

# Food-specific IgG4-guided exclusion diets improve symptoms in Crohn's disease: a pilot study

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## Abstract

**Aim** Exclusion diets have been shown to prolong remission in Crohn's disease (CD). We assessed IgG4-targeted exclusion diets in patients with CD.

**Method** Forty patients with symptomatic CD were recruited. Their sera were tested for IgG4 antibodies to 14 specific food antigens and each subject's four most reactive foods were excluded for 4 weeks. Disease activity was assessed using a modified CD activity index (mCDAI). Questionnaire and inflammatory markers were measured before and on completion of the exclusion diet.

**Results** Eleven patients did not complete the study, leaving 29 for analysis. Of these, 26 (90%) reported

symptomatic improvement with a reduction in mCDAI from a mean of 171–97.5 ( $P = 0.0001$ ). The ESR fell from 23 to 17 mm/h ( $P = 0.021$ ) and the IgG4 titres for the excluded foods fell from a mean of 3015–2306 mcgA/l ( $P = 0.003$ ).

**Conclusion** IgG4-guided exclusion diets resulted in significant symptomatic improvement with an objective fall in an inflammatory marker. This approach may be useful in clinical practice.

**Keywords** Crohn's disease, IgG4, exclusion diet, disease activity

## Introduction

It has been shown that diet and nutrition are important in the causation and treatment of Crohn's disease (CD) [1–4]. Medical treatment is aimed at immune suppression, and surgical treatment is reserved mainly for complications of the disease. Medical therapy also includes bowel rest, specific food supplementation and reduction of dietary antigen exposure with a view to downscaling the immune response to food sensitivity.

CD has been shown to respond to exclusion diets [5], but this approach is unattractive for the patient. Exclusion or elimination diets are administered either by excluding most foods until symptoms resolve, with the gradual reintroduction of foods, excluding those that cause symptoms, or by restricting foods recalled by the patient to be specific triggers of worsening of the disease. If there was a method of personalizing an exclusion diet, compliance might be higher and greater symptomatic benefit achieved.

IgG1 and IgG4 have both been implicated as dominating subclasses of antibodies to food antigens. While IgG1 is an initial responder, IgG4 is produced following chronic exposure to the antigen [6]. Our group has previously investigated the use of IgG4-targeted diets in patients with irritable bowel syndrome showing symptomatic improvement [7]. We have also shown that patients with Crohn's have higher levels of IgG4 responses to specific food antigens when compared with healthy controls [8].

Only one other study has studied food-specific IgG4 levels in CD [9]. In that study, 15 patients with CD, 15 with ulcerative colitis and 10 healthy controls were tested against five food types [9]. Patients with CD had higher IgG4 titres to soybean than the ulcerative colitis (UC) and control groups. They also demonstrated that patients with CD had significantly higher incidences of food allergies, drug allergies and atopic dermatitis. However, no work on exclusion diets was carried out.

The aim of this study was to determine whether an IgG4-based exclusion diet might result in symptomatic improvement and reduction in the level of inflammatory markers in patients with CD.

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## Method

### Patients

The local research ethics board approved the trial (06/Q0803/33). All patients gave their written informed consent. Forty patients with CD were recruited from the colorectal outpatient clinic. A history, physical examination and blood tests were carried out in all patients. Flexible sigmoidoscopy or colonoscopy had been performed previously to provide histological confirmation of disease. Patients with indeterminate/ulcerative colitis, irritable bowel syndrome, coeliac disease, lactose intolerance, other significant gastrointestinal disorders, and those who had recent surgery (within 3 months) were excluded. Pregnancy, concurrent malignancy and major psychiatric disorder were also exclusion criteria. Patients with severe disease requiring high-dose steroids were also excluded. Patients were not excluded because of previous surgery, unless it had taken place within the previous 3 months.

All patients filled in a validated questionnaire before and after completion of the exclusion diet. They were scored using a modified CD activity index score (mCDAI) [10], which is a variation of the scoring system designed by Best *et al.* [11]. Components of the scoring system included abdominal pain rating, general well-being, number of bowel movements per 24 h, number of extra-intestinal manifestations and presence of an abdominal mass. A score of over 150 represented clinically active disease and a fall of 70 represented a significant clinical reduction in symptoms.

