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Research Submission

IgG-Based Elimination Diet in Migraine Plus Irritable Bowel Syndrome

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Objectives.—To evaluate therapeutic potential of the immunoglobulin G (IgG)-based elimination diet among migraine patients with irritable bowel syndrome (IBS).

Background.—Food elimination has been suggested as an effective and inexpensive therapeutic strategy in patients with migraine and concomitant IBS in the past studies.

Methods.—A total of 21 patients (mean [standard deviation] age: 38.0 [11.2] years; 85.7% females) diagnosed with migraine and IBS were included in this double-blind, randomized, controlled, cross-over clinical trial composed of baseline (usual diet), first diet (elimination or provocation diets), and second diet (interchange of elimination or provocations diets) phases and 4 visits.

Results.—IgG antibody tests against 270 food allergens revealed mean (standard deviation) reaction count to be 23.1 (14.1). Compared with baseline levels, elimination diet per se was associated with significant reductions in attack count (4.8 [2.1] vs 2.7 [2.0]; $P < .001$), maximum attack duration (2.6 [0.6] vs 1.4 [1.1] days; $P < .001$), mean attack duration (1.8 [0.5] vs 1.1 [0.8] days; $P < .01$), maximum attack severity (visual analog scale 8.5 [1.4] vs visual analog scale 6.6 [3.3]; $P < .001$), and number of attacks with acute medication (4.0 [1.5] vs 1.9 [1.8]; $P < .001$). There was a significant reduction in pain-bloating severity (1.8 [1.3] vs 3.2 [0.8]; $P < .05$), pain-bloating within the last 10 days (3.2 [2.8] vs 5.5 [3.1]; $P < .05$), and improvement obtained in quality of life (3.6 [1.4] vs 2.9 [1.0]; $P < .05$) by the elimination diet as compared with provocation diet.

Conclusions.—Our findings indicate that food elimination based on IgG antibodies in migraine patients who suffer from concomitant IBS may effectively reduce symptoms from both disorders with possible positive impact on the quality of life of the patients as well as potential savings to the health-care system.

Key words: migraine, irritable bowel syndrome, elimination diet, immunoglobulin G antibody, food antigen

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Migraine is characterized by recurrent unilateral headache usually accompanied by nausea/vomiting, photophobia, and/or phonophobia,[1] with 1-year-period prevalence of 10-12% in adults, 6% among men, and 15-18% in women.[2] The mechanisms underlying primary migraine are still unknown.[3] Sensitivity to particular food is one of the most common triggers of migraine.[4,5] Immunoglobulin (IgG) antibodies against various food antigens have been reported to be associated with migraine.[6] Accordingly, consumption of IgG-reactive food elimination diets for a specific period provided decrease in headache attacks and significant improvement in symptoms.[1]

Irritable bowel syndrome (IBS) is a multifactorial condition involving a number of different mechanisms.[7] Patients with IBS often strongly believe that dietary intolerance significantly contributes to their symptomatology, and some benefit from eliminating certain foods from their diet.[8] Besides, several studies reported significant improvement in IBS by food elimination based on IgG antibodies against food antigens.[8-11]

IBS patients are likely to suffer from migraine more than control subjects.[12] Past studies suggested food elimination as an effective and inexpensive therapeutic strategy in patients with migraine and concomitant IBS.[13] Therefore, the present study was designed to evaluate therapeutic potential of the IgG-based elimination diet among migraine patients with IBS via a double-blind, randomized, controlled, clinical trial with a cross-over design.

SUBJECTS AND METHODS

Subjects.—Of 28 patients enrolled, a total of 21 patients diagnosed with migraine according to the criteria of the International Classification of Headache Disorders[14] and accompanying uncomplicated IBS (all bowel habit subtypes) according to the ROME III criteria,[15] being followed by the Headache Outpatient Clinic of Neurology Department and the Gastroenterology Department of Acibadem University School of Medicine, Istanbul, Turkey, were included in this double-blind, randomized, controlled, cross-over, clinical trial. Seven patients were excluded due to unplanned pregnancy, difficulty to maintain the diet, or lack of keeping records.

To have migraine diagnosis for at least 6 months and at least 2 migraine attacks, and 4 headache days within the last month; to be aged 18-65 years; to have abdominal discomfort for at least 12-week duration in the previous year, which need not be continuous; and to be treated with preventive medications unchanged at least for 6 months or with acute attack medications only were the inclusion criteria. Patients who had medication-overuse headache, pure menstrual migraine, or any other associated headache disorder, inflammatory bowel disease, celiac disease, known lactose intolerance, previous major abdominal surgery, or other significant gastrointestinal disorder were excluded from the study. In addition, "advanced" cardiac, respiratory, renal, or hepatic diseases; and malignancy, major psychiatric disorders, or a history of drug/alcohol abuse and pregnancy at the time of study enrollment and during the study were considered as exclusion criteria.

