalbumin-specific immunoglobulin G and subclass responses through the first 5 years of life in relation to duration of egg sensitization and the development of asthma

Der Einfluss von Hühnereiweiß-spezifischem Immunglobulin G und Subklassen während der ersten 5 Lebensjahre im Verhältnis zur Dauer des Kontakts mit dem Allergen Ei und die Entwicklung von Asthma

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Zusammenfassung:

Hintergrund: Ei-Sensibilisierung, besonders anhaltende Sensibilisierung ist ein Risiko-Faktor für späteres Asthma. Dennoch ist wenig bekannt, welche Verantwortung IgG und dessen Subklassen in Bezug auf das Ausbrechen von Asthma haben.

Zielsetzung: Die Untersuchung, ob der Kontakt mit Hühner-Ovalbumin (OVA)-spezifischem IgG und dessen Subklassen in den ersten fünf Lebensjahren späteres Asthma begünstigt.

Testpersonen und Methoden: Der größte Teil der Testpersonen (n=46) stammt von atopischen Eltern ab. Diese Probanden sind vorausblickend auf die Entwicklung von Asthma ausgewertet worden. Die Ei-Sensibilisierung wurde klassifiziert in vorübergehend (ein Jahr positiver Ei Pricktest) und in anhaltend (mindestens 2 Jahre positiver Prick-Test). Die Konzentration im Blut von Ovalbumin-spezifischen IgG-Antikörpern sowie IgG 1 und IgG 4 wurde im Alter von 6 Monaten, 1 Jahr und 5 Jahren mittels ELISA-Verfahren festgestellt. Beim Neugeborenen wurde Blut aus der Nabelschnur entnommen.

Ergebnisse: Die Beweglichkeit der Ovalbumin spezifischen IgGs und IgG 1-Antikörper, nicht die der IgG4, differierte zwischen ei-sensibilisierten und nicht-ei-sensibilisierten (NES) Kindern. Nur die ständig ei-sensibilisierten Kinder hatten eine erhöhte OVA IgG und IgG1-Konzentration durch das erste Lebensjahr hindurch. Mit 1 Jahr wiesen sie bereits signifikant höhere OVA IgG und IgG1 Konzentrationen als nur vorübergehend oder gar nicht reagierende Kinder auf. Hohes OVA IgG1 kann mit einem späteren Ausbruch von Asthma zusammenhängen: Eine OVA IgG1-Konzentration, die größer als 14 500 U, bei einem Alter von 1 Lebensjahr ist, kann eine Anfälligkeit für Asthma zu 64 % und eine Ausprägung bis zu 74 % vorhersagen

Fazit: OVA IgG und dessen Subklassen sind verantwortlich für die Dauer einer Ei-Sensibilisierung Die Messgröße der OVA IgG1-Konzentration im Kindesalter könnte ein praktische Hilfe zur Identifizierung eines erhöhten Asthma-Risikos sein.

Ovalbumin-specific immunoglobulin G and subclass responses through the first 5 years of life in relation to duration of egg sensitization and the development of asthma

G. H. S. Vance^{*}, C. A. Thornton^{*}, T. N. Bryant[†], J. A. Warner^{*} and J. O. Warner^{*}

Summary

Background Egg sensitization, particularly persistent sensitization, is a risk factor for later asthma. However, little is known about accompanying IgG and subclass responses and how they might relate to asthmatic outcome.

Objective To characterize hen's egg ovalbumin (OVA) IgG and subclass responses through the first 5 years of life in relation to duration of egg sensitization and later asthma.

Subjects and methods The subjects ($n=46$) formed part of a larger cohort, born to atopic parents, who had been evaluated prospectively for the development of asthma. Egg sensitization was classified as transient (positive egg skin prick test at 1 year only) or persistent (positive skin test for at least 2 years). Plasma OVA IgG, IgG1 and IgG4 concentrations at birth (cord), 6 months, 1 and 5 years of age were measured by ELISA.

Results The kinetics of OVA IgG and IgG1 responses, but not IgG4, differed between egg sensitized and non-egg sensitized (NES) children. Only persistently sensitized children had a rise in OVA IgG1 concentration through the first year of life, and at 1 year of age they had significantly higher OVA IgG and IgG1 than either transiently sensitized or NES children. High OVA IgG1 was associated with later asthma: at 1 year of age, OVA IgG1 greater than 14 500 U predicted asthma with a sensitivity 64% and specificity 74%.

Conclusion OVA IgG and subclass responses relate to the duration of egg sensitization. Measurement of OVA IgG1 concentration in infancy might offer a useful adjunct to identify those at an increased risk of asthma.

Serum antibodies to dietary antigens in patients with HIV-1 infection

Serumantikörper gegen Nahrungsantigene bei Patienten mit HIV-1 Infektion

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1) Diarrhoe ist eine bekannte Komplikation einer HIV-1 Infektion. Bei einem beträchtlichem Teil der Patienten, besonders in einem frühen Stadium der Krankheit, bleibt die Ursache der Diarrhoe trotz intensiver Untersuchungen unklar.

Erhöhte Werte an Serumantikörpern gegen Nahrungsproteine sind bei HIV infizierten Kindern beschrieben worden, ganz ähnlich wie bei Patienten mit nicht IgE-vermittelter gastrointestinaler Lebensmittelunverträglichkeit, Zöliakie oder Reizdarm. Es wird vermutet, diese Anomalien resultieren aus einer erhöhten Darmpermeabilität, die zu einer verstärkten Aufnahme von Nahrungsantigenen und einer anomalen lymphoiden IgG Reaktion bei diesen Patienten führt.

Erhöhte Darmpermeabilität und erhöhte IgG Werte in Schleimhautsekreten wurden auch bei Patienten, die mit HIV-1 infiziert sind, gefunden. Da anormale Immunität gegen Nahrungsantigene zur Pathogenese der Diarrhoe beiträgt, untersuchten wir Serumantikörper auf Nahrungsproteine bei HIV-1 infizierten Patienten mit und ohne Diarrhoe.

2) Unsere Ergebnisse zeigen eine Erhöhung an Serumantikörpern gegen 4 übliche Nahrungsproteinen bei HIV infizierten Patienten. Dies jedoch nicht aufgrund einer unspezifischen polyklonalen B-Zellaktivierung, da die Immunoglobulinwerte immer noch erhöht waren, als die Antikörperwerte hinsichtlich der Gesamtimmunoglobulinkonzentration korrigiert wurden. Das Entstehen der Antikörper gegen Nahrungsproteine im Serum deutet auf einen anormalen Zugang der Antigene zum lymphoiden Immunsystem, wahrscheinlich durch eine geschädigte Schutzfunktion des Epithels. Obwohl wir nicht speziell die lokale humorale Immunität untersuchten, zeigen die erhöhte lymphoide IgG Produktion bei HIV infizierten Patienten und die hohen IgG Werte in duodenalen Sekreten bei HIV infizierten Patienten, die beträchtliche Absonderung von Serumantikörpern in den Darm. Im Gegensatz der durch sekretorisches Immunoglobulin A vermittelten Immunexklusion, bilden IgG Antikörper gegen Nahrungsproteine Immunkomplexe und aktivieren das Komplementsystem, wenn ihr jeweiliges Antigen in der Schleimhaut vorhanden ist.

Die folgende Schleimhautentzündung, die oft im Darm von HIV Patienten beobachtet wird, kann nicht nur einen Teufelskreis auslösen, der unwiederbringlich die Schutzfunktion des Epithels schädigt, sondern auch die Pathogenese der Diarrhoe fördert. Die erhöhte Immunität gegen Nahrungsproteine bei HIV Infektion die durch unsere Studie belegt wird, läßt vermuten, daß HIV infizierte Patienten von einem ernährungstechnischen Eingriff profitieren. Dies sollte hauptsächlich bei HIV infizierten Patienten mit hohen Titern an Serumantikörpern gegen Nahrungsantigenen, untersucht werden.

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Serum antibodies to dietary antigens in patients with HIV-1 infection

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Diarrhoea is a common complication of HIV-1 infection [1], but in a considerable proportion of patients, especially in earlier stages of the disease, the cause of diarrhoea remains unclear despite extensive investigation [2]. Increased levels of serum antibodies against food proteins have been described in HIV-infected children [3], similar to patients with non-IgE-mediated gastrointestinal food hypersensitivity [4], coeliac disease [5], or chronic inflammatory bowel disease [6]. These abnormalities are thought to result from increased gut permeability leading to increased uptake of dietary antigens and an aberrant mucosal IgG response in these patients [7]. Increased intestinal permeability [8] and an increase of IgG in mucosal secretions [9] have also been found in patients infected with HIV-1. Since abnormal immunity to dietary antigens may contribute to the pathogenesis of diarrhoea, we investigated serum antibodies to food proteins in HIV-1-infected patients with and without diarrhoea.

Sera from 70 consecutive HIV-infected patients (65 men, five women) attending the HIV outpatient clinic were studied. Forty-three patients had AIDS. The median age was 44 years (range, 29-64 years) and the median CD4 T-cell count was $65 \times 10^6/l$ (range, $4-987 \times 10^6/l$). Eleven HIV-infected patients had diarrhoea. In six of these patients an enteric pathogen was found (*Salmonella* sp. and microsporidia infection each in two patients, *Mycobacterium avium* complex and *Isospora belli* infection in one patient, and one patient with microsporidia had additional coronavirus infection). Blood samples from 20 healthy controls (15 men, five women; mean age, 55.5 years; range, 18-73 years) not at risk for HIV infection and without evidence for immune defect served as controls.

Serum IgG, IgA and IgM titres against the dietary antigens β -lactoglobulin, α -lactalbumin, ovalbumin, and soy protein, and the non-dietary antigen tetanus toxoid were measured by enzyme-linked immunosorbent assay. Because serum immunoglobulins are unspecifically increased in HIV-infected patients compared with controls, antibody titres were corrected for serum immunoglobulin concentrations as measured by single radial immunodiffusion. Serum IgG, IgA and IgM antibody levels against all food proteins (except anti- β -lactoglobulin IgM) were significantly higher in HIV-infected patients than in controls. In contrast, IgG antibody titres against tetanus toxoid were decreased in HIV-infected patients compared with controls (each $P < 0.05$; Fig. 1). No differences were found for IgA and IgM antibody titres against tetanus toxoid. When antibody titres were expressed in relation to the respective serum immunoglobulin concentration, IgG antibody levels against all food proteins tested were still increased (each $P < 0.01$), although IgG against tetanus toxoid was decreased in HIV-infected patients compared with controls. Relative IgA and IgM titres against the tested proteins were similar in HIV-infected patients and controls. No differences were found between HIV-infected patients with and without AIDS. Median antibody titres for IgG, IgA, and IgM against all tested food proteins were higher in HIV-infected patients with diarrhoea than in patients who had no diarrhoea, but a significant difference was found only for IgG antibodies against ovalbumin ($P < 0.05$).