### Food-specific serum IgG4 antibodies

Fifteen millilitres of blood were obtained from each patient and centrifuged at  $700 \times g$  for 10 minutes to separate the serum. The IgG4 titres in the serum to 14 common foodstuffs were measured using a commercially available radioimmuno-fluorescence assay (Phadia Ltd, Milton Keynes, UK). These included egg white, egg yolk, potato, tomato, cheddar cheese, rice, beef, lamb, pork, soya, peanuts, wheat, yeast and chicken. The serum was incubated with a cellulose cap containing the foodstuff of interest. Excess antibody was washed away and the cap was incubated with a fluorescent-labelled mouse anti-IgG antibody; the activity was then measured by a fluorometer after enzyme activation. The measurements ranged between 1.5 and 30 000 mcg/l. A value greater than or equal to 250 mcg/l was classified as a mild reaction, 500 mcg/l as moderate, and 1000 mcg/l was considered to be a strong reaction.

### Diet

The patients were asked to exclude the four most immunoreactive food types from their diet for a period of 4 weeks. If a patient had already excluded any of these, the next most sensitive food was selected. If patients had more than four foods to which they were sensitive, they were given this information and were offered the option to exclude these foods in addition. This was performed with the assistance of a dietician who was able to suggest suitable replacements. To improve compliance, patients were provided with telephone numbers and email addresses to permit easy contact with the department in the event of any query. The patients were also contacted in the middle of the period to assess compliance and arrange an end of diet meeting for reassessment.

### Statistical analysis

Changes in mCDAI pre- and post-diet were evaluated for statistical significance using the paired t-test (two-tailed). A value of  $P < 0.05$  was taken as significant. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA).

## Results

Forty patients were recruited. Eleven did not complete the trial. Five were noncompliant with the diet, 1 became pregnant, 2 moved away and 3 had elective surgery (2 stricturoplasties and 1 abscess drainage). The mean age of the 29 patients who completed the trial was 39.3 (SD = 12.2) years (range 18–63). Prior surgical procedures and disease distribution are shown in Table 1. The most common foods excluded were egg white and yolk, cheddar cheese, beef, pork and wheat (Fig. 1).

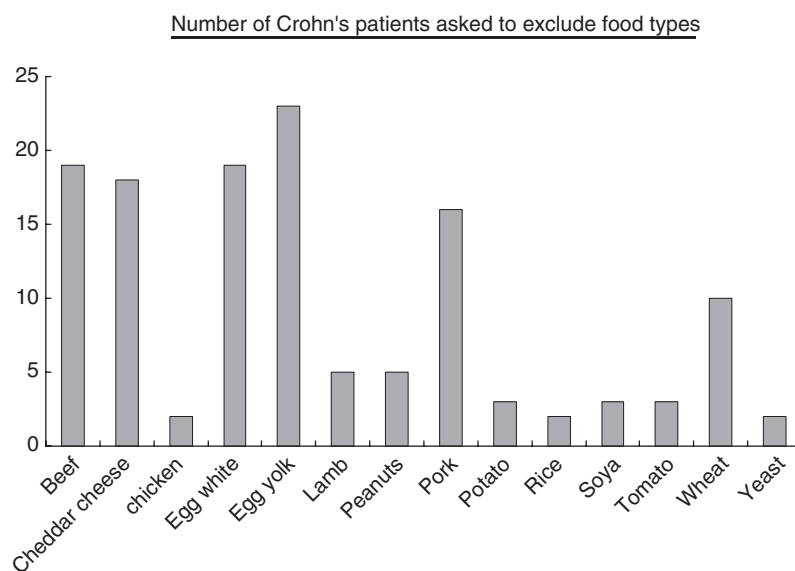
The mean mCDAI score ( $n = 29$ ) on entry to the trial was  $171 \pm 108$ . This fell to a mean mCDAI of  $97.5 \pm 87$  after completion of the 4-week diet ( $P = 0.0001$ ) (Fig. 2). The greatest improvement was seen in number of bowel movements per day, where the mean fell from 4 to 2 ( $P = 0.0001$ ). The mean pain rating fell from 0.71 to 0.43 ( $P = 0.030$ ). The general 'well-being' rating improved from 0.88 to 0.63 ( $P = 0.045$ ). The extra-intestinal manifestations score fell from a mean of 0.64 to 0.29 in the 13 patients reporting joint pains, skin conditions, perianal symptoms and uveitis. The mean erythrocyte sedimentation rate (ESR) fell from  $22.3 \pm 16.0$  to  $17.1 \pm 15.2$  ( $P = 0.032$ ). C-reactive protein and albumin levels did not change significantly.