Ethics.—The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study that was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

Study Procedures and Assessments.—Our study was designed as a double-blind, randomized, controlled, cross-over, clinical trial composed of 3 phases, including baseline (run-in) phase (usual diet), first diet phase (elimination or provocation diets, customized based on sensitivity results), and second diet (interchange of elimination or provocation diets) phase with a total of 4 evaluation visits per patient (Figure). The patients visited the same headache and gastroenterology physician during the whole study, and they were encouraged not to modify the medications used during the course of the trial.

At the first visit, patients who fulfilled the patient selection criteria were asked to fill out a headache diary and watch their symptoms of gastric discomfort for 6 weeks. The diary included questions on attack count, headache days, attack duration (days), and headache severity (via a 0-10 pain numeric rating

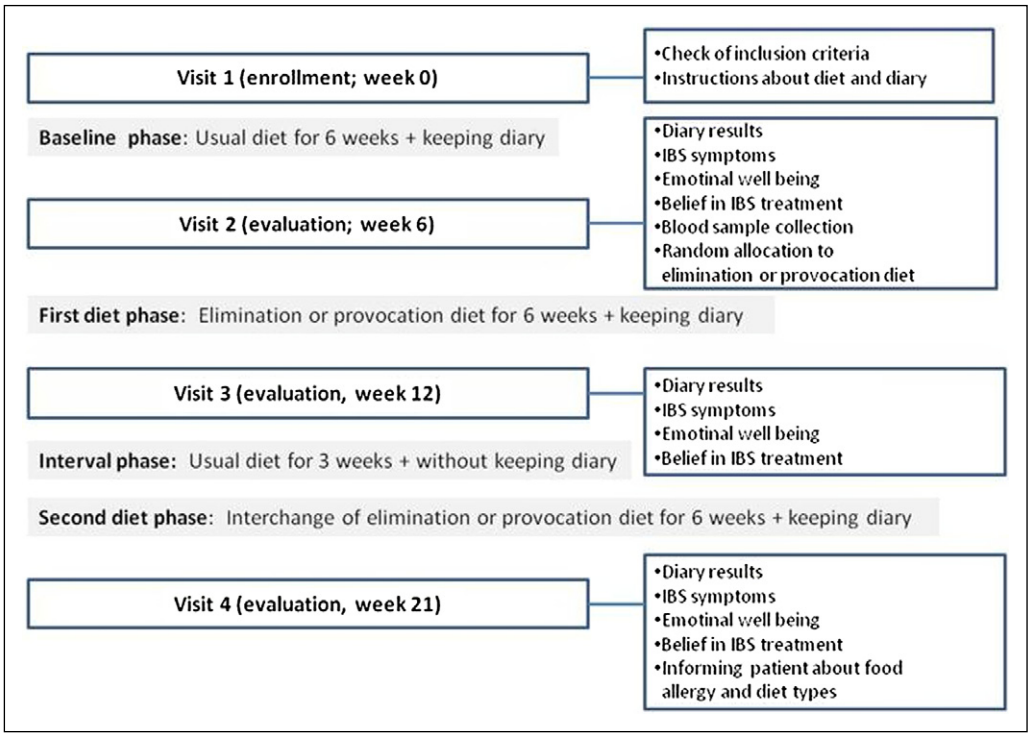

Figure.—Study flow chart. IBS = irritable bowel syndrome.

scale), and acute and overall medication use. The patients were kept on their usual daily diet during this 6-week baseline run-in period.

At the second visit, the diaries were returned by the patients, and emotional well-being was evaluated considering happiness at home, happiness at work, quality of life (QoL), belief in IBS treatment (via a 0-5 numeric rating scale: 0, worst; 5, best); fear of illness and objective clinical findings of IBS symptoms including pain-bloating frequency and severity (within the last 10 days), number of defecation days (per week), diarrhea-constipation severity, and symptoms of urgency, straining, and inability to fully empty the bowel via an IBS symptoms severity scale modified from that first described by Francis et al[16] were recorded (0, best; 5, worst) (see Appendix A). Additionally, blood samples were collected from each patient to detect IgG antibody titers to 270 food allergens to identify mean reaction (abnormally high titer) count by enzyme-linked immunosorbent assay (ELISA).

During the first diet phase of 6 weeks of patients were allocated to either an elimination (excluding; n = 11) or a provocation (including; n = 10) diet via simple randomization procedures using a computer-generated list of random numbers based on their sensitivity results for 6-week run-in period. During this first diet phase of 6 weeks, they were also asked to fill a headache diary.