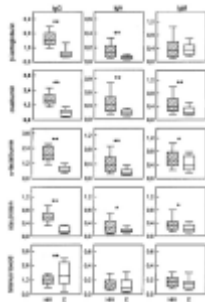


Fig. 1. Serum IgG, IgA and IgM antibodies to the dietary proteins β -lactoglobulin, ovalbumin, α -lactalbumin, soy protein and the non-dietary protein tetanus toxoid. Antibodies were measured by enzyme-linked immunosorbent assay in 70 HIV-infected patients, of whom 43 had AIDS, and in 20 healthy controls. IgG, IgA and IgM antibody levels against all food proteins (except IgM anti- β -lactoglobulin antibodies), but not against tetanus toxoid, were significantly higher in HIV-infected patients than in controls (C). * $P < 0.05$, compared with controls; ** $P < 0.01$, compared with controls.

Our results show an increase of serum antibodies against four common food proteins in HIV-infected patients. This is not due to unspecific polyclonal B-cell activation because immunoglobulin levels were still increased when antibody levels were corrected for total immunoglobulin concentration. In addition, no increase of serum antibodies against the non-dietary protein tetanus toxoid was observed. The appearance of antibodies to food proteins in serum indicates an abnormal access of these antigens to the mucosal immune system, probably due to an impaired epithelial barrier function [8]. Although we did not specifically investigate local humoral immunity, the increased mucosal production of IgG in HIV-infected patients [10] and the high IgG levels in duodenal secretions of HIV-infected patients [11] indicate considerable transudation of serum antibodies into the gut. In contrast to the immune exclusion mediated by secretory IgA, IgG antibodies to food proteins will form immune complexes if their respective antigens are present in the mucosa and will activate complement [12]. The resulting mucosal inflammation that is frequently observed in the intestine of HIV-infected patients [13] may not only establish a vicious circle perpetuating impairment of epithelial barrier function but could also contribute to the pathogenesis of diarrhoea. The increased immunity to food proteins in HIV infection shown in our study suggests that HIV-infected patients might benefit from nutritional interventions. This should be tested primarily in HIV-infected patients with high titres of serum antibodies to dietary antigens.

References

- Ullrich R, Heise W, Bergs C, L'age M, Riecken EO, Zeitz M: **Gastrointestinal symptoms in patients infected with human immunodeficiency virus: relevance of infective agents isolated from gastrointestinal tract.** *Gut* 1992, **33**:1080-1084.
[Medline Link] [Context Link]
- Wilcox M, Schwartz DA, Cotsonis G, Thompson III SE: **Chronic unexplained diarrhea in human immunodeficiency virus infection: determination of the best diagnostic approach.** *Gastroenterology* 1996, **110**:30-37.
[Medline Link] [Context Link]
- Quesnel A, Moja PH, Blanche S, Griscelli C, Genin C: **Early impairment of gut mucosal immunity in HIV-1-infected children.** *Clin Exp Immunol* 1994, **97**:380-385.
[Medline Link] [Context Link]
- Pearson JR, Kingston D, Shiner M: **Antibody production to milk proteins in the jejunal mucosa of children with cow's milk protein intolerance.** *Pediatr Res* 1983, **17**:406-412.
[Medline Link] [Context Link]
- Hvatum M, Brandtzaeg P: **Serum IgG subclass antibodies to a variety of food antigens in patients with coeliac disease.** *Gut* 1992, **33**:632-638.
[Medline Link] [Context Link]
- Knoflauch P, Park BH, Cunningham R, Weiser MM, Albin B: **Serum antibodies to cow's milk proteins in ulcerative colitis and Crohn's disease.** *Gastroenterology* 1987, **92**:479-485.
[Medline Link] [Context Link]
- Husby S, Foged N, Host A, Svehag SE: **Passage of dietary antigens into the blood of children with coeliac disease. Quantification and size distribution of absorbed antigens.** *Gut* 1987, **28**:1062-1072.
[Medline Link] [Context Link]
- Stockmann M, Fromm M, Schmitz H, Schmidt W, Riecken E-O, Schulzke J-D: **Duodenal biopsies of HIV-infected patients with diarrhoea exhibit epithelial barrier defects but no active secretion.** *AIDS* 1998, **12**:43-51.
[Medline Link] [Fulltext Link] [CrossRef] [Context Link]
- Schneider T, Zippel T, Schmidt W, et al.: **Abnormal predominance of IgG in HIV-specific antibodies produced by short-term cultured duodenal biopsy specimens from HIV-infected patients.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1998, **16**:333-339.
[Medline Link] [Fulltext Link] [Context Link]
- Schneider T, Zippel T, Schmidt W, et al.: **Increased immunoglobulin G production by short term cultured duodenal biopsy samples from HIV infected patients.** *Gut* 1998, **42**:357-361.
[Medline Link] [Context Link]

11. Janoff ED, Jackson S, Wahl SM, Thomas K, Peterman JH, Smith PD: **Intestinal mucosal immunoglobulins during human immunodeficiency virus type 1 infection.** *J Infect Dis* 1994, **170**:299-307.

[\[Medline Link\]](#) [\[Context Link\]](#)

12. Halstensen TS, Das KM, Bandtzaeg P: **Epithelial deposits of immunoglobulin G1 and activated complement colocalise with the Mr 40 kD putative autoantigen in ulcerative colitis.** *Gut* 1993, **34**:650-657.

[\[Medline Link\]](#) [\[Context Link\]](#)

13. Kotler DP, Reka S, Cayton F: **Intestinal mucosal inflammation associated with human immunodeficiency virus infection.** *Dig Dis Sci* 1993, **38**:1119-1127.

[\[Context Link\]](#)

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Behandlung von verzögerter Nahrungsmittelallergie basierend auf spezifischer IgG RAST Messung

Dixon 2000 – American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc.

1) Diese vorläufige, beschreibende Studie nach ausführlicher klinischer Erfahrung zeigt spezifische IgG Nahrungsmittel-Rast Messungen, die bei 114 aufeinanderfolgenden Patienten mit stark positiver Krankheitsgeschichte bei verzögerter Nahrungsmittelallergie durchgeführt wurde. Elimination der positiven Nahrungsmittel war das einzige Mittel der Behandlung. Die Symptome, die zum Einsatz des Tests geführt haben, sind aufgeführt und die Methode der Aufarbeitung wurde geprüft. Das Gesamtergebnis zeigt eine 71%ige Erfolgsrate bei allen Symptomen mit einer Mindestverbesserung von 75%. Von besonderem Interesse war die Gruppe der Patienten mit chronischen, zur Erwerbsunfähigkeit führenden Symptomen, die auf andere intensive Behandlungsmethoden, nicht angesprochen hat. Während 70% (aller Patienten) eine Verbesserung von 75% erreicht haben, erzielten 20% dieser Gruppe eine 100% Linderung.

2) ...Ziel der Studie war es zu ermitteln, ob die Symptome der Patienten signifikant bessern würden bei einfacher Elimination von positiven Nahrungsmitteln und um zu entscheiden, ob weitere wissenschaftliche Studien angemessen sind

3) Methode

.... Patienten mit Nasalpolypen and Asthma stehen unter dem Verdacht der sofortigen und verzögerten Hypersensibilität. Sowohl Patienten mit Kopfschmerzen, Migräne und Sinusschmerzen, als auch Patienten mit Menierers Syndrom und solche mit Haltungsschwindel stehen im Verdacht eine verzögerte Nahrungsmittelallergie zu haben.

Wenn die Krankheitsgeschichte Nahrungsmittelallergie vermuten liess, wurden Patienten gebeten, eine zweiwöchiges Diätgebuch zu führen.

4) Table 3 zeigt die Verbesserung nach Elimination:

Symptom	No. Reported	>75% improvement	100% improvement
Diarrhoe	20	90%	45%
Krämpfe	13	84%	38%
Husten	22	77%	36%
Kopfschmerzen zervikal	15	73%	20%
Übelkeit	17	70%	24%
Aufstossen	13	69%	15%
Heiserkeit	20	65%	15%
Räuspern	29	65%	28%
Nasenlaufen	36	63%	17%
Ohrenverstopfung	17	64%	29%
Nasenverstopfung	40	62%	20%
Asthma	13	61%	15%
Sinusschmerzen	33	60%	24%
Blähung	26	57%	12%
Augenjucken	19	57%	26%
Niesen	20	55%	20%
Ohrensausen	11	54%	27%
Feuchte Augen	15	53%	6%
Müdigkeit nach dem Essen	31	51%	23%
Schwindel	24	50%	21%
Ohrengeräusch	18	50%	5%
Hautausschlag	12	50%	8%
chronische Müdigkeit	25	48%	0%
Migräne Kopfschmerzen	19	47%	16%
Hautjucken	14	35%	7%

Ein Symptom ist nicht aufgeführt, wenn es weniger als 10 mal vorkam.

5) Schlussfolgerung

Spezifische IgG für häufig zu sich genommene Nahrungsmittel können in Erwägung gezogen werden, wenn chronische Symptome für Nahrungsmittelallergien vorhanden und konservative Behandlungsverfahren nicht erfolgreich sind. Verzögerte Nahrungsmittelallergien entstehen häufig bei atopischen Patienten, die auch an Inhalationsallergien leiden...

Die Elimination von positiven Nahrungsmitteln ist erfolgreich zur signifikanten Reduzierung von Symptomen. 25% der Untersuchten hatten arbeitsunfähig machende Symptome und erreichten eine 80%ige oder stärkere Verbesserung. Wobei 20% davon eine 100%ige Verbesserung erzielten und 50% eine 90%ige Linderung erreichten. Von den 80 untersuchten Patienten, erzielten 71% eine 75%ige oder stärkere Verbesserung...

Nahrungsmittel-Unverträglichkeiten

Die Bedeutung von IgG – Antikörpern gegen Nahrungsmittel in Zusammenhang mit chronischen Beschwerden

Kein anderes Thema wird derzeit in der Presse so konträr diskutiert wie der Sinn einer IgG-Diagnostik auf Nahrungsmittelunverträglichkeiten. Während die Verbände der Allergologen von Betrug ausgehen, sehen Anbieter, aber auch zahlreiche Anwender dieser Testverfahren eine Chance, Nahrungsmittel als Entzündungsauslöser für chronische Beschwerden zu erkennen.

Prinzip einer auf IgG-basierenden Ernährungstherapie

Mittels ELISA Technologie wird das Serum von Patienten auf spezifische IgG-Antikörper gegen eine Vielzahl von Nahrungsmitteln getestet. Abhängig von der Reaktionsstärke sollen anschließend „positiv“ getestete Nahrungsmittel über einen längeren Zeitraum konsequent gemieden werden. Nach ca. 8 Wochen werden Nahrungsmittel einzeln wieder in die Ernährung eingeführt. Dabei wird beobachtet, ob durch den Verzehr dieser Nahrungsmittel wieder eine Verschlechterung der persönlichen Beschwerden eintritt oder nicht. Davon abhängig können Nahrungsmittel anschließend wieder in einer Rotationsernährung konsumiert werden.

Die Argumente der Kritiker

Von Kritikern des Verfahrens wird immer wieder dargestellt, dass man über IgG-Diagnostik keine Nahrungsmittel-Unverträglichkeiten nachweisen könne, dass IgG-Antikörper lediglich widerspiegeln, was man vorher gegessen hat und man diese auch bei Gesunden vorfinde, so dass sie keine medizinische Relevanz hätten.