IgG4 seroreactivities checked at the end of the dietary period in 24 of the 29 patients showed a significant fall ( $P = 0.003$ ). When excluded foodstuffs were analysed

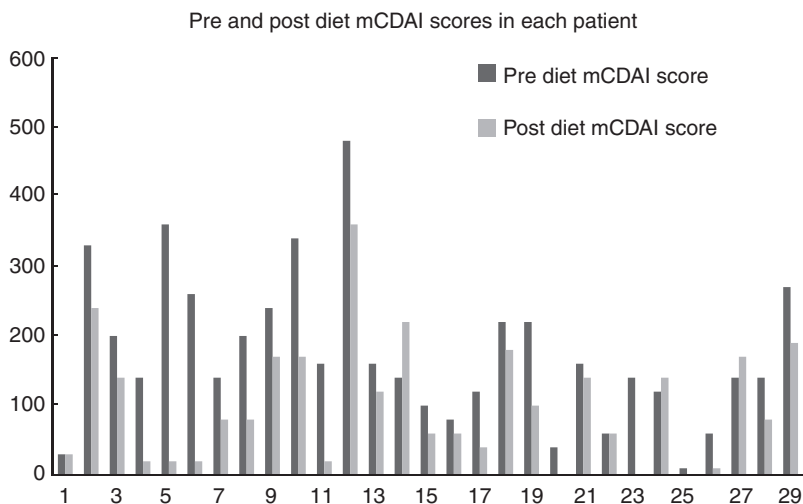
**Table 1** Age, gender, previous surgery, disease location, current treatment and smoking status in 29 patients included in the study.

Patient number	Age	Sex	Previous surgery	Disease location	Treatment	Smoking status
1	27	F	SP	DI/C	Azathioprine 150 mg od, Asacol 1200 mg bd	≥ 15
2	22	M	SP/ICR	IC/P	Pentasa 1 g bd	Never
3	50	F	SBR/SP	DI	Nil	Ex
4	57	M	Nil	C	Asacol 400 mg tds	< 15
5	31	F	SP/SBR/ICR	DI/IC/C	Nil	Never
6	30	M	SBR/IL	DI/P	Infliximab	Never
7	40	F	Nil	DI/IC	Azathioprine 100 mg od	Ex
8	37	F	Nil	DI/IC/C	Asacol 800 mg tds predfoam prn	Never
9	25	F	Nil	DI	Nil	Ex
10	32	F	IL/ICR	DI/IC/C	Nil	< 15
11	18	M	SBR	DI	Nil	Never
12	57	F	ICR	IC	Asacol 400 mg tds	Never
13	63	F	CR/ICR	DI/IC/C	Asacol 400 mg tds	Never
14	32	F	SP	DI	Mercaptopurine 10 mg pentasa 2 g	Never
15	34	M	IL	DI	Nil	< 15
16	47	M	IRA + PR	C	Nil	Ex
17	42	F	Nil	C	Asacol 800 mg tds	Never
18	39	F	SBR	DI	Pentasa 1 g bd	Never
19	35	F	ICR	IC	Asacol 800 mg tds	< 15
20	50	F	IRA	DI//IC/C	Asacol 800 mg tds	≥ 15
21	38	M	ICR/CR/SBR	DI//IC/C/P	Infliximab	Never
22	43	M	IRA	DI	Nil	Never
23	28	F	Nil	C	Asacol 400 mg tds	< 15
24	35	F	ICR	DI/IC/C	Nil	Never
25	68	F	Nil	C	Nil	Never
26	39	M	Nil	C/P	Asacol 400 mg tds	Never
27	48	M	Nil	DI	Nil	≥ 15
28	46	F	IRA	C	Nil	< 15
29	27	M	ICR	DI/IC	Asacol 800 mg tds	Never