At visit 3, performed at the end of the first diet phase, patients returned their headache diaries for evaluation, and data on emotional well-being, belief in IBS treatment, and IBS symptoms during the first diet phase were recorded. Then, the patients were asked to return to their usual diets for 3 weeks of washout period without keeping a diary.

After washout, the patients who were on elimination diet in the first diet phase were given provocation diet and vice versa for 6 weeks during which they were asked to fill a headache diary. Patients were reassessed after the second diet phase at the 3rd and the 4th visit.

All patients and clinical staff in the headache clinic and gastroenterology department were blinded to the group assignment of all patients during the study. The allocation sequence was concealed from

the researcher enrolling and assessing participants in sequentially numbered, opaque, sealed, and stapled envelopes. Patients were given their allocated diet by 2 qualified dieticians. Because of the double-blind nature of the study design, the patients have been informed that some of the foods might be provoking and encouraged to consume certain foods during both diet periods. The diet codes were broken, and patients were informed about their food allergy results, the order of the types of their diets, and if they prefer how to continue their diet according to the results.

IgG Antibody Detection Against Food Antigens.—IgG antibodies against 270 food antigens were detected using a commercially available ELISA test (ImuPro 300 test; Evomed/R-Biopharm AG, Darmstadt, Germany), previously used by Wilders-Truschnig et al.[17] IgG calibration was performed against the international reference material 1st World Health Organization International Reference Preparation 67/86 for human IgG. Quantitative measurements are reported in mg/L. Detection limit was 2.5 g/L, normalized cut-off value was 7.5 mg/L, according to the validation protocol provided by the manufacturer. All values above 7.5 mg/L were considered as positive reaction to the corresponding food.

Diet Preparation.—Being arranged according to the IgG antibody results, the elimination diet consisted of a defined panel of IgG-negative food, while the provocation diet consisted of a panel of IgG-positive food. Both elimination diet and provocation diet did not differ in calorie content. In both diet phases, patients were never forced to eat or avoid from certain foods to protect the blindness of patients and their physician for the type of diet phase (elimination or provocation). Instead, they were asked to follow their specially arranged diet list exactly and not to consume any other food in any diet phase. Both patients and physicians were blind to the type of diet and IgG tests.

Statistical Analysis.—Statistical analysis was made using the computer software SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA). For comparisons between baseline phase and provocation phase, baseline phase and elimination phase, and provocation phase and elimination phase, paired *t*-test or Wilcoxon signed-rank test were used; for comparisons between patients whose first diet phase was elimination diet and patients whose second diet phase was elimination diet (to test the "period effect"), unpaired *t*-test or Mann–Whitney test were used according to the distribution pattern of the data. Multiple comparisons were made by using repeated measures variance analysis (RM-ANOVA). Diet sequence was selected as a covariate in repeated measures, which may eliminate the cross-over effect. If a main effect is observed, subgroup analyses were also performed. Overall significance level was set as 0.05, and Bonferroni methodology was used for subgroups analyses.

Data are expressed as "mean (standard deviation [SD])," minimum-maximum, median (25th-75th percentile) and percent (%) where appropriate. $P < .05$ was considered statistically significant.

RESULTS

Study Population and Basic Demographic and Clinical Features.—The mean (SD) age of the study patients (n = 21) was 38.0 (11.2) years, and 85.7% were females. Most of patients were university graduates (85.7%), while 4.8% and 9.5% were primary and secondary school graduates, respectively.

The mean (SD) duration of migraine was 10.8 (9.8) (range 3-36) years and the duration of IBS was 10.8 (11.9) (range 2-53) years. All patients were using acute attack medication, and for migraine attacks, 4 (19.0%) patients were also identified to be under preventive medication; but, none of the patients were on a preventive medication for IBS symptoms. IgG antibody tests against 270 food allergens revealed mean (SD) reaction count (abnormally high titer) to be 23.1 (14.1) (range 6-75). According to food categories listed in Table 1, from the most to least frequent IgG positivity, seeds and nuts (86.0), and grain with gluten (76.0%) were the foods with most frequent IgG positivity.

The patients were questioned regarding adverse events. There was no adverse event leading to discontinuation of the given diet.