Die Position der Befürworter

Es ist nicht natürlich, dass der Organismus IgG-Antikörper gegen Nahrungsmittel bildet. Dabei handelt es sich um Typ-3 Reaktionen, die unter die Kategorie der Nahrungsmittelallergien fallen. Diese haben eine Relevanz, wie in ersten Studien nachgewiesen werden konnte und wie aus dem immunologischen Verständnis heraus deutlich wird.

Die Nomenklatur für Nahrungsmittel-Unverträglichkeiten

Unverträglichkeitsreaktionen auf Nahrungsmittel können durch verschiedene Reaktionsmechanismen ausgelöst werden. Dabei unterscheidet man zwischen immunologischen und nichtimmunologischen Vorgängen.

Echte Allergien sind per definitionem immunologisch bedingt. Nach erfolgter Sensibilisierung kommt es bei erneutem Kontakt mit dem Nahrungsmittelallergen zu pathologischen Reaktionen.

Man unterscheidet bei Nahrungsmittelallergien zwischen verschiedenen Reaktionstypen.

Die bekannteste ist die Typ-1 Reaktion, d. h. IgE-vermittelt. Die Symptome treten innerhalb von ca. 30 Minuten nach Allergenkontakt (Sofort-Typ-Reaktion) auf.

Daneben gibt es die Reaktionstypen 2 – 4. Dabei lassen sich IgG-Antikörper, aber auch IgA- und IgM-Antikörper nachweisen.

Die Latenzzeit bis zum Auftreten der Symptome beträgt Stunden bis Tage, deshalb auch der häufig verwendete Begriff einer „verzögerten Allergie“. Die lange Latenzzeit erschwert die Erkennung von Nahrungsmittel-Allergien des Typ-3. Ein Zusammenhang zwischen Beschwerden und dem Verzehr von bestimmten Nahrungsmitteln ist nicht auf den ersten Blick zu erkennen. Diese Tatsache lässt der Diagnostik der Typ-3 Reaktionen eine besondere Bedeutung zukommen.

IgG-Diagnostik auf Nahrungsmittel-Allergien vom Typ3

Mit der IgG-Diagnostik bei Nahrungsmittel-Unverträglichkeiten weist man keine klassische Allergie des Typ 1 nach, vielmehr liegt der Focus auf der Typ-3 Reaktion. Die Diagnostik spielt daher auch keine Rolle bei allergologischen Fragestellungen, sondern bei Erkrankungen, die auf einen chronischen Entzündungsprozess zurückzuführen sind.

Neueste Studien zeigen, dass Nahrungsmittelallergien vom Typ-3 häufig sind. Eine Studie, die 1537 Probanden beinhaltet, zeigt, dass 20,8 % der erwachsenen Bevölkerung eine Lebensmittelüberempfindlichkeit hat (Schäfer et al., 2001)

Die British Allergy Foundation geht davon aus, dass 45% der Bevölkerung in Europa und in den USA an einer Lebensmittel-Intoleranz oder -Überempfindlichkeit leidet. Die Überempfindlichkeitsreaktionen sind die häufigste Ursache von chronischen Erkrankungen in Industrieländern. Mindestens ein Drittel der Bevölkerung ist hiervon betroffen.(Pascual et al., 2000)

Relevanz von IgG-Antikörpern

Zur Aufklärung der Relevanz von spezifischen IgG-Antikörpern muss man sich mit zwei Fragen beschäftigen.

Ist es natürlich, dass der Organismus Antikörper gegen Nahrungsmittel bildet? Sind Antikörper nachweisbar, welche Rolle spielen diese Antikörper in Zusammenhang mit chronischen Beschwerden?

Zur Frage, ob der Organismus normalerweise überhaupt Antikörper gegen Nahrungsmittel bildet: Der Dünndarm und das lymphatische Gewebe des Dünndarms

stellen die wichtigsten Kompartimente des menschlichen Immunsystems dar und sind ständig gegenüber Antigenen exponiert. Diese Lymphozytenpopulation besitzt Eigenschaften, die sie eindeutig von Zellen aus anderen peripheren Kompartimenten des Immunsystems unterscheiden. Ihre zytotoxische Aktivität ist schwach, dagegen ist ihre suppressive Aktivität sehr ausgeprägt (Camerini et al., 1993 ; Sydora et al., 1993; Chehade et al., 2004). Ihre Aufgabe besteht darin, die Antigene, die von Nutzen sind, wie Lebensmittelantigene und die physiologische Darmflora, von potentiell darmpathogenen Keimen und Antigenen zu differenzieren. Deshalb sind sie geprägt von einer hohen Lebensmitteltoleranz, also einer "Nichtantwort" der Lymphozyten gegenüber Lebensmittelantigenen.

Deshalb werden höchstwahrscheinlich IgG-Antikörper gegen Lebensmittel im Normalfall nicht gebildet und sind nur dann nachweisbar, wenn eine Unverträglichkeit, in Folge einer vorübergehenden oder persistierenden erhöhten Darmpermeabilität, besteht.

Ein ganz anderer Aspekt beantwortet diese Frage zusätzlich:

Es ist keine normale Reaktion des Organismus, gegen Alles Antikörper zu produzieren, womit er Kontakt hat. Wäre das der Fall, wären wir nicht überlebensfähig. In der absoluten Mehrzahl der Fälle verfügt der Organismus über eine ausgeprägte Toleranz. Nur in Ausnahmefällen werden beim Kontakt mit sich nicht vermehrfähigen Antigenen Antikörper gebildet. In diesem Kontext ist also das Vorliegen von IgG-Antikörpern nicht nur Zeichen eines Kontakts mit einem Antigen, sondern ein Zeichen für eine **anormale Abwehrreaktion** des Körpers.

Wäre dem nicht so, müssten alle Menschen in Deutschland Antikörper gegen Hefe, Milch, Eier, Weizen, Gluten usw. haben. Deutschland wäre eine Nation von Morbus Crohn-Kranken (Antikörper gegen Hefe ASCA gelten als Bestätigungstest) und Zöliakiekranken (Gluten). Dem ist natürlich nicht so.

Zur zweiten Frage: Welche Funktion übernehmen IgG-Antikörper im Organismus?

Aus klassischer infektionsserologischer Sicht ist die Präsenz spezifischer Antikörper ein Zeichen einer vorher abgelaufenen Immunreaktion. Das heißt, der Organismus hat ein bestimmtes Antigen erkannt und Antikörper dagegen gebildet. Tritt das Antigen erneut in den Organismus ein, wird es sofort von den Antikörpern gebunden und neutralisiert. Handelt es sich dabei - und das ist in der Regel so - um IgG1 oder IgG3 Antikörper, wird eine Entzündungsreaktion eingeleitet, die zur Zerstörung des Komplexes führt.

Ist der Antikörper gegen Infektionskeime gerichtet, ist diese Reaktion absolut erwünscht - schützt sie doch den Organismus vor der Verbreitung des Infektionskeimes. Man bezeichnet das als Immunisierung.

Antikörper werden aber nicht nur gegen Infektionskeime gebildet, sondern auch gegen Strukturen (Proteine, Peptide, Zellinhaltsstoffe) die sich nicht vermehren können und a priori nicht schädlich sind. Ja, es werden sogar Antikörper gegen körpereigene Strukturen gebildet, die dann als Autoimmunantikörper bezeichnet und für die ent-

sprechenden Autoimmunkrankheiten verantwortlich gemacht werden oder aber als Marker hierfür dienen.

Das Vorliegen entsprechender Antikörper belegt eine Abwehr des Organismus gegen diese Nahrungsmittel und bedeutet eine Entzündungsreaktion nach deren Verzehr.

Im Gegensatz zu einer Immunisierung etwa gegen Hepatitis-Viren, denen man sehr selten im Leben begegnet und wo daher eine Immunreaktion ohne bleibende Schäden abläuft, kann der regelmäßige Kontakt zu Nahrungsmitteln, gegen die Antikörper vorliegen, zu einer Überladung von Immunkomplexen führen, die nicht mehr sofort von den Fresszellen zerstört werden können. Diese werden dann in den Blutkreislauf eintreten und sich - mit Hilfe vom Komplementsystem gebildeten Adhäsionsmolekülen - im Gewebe ablagern und dort von Fresszellen zerstört werden. Dabei kommt es zu lokalen Entzündungsprozessen und das umliegende Gewebe kann zerstört werden. Welches Gewebe oder Organ betroffen wird, hängt von der genetischen Veranlagung, vorheriger Traumatisierung und möglicherweise von der Art des Nahrungsmittels ab.

Bestehen bereits chronische Entzündungen oder Autoimmunkrankheiten anderer Genese, kann der Genuss von Nahrungsmitteln, gegen die Antikörper nachweisbar sind, diesen Prozess durch Ablagerung von Immunkomplexen verstärken und unterhalten. Entsprechende Erfolge bei Meidung dieser Nahrungsmittel konnten insbesondere bei Autoimmunthyreoiditis, aber auch bei anderen Autoimmunkrankheiten durch Abfall der entsprechenden Autoantikörper nachgewiesen werden

Erfahrungen und neueste Ergebnisse einer auf IgG basierenden Ernährungsumstellung

In einer prospektiven multizentrischen Anwendungsbeobachtung zu Wirksamkeit und Akzeptanz einer auf IgG basierenden Ernährungsumstellung bei Gewichtsproblemen und/oder anderen Krankheitsbildern, die auf eine Nahrungsmittelunverträglichkeit hinweisen, wurden folgende Ergebnisse ermittelt;

- 166 Ärzte hatten bis August 2004 die Behandlung von 538 Patienten in auswertbarer Form dokumentiert
- Bei allen vorgegebenen Begleitsymptomen (z.B. Migräne, Völlegefühl, Gelenkbeschwerden und Erschöpfung) konnten hohe Besserungsraten zwischen 61% und 81% ermittelt werden. Bei den konsequenten Patienten lagen die Besserungsraten z.T. deutlich höher
- Bei 77% der Patienten hatte sich das Allgemeinbefinden verbessert.
- (konsequente Patienten 87%)
- Wirksamkeitsbeurteilung „sehr gut“ oder „gut“: 70% der Patienten
- (konsequente Patienten: 84%), 66% der Ärzte.
- 87% aller Patienten (92% der konsequenten Patienten) und 86% der Ärzte würden die Methode weiterempfehlen

Erste anerkannte Studien sind bzw. werden veröffentlicht

Im Jahre 2004 wurden die Ergebnisse einer randomisierten Double-blind-placebo-kontrollierten klinischen Studie in der Fachzeitschrift „Gut“ publiziert. Die Ergebnisse dieser Studie zeigen, dass bei Patienten mit Reizdarm eine Ausschlussdiät basierend auf dem individuellen Unverträglichkeitsprofil (IgG-Antikörper gegen Lebensmittel) zu besseren Ergebnissen führte als bei Kontrollpatienten mit einer Diät, die ihre Unverträglichkeiten nicht widerspiegelte. (Atkinson et al., 2004) Die Unterschiede zwischen den behandelten Patienten und der Kontrollgruppe waren statistisch signifikant.

Weitere Studien sind zur Veröffentlichung eingereicht und zeigen überaus interessante Ergebnisse. So gibt es erste Hinweise, dass abhängig von den Symptomen ganz spezifische Reaktionsmuster auftauchen. Weiterhin gibt es signifikante Unterschiede zwischen Gesunden und Symptomträgern im Hinblick auf Reaktionsanzahl und -stärke.