IRA, ileorectal anastomosis; SP, strictureplasty; ICR, ileocaecal resection; CR, colonic resection; SBR, small bowel resection; PR, proctectomy; IL, ileostomy; PPC, panproctocolectomy; DI, distal ileum; IC, ileocaecal junction; C, colon; P, perianal.



**Figure 1** The number of patients asked to exclude each food type based on the serum IgG4 antibody titre.



**Figure 2** Modified Crohn's disease activity index scores before and after the 4-week exclusion diet in 29 patients included in the study.

separately, there was a drop in the mean IgG4 from 3015 to 2306 mcgA/l ( $P = 0.008$ ). For nonexcluded foods, the mean IgG4 rose from 235 to 282 mcgA/l ( $P = 0.088$ ).

## Discussion

The study demonstrated that patients with CD experience a significant improvement in symptoms in response to a 'food-specific IgG4'-targeted exclusion diet. Pain severity, bowel frequency, general well-being and extra-intestinal manifestations, as quantified by mCDAI scores, all showed statistically significant improvement with the diet. The symptomatic improvement reported by the patients was supported by objective evidence of reduced inflammation as judged by the level of the ESR.

Current methods for applying exclusion or elimination diets are unappealing to patients because of their complexity. These techniques are employed primarily because there are no available methods of testing food sensitivity objectively. Unlike the approaches discussed earlier, the 'targeted exclusion diet' employed in this study is personally tailored to the individual patient based on their serum IgG4 antibody titres. This approach has several advantages. First, by excluding only those foods that are associated with an increased antibody titre, it provides objectivity. Patients are more likely to comply since it is more evidence based. Second, as the diet is tailored to an individual patient, it avoids the need to exclude large numbers of foods from the diet. Third, clinicians are likely to be more confident in prescribing exclusion diets based on objective methodology.

The sample size was small and the duration of the study was short since it was a pilot study. These are clearly limitations, but the results give sufficiently positive data to encourage a larger investigation. Only 14 common

foods were tested and therefore the assessment of intolerance was limited. A larger panel of foodstuffs could have identified more sensitivities, possibly resulting in further improvement of symptoms in a greater number of patients.

An open dietary elimination was adopted as used in most studies in the field, since it is technically difficult to perform double-blind exclusion diet studies. It is impractical to blind a patient to a diet, as this would require changing the appearance, smell and consistency of the food. Although this means that a placebo response cannot be excluded with certainty, the magnitude of the improvement in symptoms and the associated objective improvement in ESR suggests that the response was real.

The use of IgG4 antibody assays in the assessment of food intolerance is controversial [12]. High IgG4 antibody titres to specific foods are usually a response to having eaten the food type recently. Our group has shown that patients with Crohn's have higher IgG4 responses to certain foods than healthy control subjects [8]. We demonstrated that its use in the assessment of food intolerance in patients with irritable bowel syndrome has shown symptomatic and physiological improvement [7]. This study has shown that there is both a significant symptomatic response and slight reduction in ESR, suggesting a fall in the degree of inflammation while providing IgG4-targeted exclusion diets to patients with CD.

The results show that by reducing gut mucosal antigen exposure based on the serum IgG4 tests, immune modulation is possible in bringing about symptomatic and inflammatory improvement. This is the first study demonstrating symptom improvement with measurable changes in CD activity and ESR in response to an IgG4-targeted exclusion diet.

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## Conflict of interest

We received equipment and reagents from Phadia Ltd, the funding source, which had no role in study design or conduct, data analysis, or the writing of the article or the decision to submit for publication. The authors declare no competing interests.

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