Headache Parameters With Respect to Phases of the Study.—Significant reductions were observed with the elimination diet compared with the run-in period in attack count, maximum attack duration,

Table 1.—The Food Categories From Most to Least Frequent Immunoglobulin G Positivity in Patients (n = 21)

Food Type	n (%)
Seeds and nuts	18 (86.0)
Grain with gluten	16 (76.0)
Spices	15 (71.0)
Fruits	15 (71.0)
Vegetables	15 (71.0)
Seafood	12 (57.0)
Eggs	12 (57.0)
Grain without gluten	10 (48.0)
Milk products	10 (48.0)
Food additives	9 (43.0)
Leguminous seeds	9 (43.0)
Coffee infusions	7 (33.0)
Yeast	6 (29.0)
Meat	5 (24.0)
Sugar products	5 (24.0)
Moss	4 (19.0)
Mushrooms	2 (10.0)
Salads	1 (0.1)

mean attack duration, maximum attack severity, number of attack that needed acute medication, and total medication intake (Table 2).

Additionally, elimination of the cross-over effect via RM-ANOVA with selection of diet sequence as a covariate also revealed significant reductions in mean (SD) attack count, number of headache days, and number of attacks with acute medication by means of elimination diet compared with baseline values ($P < .001$ for each) and also compared with provocation diet values for attack count ($P = .025$) and number of attacks with acute medication ($P = .014$) (Table 2).

IBS Symptom Scores With Respect to Phases of the Study.—Significant reductions were observed with the elimination diet compared with the run-in period in all symptoms except number of defecation days per week (Table 3). However, during provocation diet use, no improvement was seen in pain-bloating severity, number of defecation days per week, QoL, and pain-bloating (Table 3). Symptom scores were significantly lower with the elimination diet compared with provocation for pain-bloating severity, diarrhea-constipation severity, QoL, and pain-bloating (Table 3).

Additionally, elimination of the cross-over effect via RM-ANOVA with selection of diet sequence as a covariate also revealed significant reductions in mean (SD) pain-bloating within the last 10 days by means of elimination diet when compared with baseline ($P < .001$) and provocation diet ($P = .019$) (Table 3).

Emotional Well-Being and Belief in IBS Treatment in Study Phases.—Elimination diet was associated with significantly higher scores for happiness at home (4.1 [1.1] vs 3.6 [1.1]; $P < .01$), happiness at work (3.2 [1.6] vs 2.7 [1.3]; $P < .02$), and belief in IBS treatment (4.3 [1.3] vs 3.9 [1.3]; $P < .05$), while lower scores for fear of illness (1.3 [1.2] vs 1.8 [1.3]; $P < .05$) (Table 3).

Headache and IBS Parameters Before and After the Interchange of Diets.—There was no significant difference between patients allocated to provocation or elimination diet in the first diet phase in terms of headache parameters. Following the second diet phase, mean (SD) attack count (4.1 [1.9] vs 2.2 [1.9]; $P < .05$) and number of attacks with acute medication (3.4 [1.8] vs 1.5 [1.7]; $P < .01$) were significantly higher for patients in the "elimination-to-provocation" group compared with patients in the "provocation-to-elimination" group (Table 4). With the elimination diet, percentage of patients with at least 30% reduction in migraine days was 66.7%, and that with at least 50% reduction was 47.6%.

Patients allocated to elimination diet in the first diet phase were determined to have lower scores for pain-bloating severity (1.1 [1.1] vs 3.2 [1.1]; $P < .01$), pain-bloating for the last 10 days (3.2 [2.0] vs 6.8 [2.8]; $P < .01$), and better scores for the QoL (4.2 [0.6] vs 2.5 [1.1]; $P < .001$) than patients allocated to provocation diet in the first diet phase (Table 4).

Nevertheless, there was no significant difference between patients in the "elimination-to-provocation" vs "provocation-to-elimination" groups in terms of median (interquartile range [IQR]) % change in headache and IBS parameters obtained from first to second diet phases (Table 4).

DISCUSSION

Although the mechanisms of IgG-mediated food allergy have not been fully elucidated, increase in the production of IgG antibodies and cytokines[18] via food allergy antigens has been proposed to result in

Table 2.—Headache Parameters with Respect to Phases of the Study (n = 21)