All diese Ergebnisse in Verbindung mit dem immunologischen Hintergrund zeigen, dass einer gezielten IgG-Diagnostik eine große Bedeutung zukommt.

Ein weiteres Beispiel für die klinische Relevanz von IgG-Antikörpern gegen Nahrungsmittel ist die serologische Diagnose und Verlaufskontrolle der Glutenunverträglichkeit. Diese entzündlich bedingte Erkrankung bleibt so lange bestehen, wie Gliadin in der Ernährung enthalten ist. Spezifische IgG Antikörper gegen Gliadin sind direkt an dem durch die Immunreaktion entstehenden Gewebsschaden im Dünndarm beteiligt. (Collin et al. 2002)

Warum wird die IgG-Diagnostik von Seiten der Allergologen so negativ bewertet?

Eine unglücklich gewählte Nomenklatur könnte die Ursache für viele Missverständnisse sein. Die Verwendung des Begriffes „Allergie“ für verschiedene Reaktionstypen mit ganz unterschiedlichen Krankheitsbildern sorgt für Verwirrung.

Wenn Allergologen von Allergie sprechen, meinen sie die Typ-1 Reaktion, die durch IgE-Antikörper vermittelt ist. Da sie sich hauptsächlich mit diesem Thema auseinandersetzen, haben sie möglicherweise eine etwas eingeschränkte Betrachtungsweise.

Aus ihrer Sicht ist es besser, IgG-Antikörper (insbesondere IgG-4) zu bilden als IgE-Antikörper, die zu einer anaphylaktischen Reaktion des Organismus führen können. Es ist richtig, dass IgG-Antikörper kein Indiz für eine Allergie, besonders vom Typ-1 sind.

IgG-4 Antikörper sind dagegen ein Hinweis auf eine allergische Reaktion, die der Organismus bewältigen konnte.

Es ist also absolut wichtig, zwischen einer Typ1-Allergie und einer Immunreaktion vom verzögerten Typ zu unterscheiden. Nicht nur die implizierten Antikörper sind un-

terschiedlich, auch der dahinter ablaufende Mechanismus unterscheidet sich erheblich.

Ist die IgG-4 Reaktion bei der Typ-1 Allergie ohne Aktivierung der Entzündungskaskade harmlos, ja geradezu erwünscht, ist die Reaktion anderer IgG-Klassen **immer** mit einer Entzündungsreaktion verbunden.

Beurteilung

Liegen Erkrankungen vor, die durch einen chronischen Entzündungsprozess verursacht werden, können Nahrungsmittel daran beteiligt sein. Insbesondere dann, wenn man keine anderen Entzündungsauslöser gefunden hat.

Damit kann die IgG-Diagnostik auf Nahrungsmittel das leisten, was Diagnostik im Allgemeinen zu leisten im Stande ist. Nämlich einen Hinweis liefern, ob der Verdacht für das Vorliegen einer Erkrankung durch eine ausführliche Anamnese diagnostisch bestätigt wird.

Letztendlich kann nur die anschließende Ernährungsumstellung den Beweis erbringen, ob die vermuteten Zusammenhänge wirklich bestehen.

Die positiven Erfahrungen mit der Ernährungsumstellung, verbunden mit dem häufig vorliegenden hohen Leidensdruck bei den Patienten, rechtfertigen eindeutig die Untersuchung auf unverträgliche Nahrungsmittel.

Standardwerk Lehrbuch zur Immunologie

„Food Allergy and Intolerance“

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Immunologische Charakteristika von Nahrungsmittel-Allergien

...“Alle vier Basistypen der Überempfindlichkeit, d.h. Typ I – IV, spielen höchstwahrscheinlich bei Nahrungsmittelallergien eine Rolle und können zum Auftreten von klinischen Symptomen führen. Die Reaktion vom Soforttyp (Typ I) und der verzögerte Reaktionstyp (Typ III) sind die meist erforschten und dokumentierten Reaktionen. In jüngster Zeit wurde die durch Nahrungsmittel ausgelöste verzögerte Reaktion vom Typ IV bei Patienten mit Rhinitis, Bronchialasthma, Atopischem Ekzem, Urticaria, Migräne u. a. nachgewiesen (Fig.35.1)“...

CMA und Intoleranz

...“Reaktionen, die durch große Mengen Kuhmilch ausgelöst werden, gelten als eine Erscheinungsform der Unverträglichkeit. Wie die Milch die Unverträglichkeitsreaktion auslöst, ist nicht bekannt, aber es handelt sich selbstverständlich um eine biologische Reaktion, da sie laut Zelltests oft mit Volumenänderungen der weißen Blutzellen einhergehen.

Aus klinischen Gesichtspunkten sind Unverträglichkeiten von wesentlich größerer Bedeutung und Häufigkeit, als klassische Nahrungsmittelallergien. Dennoch behandeln viele Allergologen Patienten mit Unverträglichkeiten nicht, mit dem Vorwand, es handele sich hierbei nicht um eine Allergie. Gleichzeitig erstaunt es, das trotz der hohen Informationsdichte von Seiten derer, die sich für Nahrungsmittel-Unverträglichkeiten interessieren, die Ignoranz auf Seiten der Spezialisten hoch ist.“...

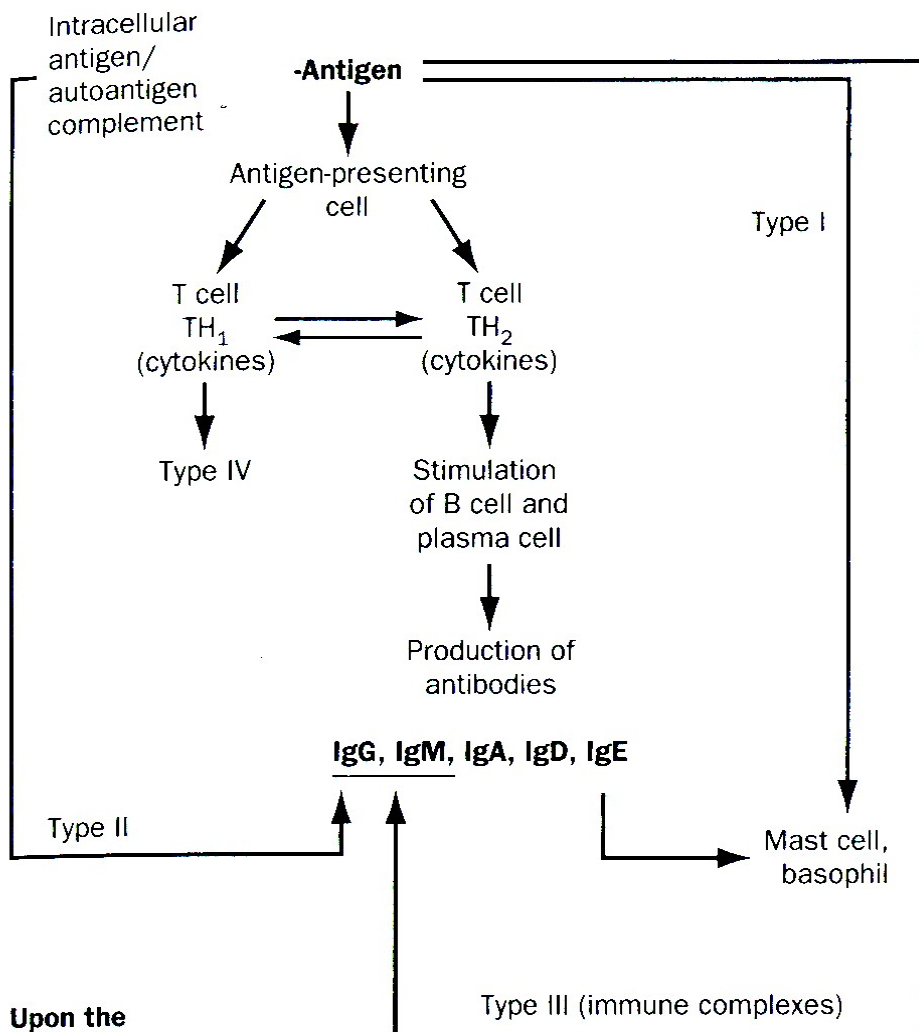
Der Schweregrad von IgE-vermittelten Reaktionen

...“IgE-vermittelte Reaktionen betreffen etwa 1-2% der Erwachsenen und 4 – 8% der Kinder.

Rhinitis

Aus allergischer Sicht

An den Symptomen der Rhinitis können drei der vier Unverträglichkeitsreaktionen (Type I, Type III, Type IV) beteiligt sein.



Upon the involvement of:

Eosinophils
 Neutrophils
 Platelets
 Monocytes
 Epithelial cells
 Goblet cells

Type I, Immediate hypersensitivity
 Type II, Cytotoxic hypersensitivity
 Type III, Late (immune complex) hypersensitivity
 Type IV, Delayed (cell-mediated) hypersensitivity

Fig. 35.1 Basic types of hypersensitivity (allergy) reactions.

Anwendungsbeobachtung

ImuPro300

Gewichtsprobleme und Nahrungsmittelunverträglichkeiten

Evomed MedizinService GmbH, Darmstadt

Kurzer Zwischenbericht 2004

(615 Patienten eingeschlossen / 538 auswertbar)

München, im September 2004

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1. Zusammenfassung

Mit der vorliegenden Anwendungsbeobachtung sollten Erkenntnisse zu Wirksamkeit von ImuPro300 bei Patienten mit Gewichtsproblemen und/oder anderen Krankheitsbildern und Symptomen, die auf eine Nahrungsmittelunverträglichkeit hindeuten wie z.B. Neurodermitis, Psoriasis, Kopfschmerzen/Migräne, Erschöpfung/Müdigkeit, rheumatische Erkrankungen sowie gastroenterologischen Beschwerden gesammelt werden.

Die Untersuchung ist als prospektive, multizentrischen Anwendungsbeobachtung konzipiert. Insgesamt sollen 300 Ärzte und Heilpraktiker die Behandlung von 1500 Patienten dokumentieren (also 5 Patienten pro Zentrum). Die Dokumentation der Behandlung können die Ärzte entweder *online* im Internet durchführen (www.online-anwendungsbeobachtung.de) oder "klassisch" mit Hilfe einer Dokumentationsmappe.

Bis Mitte August 2004 hatten 166 Ärzte mit der Dokumentation von 615 Patienten begonnen. Grundlage des vorliegenden Zwischenberichtes bildete die Auswertung der bis jetzt bereits abgeschlossenen Dokumentationen (d.h. Vorliegen von verwertbare Angaben zu Aufnahme- und Kontrollbesuch) von 538 Patienten.

Von den 538 Patienten waren 77,5% weiblichen- und 22,5% männlichen Geschlechts. Die Patienten waren zwischen 2 und 82 Jahre alt (Mittelwert: 46,6 Jahre) und der mittlere Body-Mass-Index betrug bei Behandlungsbeginn 29,3 kg/m².

Mit 38,8% waren die meisten Patienten adipös (42,0% der weiblichen-, 28,1% der männlichen Patienten). Ein knappes Drittel aller Patienten war übergewichtig (31,2%), 24,7% waren normalgewichtig und 1,9% untergewichtig.

Bezüglich des Ernährungsverhaltens wurde u.a. Folgendes dokumentiert: "häufig Heißhungerattacken" (52% der weiblichen, 41% der männlichen Patienten), "Oft Süßigkeiten (47% / 63%), "häufig Fertiggerichte" (16% / 27%) sowie "häufig Fast Food (11% / 29%). Das Ernährungsverhalten war dabei bei den unter 40jährigen

deutlich ungesünder als bei den restlichen Patienten. Weitere Belastungs- und Risikofaktoren waren "Bewegungsmangel" (53% der Frauen, 54% der Männer), "Alkohol" (27% /48%) und "Nikotin" (19% / 16%).

Der Bluttest zur Aufdeckung der Lebensmittelunverträglichkeiten ergab folgende Ergebnisse: Im Mittel hatten die Patienten 40 Lebensmittelreaktionen. Tendenziell hatten die "unter 40jährigen" etwas mehr (43,6 Reaktionen) und die "über 50jährigen" etwas weniger Reaktionen (37,5). Im Mittel waren 7,5 Reaktionen sehr ausgeprägt (Stärke 3 und 4). Auch bei den starken Reaktionen lagen die "über 50jährigen" mit 6 Reaktionen deutlich unter denen der jüngeren Patienten unter 40 Jahren mit im Mittel 9,6 Reaktionen der Stärke 3 und 4.

Das Umstellungsgespräch fand im Mittel 16 Tage nach der Blutentnahme statt.

Der Beobachtungszeitraum (Datum des Umstellungsgesprächs bis zum Zeitpunkt des Kontrollbesuches) betrug im Mittel 72 Tage (Median: 64 Tage).

Für 519 der 538 dokumentierten Patienten lagen Gewichtsangaben für den Zeitpunkt vor der Ernährungsumstellung sowie zum Kontrollbesuch vor.

Im Laufe der ca. 8wöchigen Ernährungsumstellung nach ImuPro konnte bei 76,3% aller Patienten ein Gewichtsrückgang dokumentiert werden.

Betrachtet man die relative Gewichtsveränderung im Vergleich zum Ausgangsgewicht, so zeigte sich, dass die Patienten im Laufe der 8wöchigen Beobachtungszeit im Mittel 3,9% ihres Körpergewichtes verloren hatten. Der maximale Gewichtsverlust betrug bei den Frauen 32%, bei den Männern 15%.

Die adipösen Patienten hatten im Mittel 5,0 % ihres Körpergewichtes verloren, die übergewichtigen 4,4 % und die normalgewichtigen Patienten 2,0 %. Die 10 untergewichtigen Patienten hatten im Mittel 2,8% zugenommen.

Bei den Patienten, die Ihre Konsequenz bei der Ernährungsumstellung mit "sehr gut" beurteilten, konnte ein Gewichtsverlust von im Mittel 5,4% des Körpergewichtes festgestellt werden (bei den konsequenten adipösen Patienten lag der mittlere Gewichtsverlust bei 6,1% der Körpergewichtes).

Zusammenfassend lässt sich sagen, dass 36% aller Patienten mehr als 5% ihres Ausgangsgewichtes verloren hatten (und zwar in der Regel ohne hypokalorische Diät). Bei den adipösen Patienten lag der Prozentsatz bei 44,9%, bei den Patienten, die sehr konsequent die Ernährungsumstellung vornahmen, hatten sogar 52,1% mehr als 5% ihres Körpergewichtes verloren (bei den sehr konsequenten adipösen Patienten waren es 64,5%).

Mit Hilfe einer 5stufigen Skala (von 0=nicht vorhanden bis 4=sehr stark) sollten die Ausprägungsgrade von 16 vorgegebenen Begleitsymptomen dokumentiert werden. Bei der nach ca. 8 Wochen stattgefundenen Kontrolldokumentation war der Ausprägungsgrad aller Symptome bei den meisten Patienten deutlich niedriger als beim Aufnahmebesuch. So hatte sich z.B. die Ausprägung des Symptoms "Völlegefühl" bei mehr als 80% der betroffenen Patienten gebessert. Bei den Patienten, die die Ernährungsumstellung sehr konsequent umgesetzt hatten, lagen die Besserungsraten meistens sogar noch deutlich höher (Zahlen in Klammern). Die Besserungsraten im Einzelnen: "Kopfschmerzen": 69,0% (75,9% bei den konsequenten Patienten), "Migräne": 76,3% (83,7%), "Akne": 60,5% (65,1%), "Neurodermitis": 69,0% (65,5%), "Jucken": 73,4% (72,2%), "Psoriasis": 62,4% (72,7%), "Völlegefühl": 80,1% (85,5%), "Blähungen": 77,5% (81,0%), "Aufstoßen": 70,9% (78,7%), "Durchfall": 67,8% (81,4%), "Magen-Darm-Beschwerden": 76,8% (87,0%), "Gelenkschmerzen": 67,7% (81,7%), "Arthrosen": 46,2% (52%), "Erschöpfung": 72,7% (80,5%), "Müdigkeit": 70,1% (75,7%) und "Gefühlsschwankungen": 66,6% (72,3%).

Zur Verdeutlichung des Therapiepotenziales sei die Entwicklung des Symptoms "Migräne" herausgegriffen: Von ehemals 75 Patienten, die zu Behandlungsbeginn unter starken oder sehr starken diesbezüglichen Beschwerden litten, waren nach 8wöchiger Ernährungsumstellung nur noch 10 Patienten übrig geblieben, die weiterhin unter starker bzw. sehr starker Migräne litten. Bei 20 Patienten (und damit mehr als einem Viertel der Betroffenen) war die Migräne ganz verschwunden.

Neben der Symptomentwicklung sollten Fragen zu den gewonnenen Erfahrungen mit ImuPro300 dokumentiert werden: Die meisten Patienten setzten die Ernährungsumstellung sehr gut (31,2%) oder gut (42,9%) um. Insgesamt 8,3% bezeichneten ihre Konsequenz als schlecht bzw. sehr schlecht.

Über 45% aller Patienten hatten *anfangs* große Probleme bei der Ernährungsumstellung. Nur 25% aller Patienten fiel die Umstellung "leicht" oder "sehr leicht".

Dagegen gaben 46% aller Patienten nach der 8wöchigen Ernährungsumstellung an, dass Ihnen die Beibehaltung ihrer neuen Essgewohnheiten *heute* keine Probleme mehr bereitet.

Bei 77,1% der Patienten hatte sich das Allgemeinbefinden beim Kontrollbesuch im Vergleich zum Aufnahmebesuch verbessert. Etwas niedriger war der Anteil dieser Gruppe bei den normalgewichtigen Patienten (66,2%), während er vor allem bei den Patienten, die ihre Nahrungsumstellung konsequent umsetzten, mit 86,9% deutlich höher war.

Bei 61 Patienten wurden unerwünschte Ereignisse dokumentiert (74 Nennungen). In 5 Fällen sahen die behandelnden Ärzte einen gesicherten Zusammenhang mit der Ernährungsumstellung nach ImuPro.

Abschließend sollte die Wirksamkeit von ImuPro300 von Ärzten und Patienten beurteilt werden. Mehr als 70% der Patienten und 66% der Ärzte beurteilten die Wirksamkeit der Nahrungsumstellung nach ImuPro mit "sehr gut" oder "gut".

Für die Patientengruppe, die die Ernährungsumstellung konsequent umgesetzt hatte, fiel die Patientenbeurteilung mit 83,9% "guten" oder "sehr guten" Bewertungen noch besser aus.

Insgesamt 86,6% aller Patienten würden ImuPro300 weiterempfehlen (Ärzte: 85,7%). Von den Patienten, die die Ernährungsumstellung sehr konsequent umsetzten, würden sogar 91,7% ImuPro300 weiterempfehlen.

2. Abbildungen

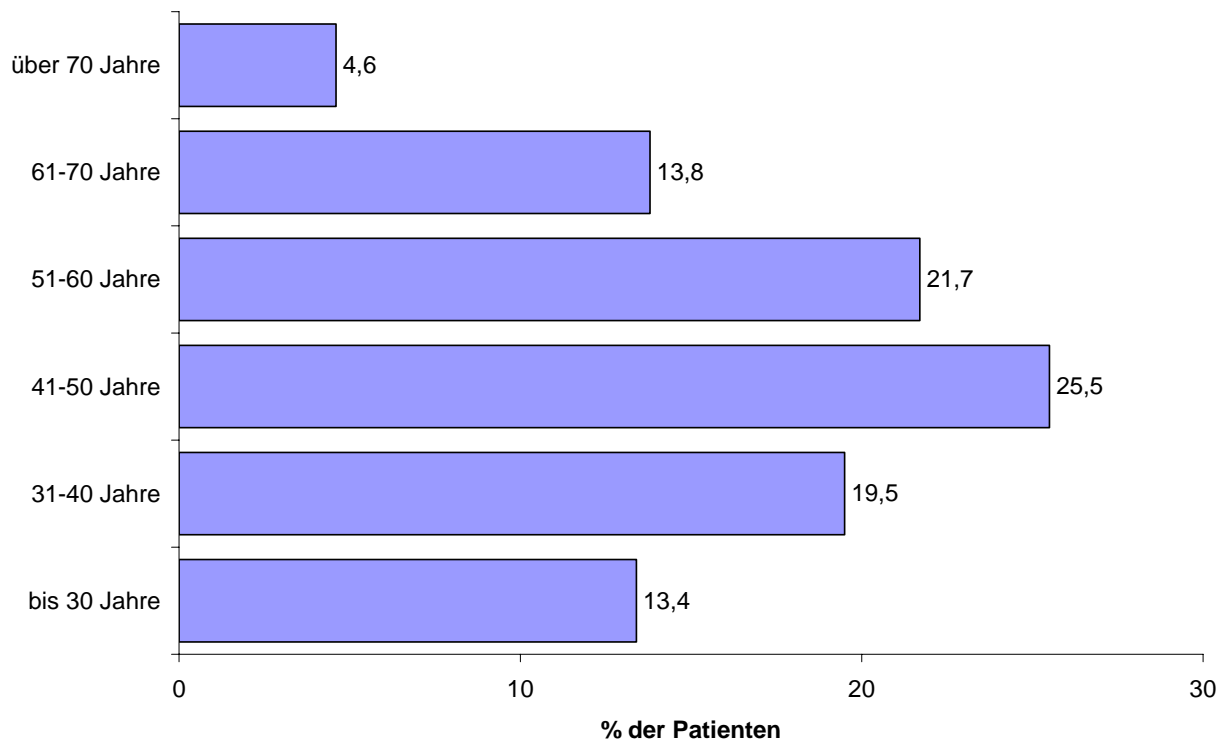


Abb. 1: Altersverteilung des Patientenkollektivs (N=538)