					RM-ANOVA[a]	Post hoc – Bonferroni
		Baseline	Provocation Diet	Elimination Diet	*P* Values	
Attack count	Mean (SD)	4.8 (2.1)	4.1 (1.6)	2.7 (2.0)***$^{++}$	.001	Baseline vs Pro: .483 Baseline vs Elim: <.001 Pro vs Elim: .017
	% change; median (min-max)		–20.0 (–66.7; 300.0)	–40.0 (–100.0; 100.0)$^{++}$		
# of headache days	Mean (SD)	12.7 (8.3)	8.6 (5.8)**	7.0 (6.7)***	.020	Baseline vs Pro: .025 Baseline vs Elim: <.001 Pro vs Elim: .393
	% change; median (min-max)		–33.3 (–80.0; 87.5)	–42.9 (–100.0; 13.3)		
Maximum attack duration (days)	Mean (SD)	2.6 (0.6)	2.2 (0.7)	1.4 (1.1)***$^{+}$	.255	—
	% change; median (min-max)		0.0 (–66.7; 200.0)	–66.7 (–100.0; 50.0)$^{+}$		
Mean attack duration (days)	Mean (SD)	1.8 (0.5)	1.5 (0.4)	1.1 (0.8)**	.908	—
	% change; median (min-max)		0.0 (–63.6; 120.0)	–37.5 (–100.0; 66.7)$^{+}$		
Maximum attack severity (0-10)	Mean (SD)	8.5 (1.4)	8.1 (1.6)	6.6 (3.3)***$^{+}$	.167	—
	% change; median (min-max)		–10.0 (–40.0; 42.9)	–14.3 (–100.0; 12.5)$^{+}$		
# of attacks with acute medication	Mean (SD)	4.0 (1.5)	3.4 (1.5)	1.9 (1.8)***$^{++}$	.009	Baseline vs Pro: .472 Baseline vs Elim: <.001 Pro vs Elim: .014
	% change; median (min-max)		–25.0 (–60.0; 100.0)	–66.6 (–100.0; 25.0)$^{++}$		
Total medication intake (tablets)	Mean (SD)	11.5 (7.6)	8.7 (6.7)*	6.7 (10.1)**	.354	—
	% change; median (min-max)		–33.3 (–83.3; 340.0)	–53.3 (–100.0; 100.0)$^{+}$		

Univariate analysis:
*$P < .05$, **$P < .01$, and ***$P < .001$ compared with baseline (Wilcoxon test).
$^{+}P < .05$, $^{++}P < .01$ compared with provocation diet (Wilcoxon test).
[a]RM-ANOVA = repeated measures analysis of variance with diet sequence as a covariate; SD = standard deviation; — = not available.

Table 3.—IBS Symptom Scores, Emotional Well-Being and Belief in IBS Treatment with Respect to Phases of the Study (n = 21)

	Baseline Phase	Provocation Diet	Elimination Diet	
IBS Symptom Scores	Mean (SD)	Mean (SD)	Mean (SD)	*P* Values[a]
Pain-bloating severity	3.5 (0.8)	3.2 (1.2)	1.8 (1.3)***$^{+}$	.361
# of defecation days (per week)	5.7 (5.4)	6.4 (4.1)	6.0 (2.7)	.299
Diarrhea-constipation severity	3.5 (1.1)	2.8 (1.4)*	1.9 (1.5)***$^{+}$	.347
Quality of life	2.9 (0.8)	2.9 (1.0)	3.6 (1.4)*$^{+}$	.525
Pain-bloating (within the last 10 days)	6.5 (2.7)	5.5 (3.1)	3.2 (2.8)***$^{+}$	.019 Baseline vs Pro: .211 Baseline vs Elim: <.001 Pro vs Elim: .019
Urgency	1.2 (1.6)	1.0 (1.7)*	0.7 (1.3)**	.206
Straining	2.4 (1.8)	1.7 (1.8)*	0.9 (1.1)***	.292
Inability to fully empty the bowel	3.5 (1.2)	2.7 (1.7)*	1.8 (1.5)**	.241
Emotional well-being				
Happiness at home	3.6 (1.1)	3.8 (1.1)	4.1 (1.1)**	.456
Happiness at work	2.7 (1.3)	3.0 (1.5)	3.2 (1.6)**	.178
Fear of illness	1.8 (1.3)	1.4 (1.5)	1.3 (1.2)*	.361
Belief in IBS treatment	3.9 (1.3)	4.1 (1.3)	4.3 (1.3)*	.098

Univariate analysis:
*$P < .05$, **$P < .01$, and ***$P < .001$ compared with baseline phase (Wilcoxon test).
$^{+}P < .05$ compared with provocation diet (Wilcoxon test).
[a]RM-ANOVA = repeated measures analysis of variance with diet sequence as a covariate.
IBS = irritable bowel syndrome; SD = standard deviation.

an inflammation response that seems to play an important role in the pathophysiology of migraine attacks.[19]

Likewise, offering a potential explanation for how dietary antigens could trigger migraine attacks, IBS patients were shown to have a greater area of intestinal mucosa occupied by mast cells than do healthy control individuals.[20] Additionally, the gut permeability defect identified in IBS patient was shown to lead to increased intake of dietary antigens to lamina propria that may ultimately result in raised IgG antibody production.[21]

Hence, tailored food elimination diet was reported to decrease lymphocyte proliferation responses, improve clinical outcomes, and decrease release of inflammatory mediators.[10]

According to our findings, IgG-based elimination diet per se was associated with significant improvement both in migraine (attack count, mean and maximum attack duration, maximum attack severity, and number of attacks with acute medication) and IBS parameters (frequency and severity of pain-bloating and QoL) when compared with baseline as well as provocation diet phases.