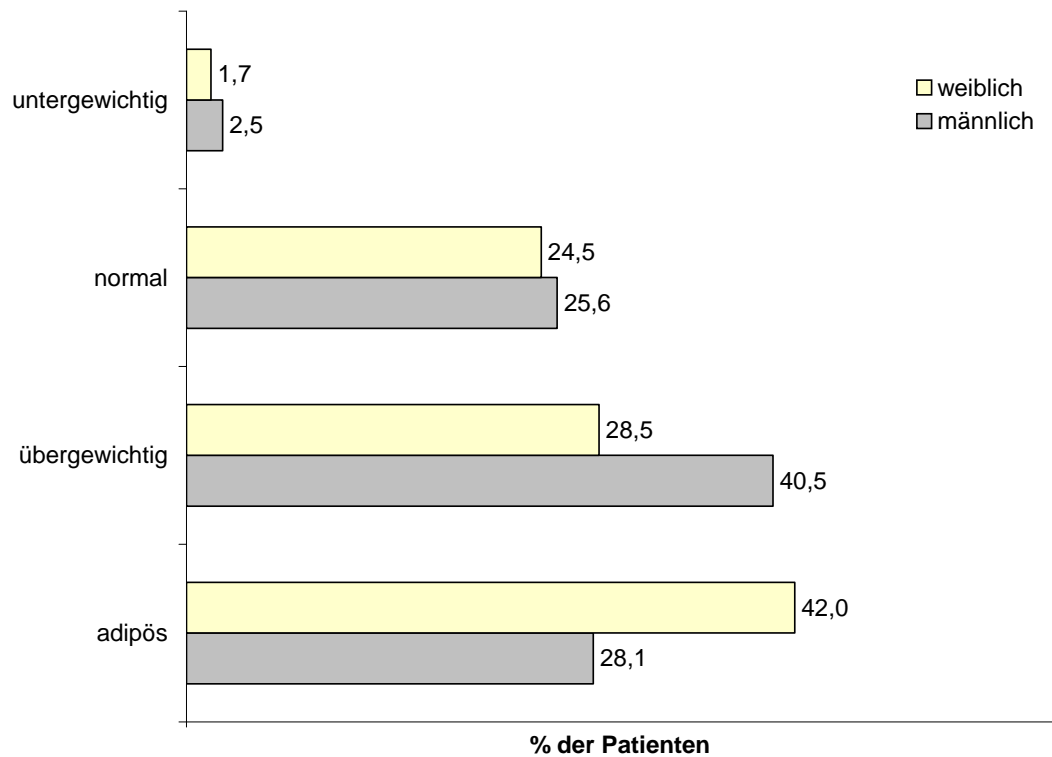


Abb. 2: Einordnung des Ausgangsgewichtes nach Geschlecht (N=538)

Aus den Angaben zu Gewicht und Größe wurde der BMI ermittelt und die Patienten nach den empfohlenen Grenzwerten der WHO für Übergewicht und Adipositas entsprechend eingeordnet.

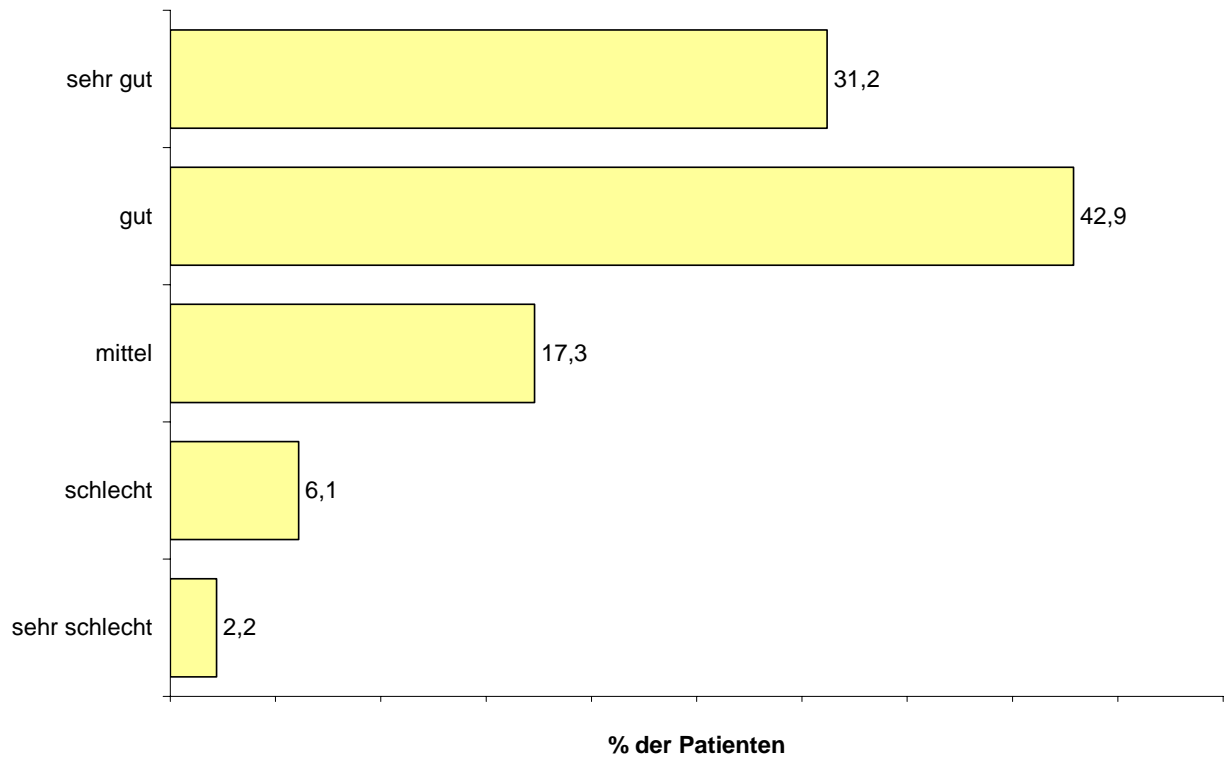


Abb. 3: Konsequenz der Ernährungsumstellung (N=538)

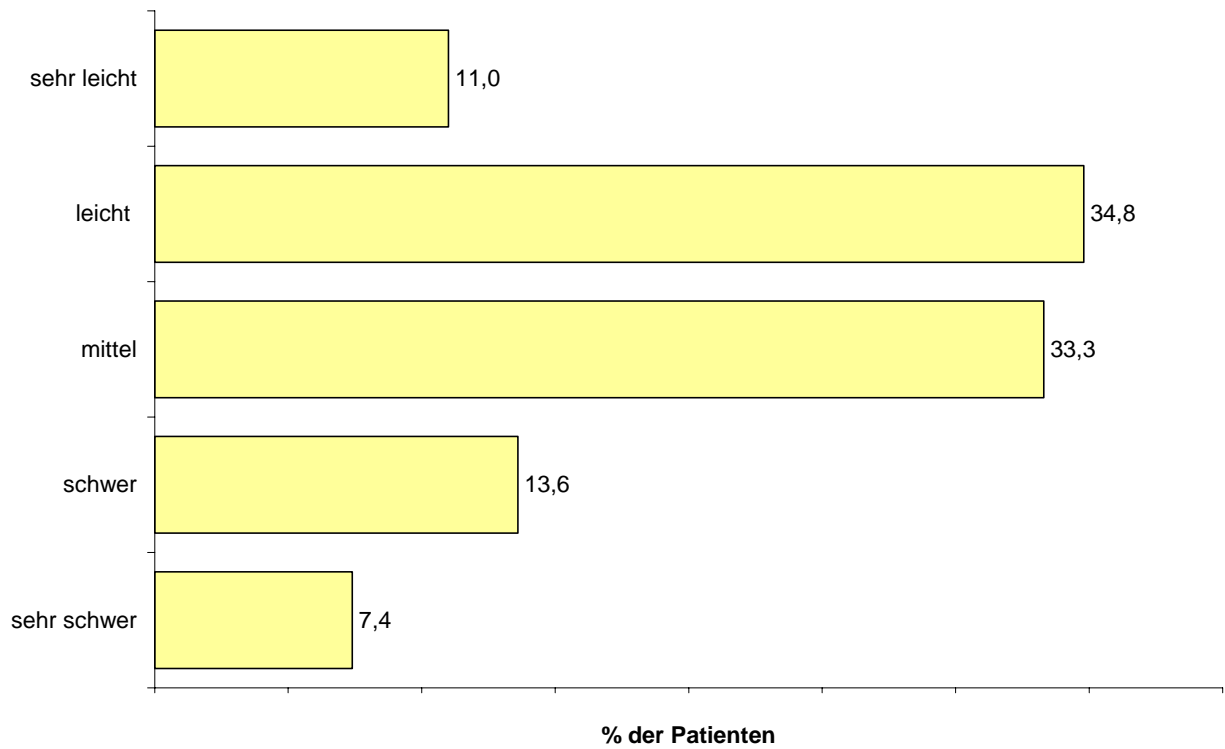


Abb. 4: Wie schwer fällt den Patienten nach ca. neun Wochen die Beibehaltung der neuen Essgewohnheiten (N=538)

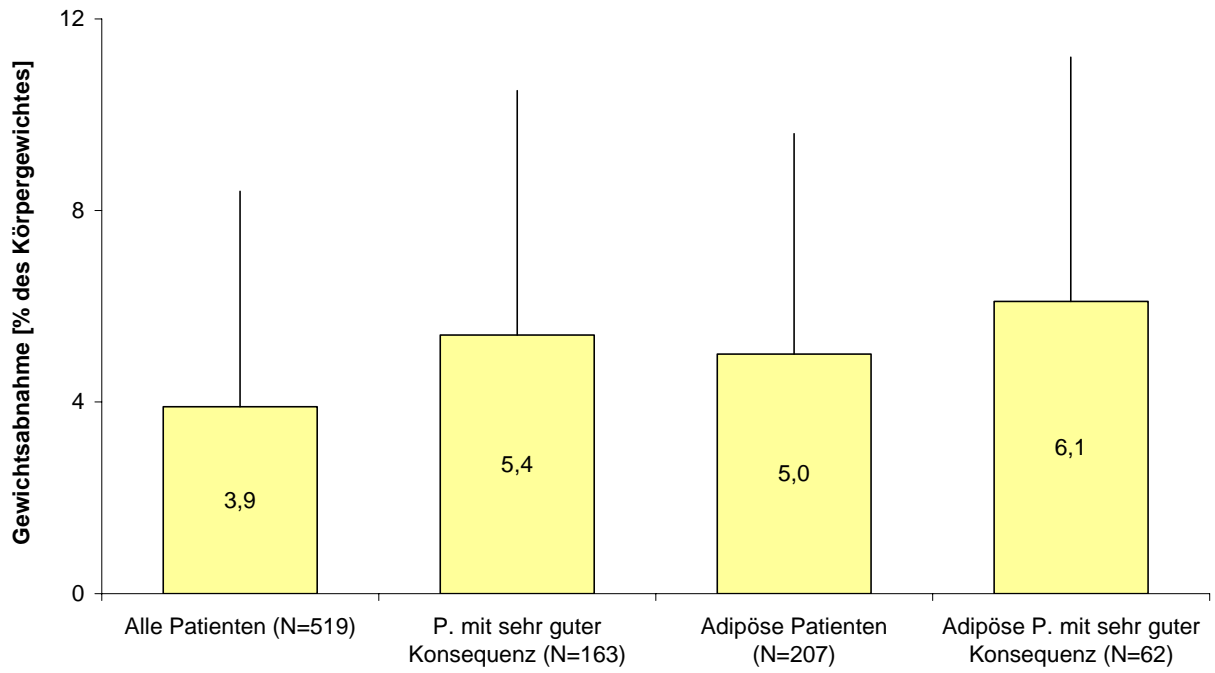
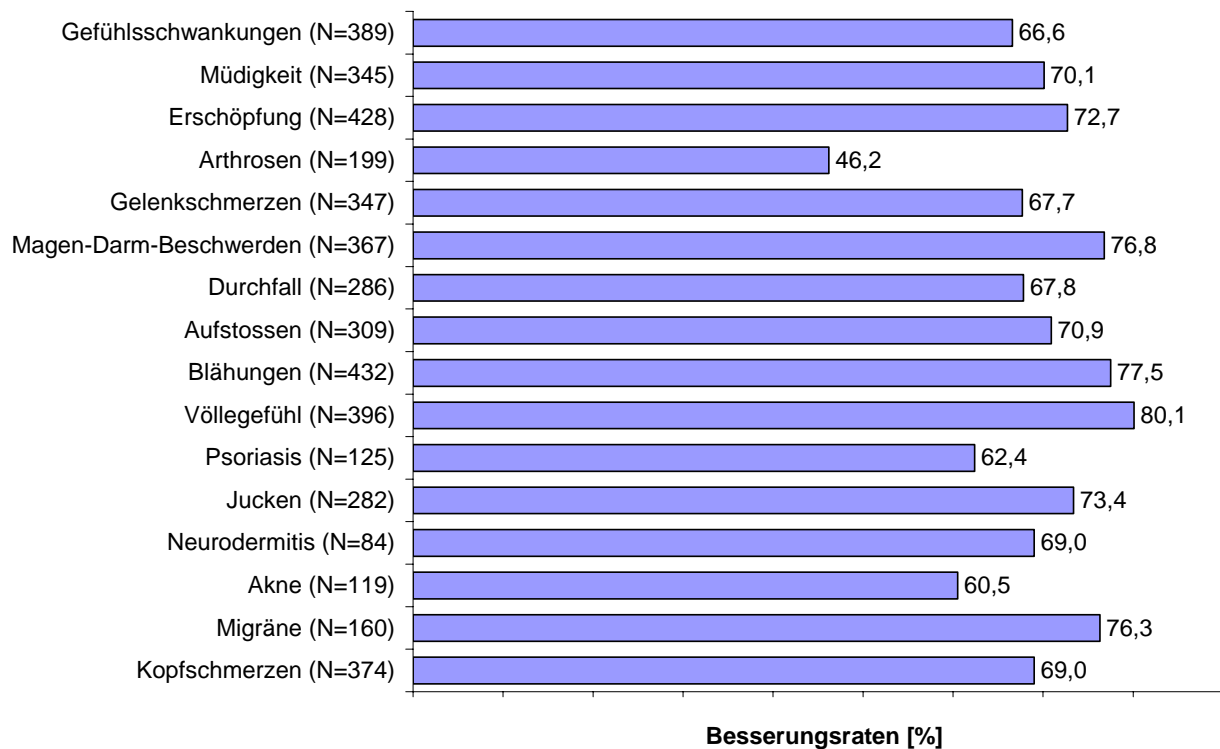


Abb. 5: Gewichtsverlust in Prozent des Körpergewichtes (Mittelwert und Standardabweichung).

**Abb. 6: Besserungsraten der Symptome**

Dargestellt ist der Anteil der Patienten, bei denen sich die Ausprägungsgrade der jeweiligen Symptome im Beobachtungszeitraum verbessert haben. Patienten, bei denen das Symptom weder beim Aufnahme- noch beim Kontrollbesuch vorhanden waren, wurden nicht berücksichtigt. Die Zahl in Klammern gibt jeweils an, bei wie vielen der 538 Patienten das jeweilige Symptom beim Aufnahmebesuch zumindest schwach ausgeprägt war (Schweregrad >0).

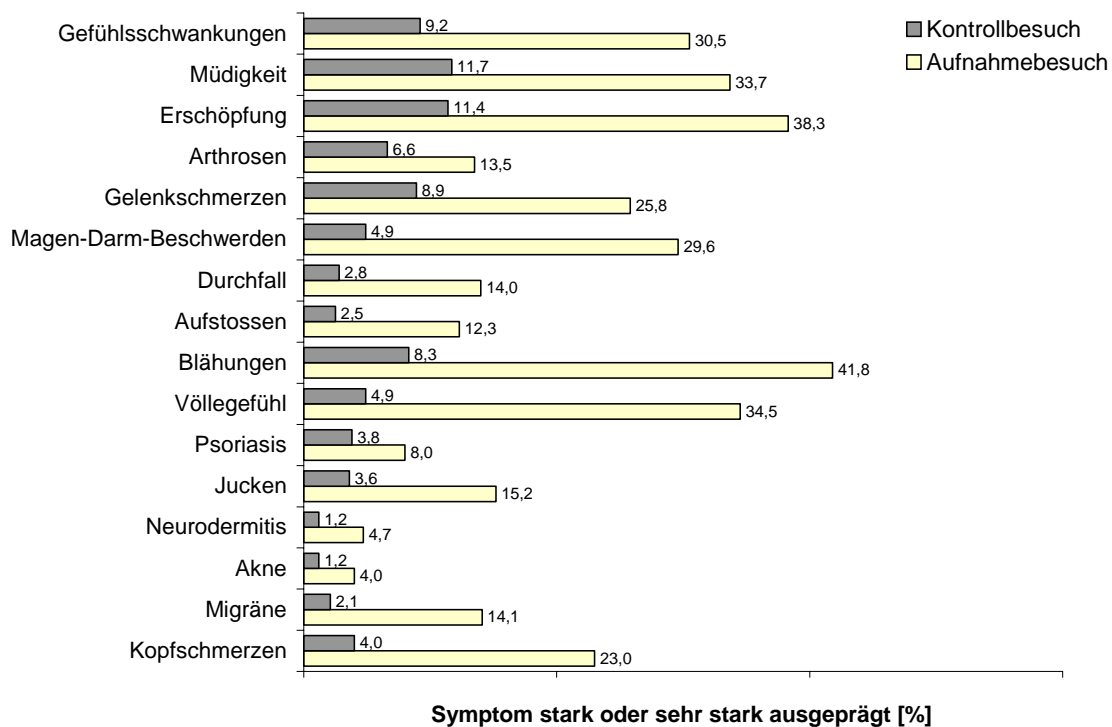


Abb. 7: Stark- bzw. sehr stark ausgeprägte Symptome bei Aufnahme- und Kontrollbesuch

Dargestellt ist der Anteil der Patienten für beide Besuche, bei denen das jeweilige Symptom "stark" oder "sehr stark" ausgeprägt war. Auswertungsgrundlagen sind bei jedem Symptom diejenigen Patienten, für die Angaben zu beiden Dokumentationszeitpunkten vorlagen.

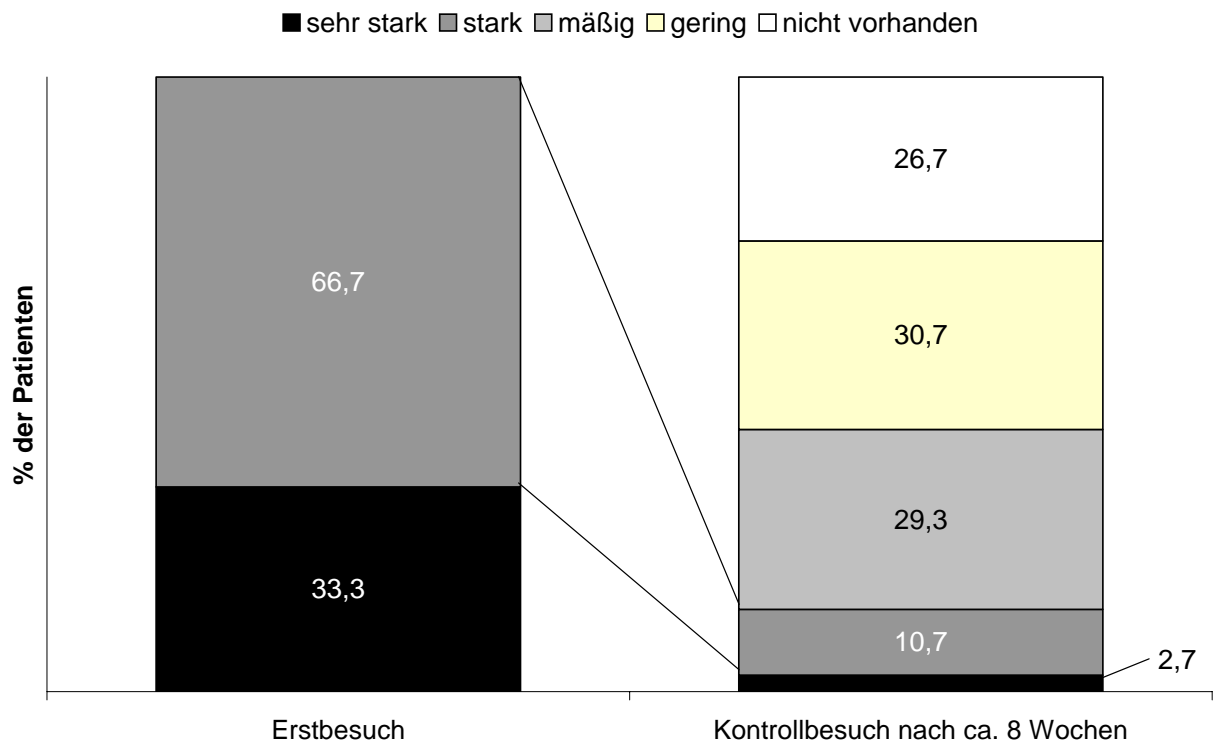


Abb. 8: Symptomentwicklung bei Patienten mit starker bzw. sehr starker Migräne (N=75)