Indeed, concomitant reduction evident in both migraine and IBS symptoms via IgG-based elimination diet in our study population is compatible with the statement that many of the clinical characteristics of IBS are conceptually similar to those of migraine. Besides, subjects with IBS have been shown to be at higher risk than controls to suffer from migraine.[12] Similarly, improvement in both migraine and colitis after a month of specific diet was reported in the literature for 6 patients with both diseases.[1] Furthermore, the improvement in celiac sufferers' migraine after changing to a gluten-free diet was also reported.[3]

Besides, efficacy of IgG-based elimination diet in migraine was also reported based on significant reduction obtained both in the number of headache days and in the number of migraine attacks in the elimination diet period compared with baseline.[22]

Table 4.—Headache and IBS Parameters Among Patients Before and After the Interchange of Diets

	Provocation-to-Elimination Group (n = 10)			Elimination-to-Provocation Group (n = 11)		
	Provocation	Elimination		Elimination	Provocation	
	Following First Diet Phase†	Following Second Diet Phase‡	% Change§	Following First Diet Phase†	Following Second Diet Phase‡	% Change§
Headache Parameters	Mean (SD)	Mean (SD)	Median (IQR)	Mean (SD)	Mean (SD)	Median (IQR)
Attack count	4.2 (2.1)	2.2 (1.9)	−55.0 (66.0)	3.1 (2.1)	4.1 (1.9)*	−33.3 (91.7)
# of headache days	8.3 (5.7)	6.0 (8.1)	−63.3 (118.6)	7.9 (5.4)	8.9 (6.1)	−5.6 (70.8)
Maximum attack duration (days)	2.3 (0.8)	1.4 (1.2)	−66.7 (87.5)	1.5 (1.1)	2.1 (0.7)	−50.0 (66.7)
Mean attack duration (days)	1.6 (0.5)	1.2 (1.0)	−36.5 (82.5)	1.1 (0.8)	1.5 (0.5)	−16.7 (50.0)
Maximum attack severity (0-10)	7.8 (1.5)	6.2 (3.8)	0.0 (87.5)	6.9 (2.8)	8.5 (1.6)	−11.1 (37.5)
# of attacks with acute medication	3.5 (1.1)	1.5 (1.7)	−63.3 (31.3)	2.3 (1.9)	3.4 (1.8)**	−33.3 (125.0)
Total medication intake (tablets)	8.8 (5.7)	6.7 (11.9)	−13.8 (128.5)	6.7 (8.7)	8.5 (7.9)	−30.0 (66.7)
IBS Parameters	Mean (SD)	Mean (SD)	Median (IQR)	Mean (SD)	Mean (SD)	Median (IQR)
Pain-bloating severity	3.2 (1.1)	1.9 (1.6)	−33.3 (95.8)	1.7 (1.1)**	3.1 (1.3)	−50.0 (66.7)
# of defecation days (per week)	5.5 (3.8)	5.3 (3.0)	0.0 (91.5)	6.5 (2.5)	7.2 (4.5)	0.0 (106.7)
Diarrhea-constipation severity	3.0 (1.8)	2.1 (1.7)	−26.7 (81.3)	1.7 (1.3)	2.6 (0.9)	−50.0 (66.7)
Quality of life	2.5 (1.1)	3.0 (1.8)	0.0 (87.5)	4.2 (0.6)***	3.3 (0.9)	25.0 (100.0)
Pain-bloating (within the last 10 days)	6.8 (2.8)	3.2 (3.6)	−43.8 (100.0)	3.2 (2.0)**	4.3 (2.9)	0.0 (95.0)
Urgency	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Straining	1.9 (1.9)	1.0 (1.2)	0.0 (43.8)	0.8 (1.0)	1.5 (1.8)	0.0 (66.7)
Inability to fully empty the bowel	3.3 (1.6)	2.0 (1.8)	−46.7 (85.0)	1.6 (1.2)*	2.1 (1.6)	0.0 (50.0)

*$P < .05$, **$P < .01$, and ***$P < .001$ compared with values of patients in "provocation-to-elimination" group.
†Following the first study diet application.
‡Following the second study diet application preceded by a washout period.
§From first to second diet phase ($P > .05$ for "provocation-to-elimination" vs "elimination-to-provocation" diets).
IBS = irritable bowel syndrome; IQR = interquartile range; SD = standard deviation.

Additionally, in a past Mexican study, IgG-based elimination diet was reported to be effective in symptomatic improvement leading to complete remission of migraine in 43 out of 65 patients without the need of medication.[1] Likewise, in 1 large-scale, double-blind trial of an elimination diet involving 88 patients treated with an oligoantigenic diet, 93% of patients with severe frequent migraine were reported to respond to the diet that eliminates all but a few sensitizing food antigens and documented to be free of headaches.[23]

As the cause of IBS remains unknown, there is no curative therapy directed to a specific target. As a result, the management of IBS has tended to focus on the amelioration of symptoms rather than disease prevention, modification, or cure.[24] In correlation to significant reduction in IBS symptoms obtained via IgG-based elimination diet in our study population, 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.[8] Accordingly, food-specific IgG4 antibodies have been demonstrated to be associated with IBS, while the 12-week exclusion diet based on IgG4 titers was reported to improve symptoms.[25] Besides, identifying and appropriately addressing food hypersensitivity and abnormal bowel microenvironment in IBS patients not previously responding to standard therapy were reported to be associated with significant clinical response. This response included objective improvement including reduction in pain and diarrhea, as well as subjective improvement considering increased QoL as in our patients.[10]

Improving QoL for the functional bowel patient has been indicated as the most important benefit that encompasses multiple domains or areas of well-being including, at a minimum, physical, psychological, and social functioning, as well as symptom improvement.[10] In this regard, significant amelioration in QoL among patients enrolled in this trial via elimination diet is worth noting.

Notably, albeit to a lesser extent than elimination diet, beneficial effect of provocation diet on certain migraine and IBS symptoms may be assumed to be associated with the cross-over design of our study, enabling consecutive use of both diets for all patients yielding same individuals to be their own controls instead of using other healthy volunteers.

In fact, reintroduction of eliminated foods was reported to result in a greater deterioration in symptoms[26] and relapse in patients who improved previously on the elimination diet[27] that suggests a real causal relation between the eliminated foods and the symptoms.[26]

Accordingly, comparison of "elimination-to-provocation" vs "provocation-to-elimination" groups in terms of headache parameters at the end of the interchange period revealed worsening in attack count as well as number of attacks with acute medication in our study population. Lack of similar triggering effect of provocation diet in case of IBS symptoms following the interchange of diets may be explained by the pronounced superiority of elimination diet to the provocation diet in the improvement of IBS symptoms of our patients at the end of the first diet phase.

Besides, elimination of the cross-over effect via RM-ANOVA, with selection of diet sequence as a covariate, also revealed significant reductions in mean (SD) attack count, number of headache days, number of attacks with acute medication, and pain-bloating within the last 10 days by means of elimination diet compared with baseline values as well as provocation diet.

Albeit no significant difference was evident between "elimination-to-provocation" vs "provocation-to-elimination" groups in terms of median (IQR) % change in headache and IBS parameters obtained from the first to the second diet phases, the overall symptom reduction in both headache and IBS parameters was the final outcome provided that the provocation diet was followed by the elimination diet. This also emphasizes the triggering role of provocation diet in induction of symptom relapse in migraine patients with IBS.

Food elimination diets and food challenges are considered to be extremely time-consuming for the patient and practitioner, and to require a high degree of patient motivation and compliance.[10] Accordingly, identification of higher percentage of patients believ-

ing in IBS treatment during elimination diet is worth noting considering the fact that the diet is an "active treatment" that if not adhered to does not seem to have an effect.

Use of exclusion diets tailored to the individual patient based on the serum IgG antibody titers was reported to have many advantages, including objectivity to the process, higher patient compliance and physician confidence, and individualization of the diet to a given patient, thereby obviating the need for excluding a large number of foods from the diet.[9]

Hence, the use of a specific diet rather than a universal migraine diet with simultaneous elimination of all known dietary triggers seems to offer a well-balanced diet in terms of safety and nutritional reasons.[27]

CONCLUSIONS

In conclusion, our findings indicate that food elimination based on IgG antibodies in migraine patients who suffer from concomitant IBS may effectively reduce symptoms from both disorders with potential savings to the health care system. In this regard, albeit small sample size of the present study necessitating caution on translation of our result to daily clinical practice, assay of IgG antibodies to food seems to have a role in helping patients with concomitant presence of migraine and IBS to identify candidate foods for elimination.

Ideally, it would have been possible to check whether the IgG response correlated with diet by a second IgG measurement after elimination or provocation. Furthermore, it would be of interest to evaluate patients presenting with IBS who happen to get migraine because patients who receive treatment for migraine can improve for many reasons besides preventive medication – patient education (which should include a focus on regular exercise, healthy meals, and avoiding fasting), relaxation/biofeedback, elimination of medication overuse, or just that fact that they tend to come in at their worst. A similar study specifically in chronic migraine patients would also be of interest. Therefore, further studies are warranted in this area.