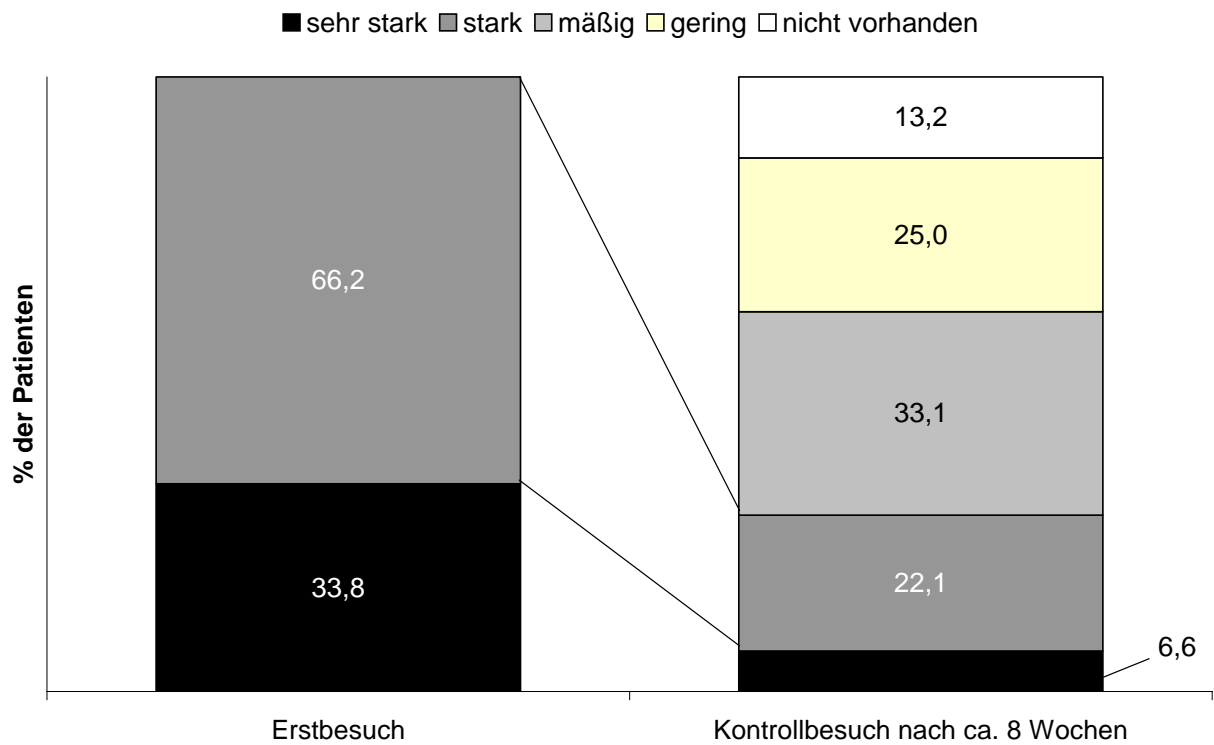


Abb. 9: Symptomentwicklung bei Patienten mit starken bzw. sehr starken Gelenkschmerzen (N=136)

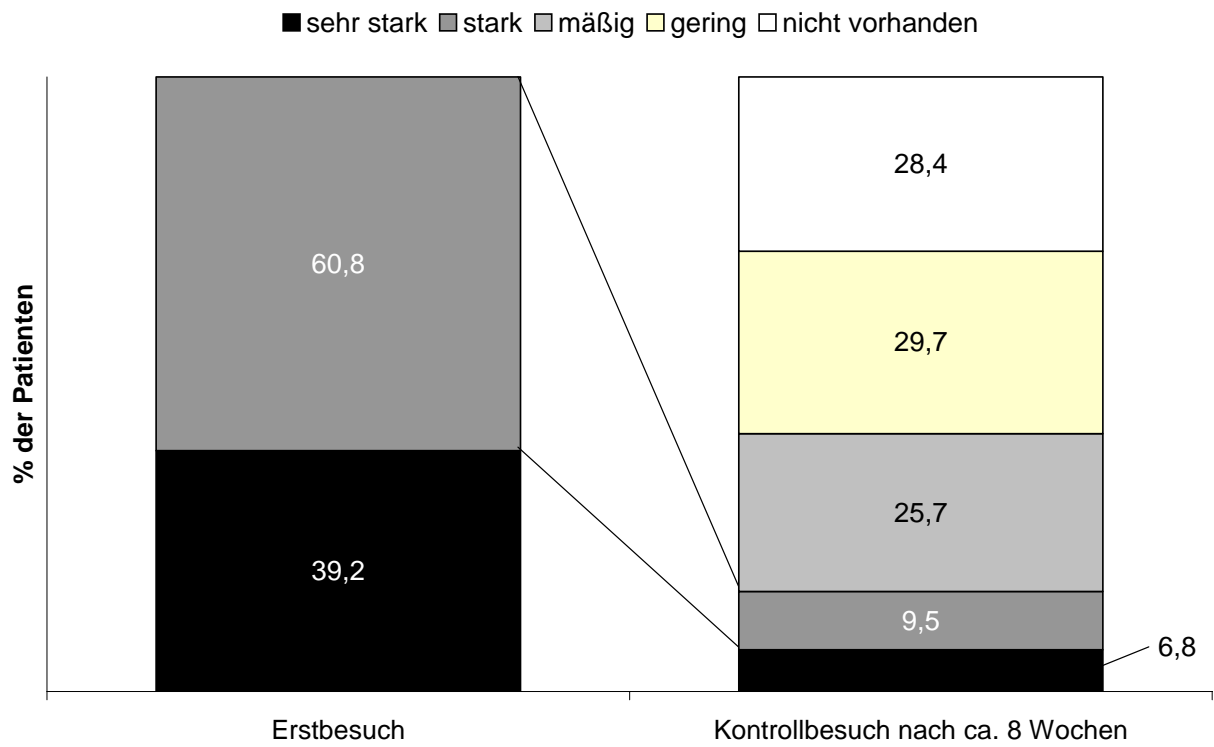


Abb. 10: Symptomentwicklung bei Patienten mit starkem bzw. sehr starkem Durchfall (N=74)

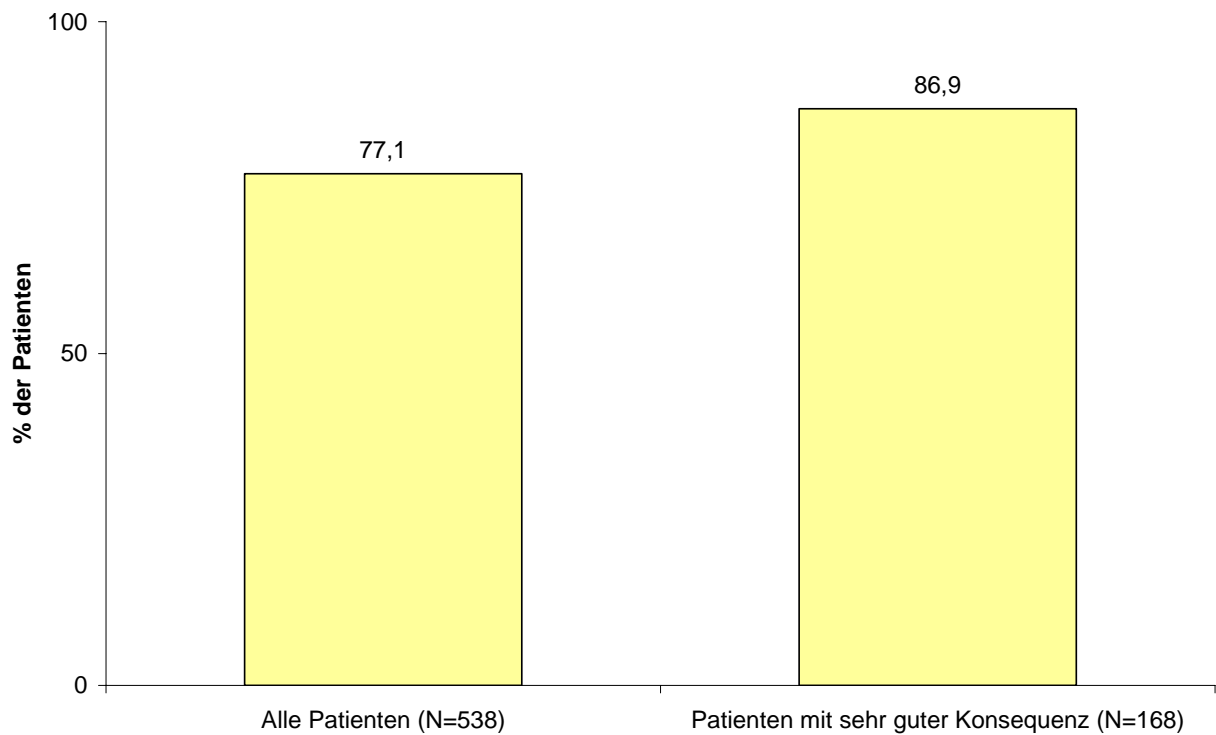
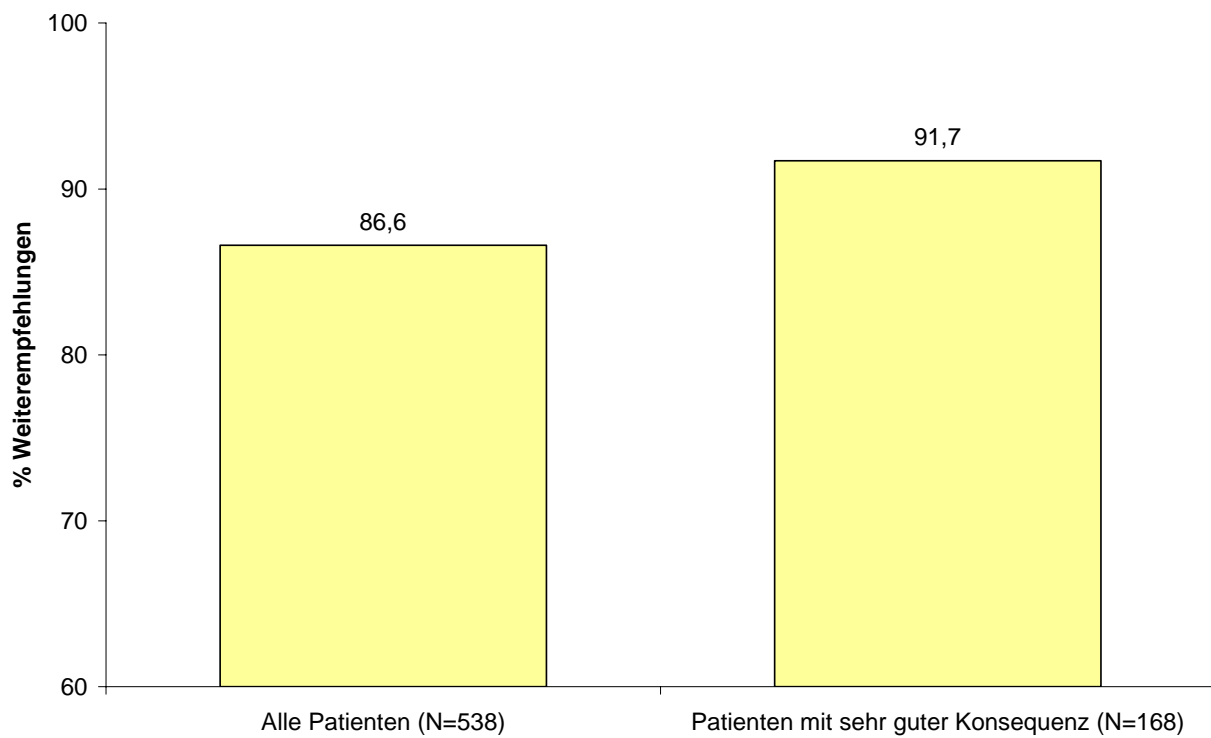


Abb. 11: Verbesserung des Allgemeinbefindens

Dargestellt ist der Anteil der Patienten bei denen sich das Allgemeinbefinden zum Zeitpunkt des Kontrollbesuchs nach ca. 8 Wochen im Vergleich zum Aufnahmebesuch verbessert hatte

**Abb. 12: Weiterempfehlungsrate**

Dargestellt ist der Anteil der Patienten, die zum Zeitpunkt des Kontrollbesuchs auf Grund der gemachten Erfahrungen ImuPro300 weiterempfehlen würden.