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REFERENCES

1. Arroyave Hernández CM, Echavarría Pinto M, Hernández Montiel HL. Food allergy mediated by IgG antibodies associated with migraine in adults. *Rev Alerg Mex*. 2007;54:162-168.
2. Rasmussen BK. Epidemiology of headache. *Cephalalgia*. 2001;21:774-777.
3. Gabrielli M, Cremonini F, Fiore G, et al. Association between migraine and celiac disease: Results from a preliminary case-control and therapeutic study. *Am J Gastroenterol*. 2003;98:625-629.
4. Diamond S, Prager J, Freitag FG. Diet and headache. Is there a link? *Postgrad Med J*. 1986;79:279-286.
5. Peatfield RC, Glover V, Littlewood JT, Sandler M, Clifford Rose F. The prevalence of diet-induced migraine. *Cephalalgia*. 1984;4:179-183.

6. Rees T, Watson D, Lipscombe S, et al. A prospective audit of food intolerance among migraine patients in primary care clinical practice. *Headache Care*. 2005;2:105-110.
7. Talley NJ, Spiller R. Irritable bowel syndrome: A little understood organic bowel disease? *Lancet*. 2002;360:555-564.
8. Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: A randomised controlled trial. *Gut*. 2004;53:1459-1464.
9. Zar S, Mincher L, Benson MJ, Kumar D. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. *Scand J Gastroenterol*. 2005; 40:800-807.
10. Drisko J, Bischoff B, Hall M, McCallum R. Treating irritable bowel syndrome with a food elimination diet followed by food challenge and probiotics. *J Am Coll Nutr*. 2006;25:514-522.
11. Zuo XL, Li YQ, Li WJ, et al. Alterations of food antigen-specific serum immunoglobulins G and E antibodies in patients with irritable bowel syndrome and functional dyspepsia. *Clin Exp Allergy*. 2007; 37:823-830.
12. Cole JA, Rothman KJ, Cabral HJ, Zhang Y, Farraye FA. Migraine, fibromyalgia, and depression among people with IBS: A prevalence study. *BMC Gastroenterol*. 2006;6:26.
13. Pascual J, Oterino A. IgG-mediated allergy: A new mechanism for migraine attacks? *Cephalalgia*. 2010;30:777-779.
14. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 2nd edition. *Cephalalgia*. 2004;24:9-160.
15. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology*. 2006;130:1377-1390.
16. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: A simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther*. 1997;11:395-402.
17. Wilders-Truschnig M, Mangge H, Lieners C, et al. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. *Exp Clin Endocrinol Diabetes*. 2008;116:241-245.
18. Bischoff SC, Crowe SE. Gastrointestinal food allergy: New insights into pathophysiology and clinical perspectives. *Gastroenterology*. 2005;128:1089-1113.
19. Pascual J, Leno C. A woman with daily headaches. *J Headache Pain*. 2005;6:91-92.
20. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology*. 2004;126:693-702.
21. Barau E, Dupont C. Modifications of intestinal permeability during food provocation procedures in pediatric irritable bowel syndrome. *J Pediatr Gastroenterol Nutr*. 1990;11:72-77.
22. Alpay K, Ertas M, Orhan EK, et al. Diet restriction in migraine, based on IgG against foods: A clinical double-blind, randomised, cross-over trial. *Cephalalgia*. 2010;30:829-837.
23. Egger J, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? A double-blind controlled trial of oligoantigenic diet treatment. *Lancet*. 1983;2:865-869.
24. Sainsbury A, Ford AC. Treatment of irritable bowel syndrome: Beyond fiber and antispasmodic agents. *Ther Adv Gastroenterol*. 2011;4:115-127.
25. Finn R, Smith M, Youngs G, Chew D, Johnson PM, Barnes RM. Immunological hypersensitivity to environmental antigens in the irritable bowel syndrome. *Br J Clin Pract*. 1987;41:1041-1043.
26. Kalliomäki MA. Food allergy and irritable bowel syndrome. *Curr Opin Gastroenterol*. 2005;21:708-711. Review.
27. Millichap JG, Yee MM. The diet factor in pediatric and adolescent migraine. *Pediatr Neurol*. 2003;28:9-15. Review.

APPENDIX A

IBS Scoring Scale

Name:. . . . . Date . . . . . .
Age, Gender:. . . . . Occupation:. . . . . .
Treatment/Medication . . . . . .

Abdominal pain, Bloating	Pretreatment	0	1	2	3	4	5
	Diet-1	0	1	2	3	4	5
	Diet-2	0	1	2	3	4	5
How many days of last 10 days did you experience abdominal pain or bloating?							
	Pretreatment	. . . .days/10 days					
	Diet-1	. . . .days/10 days					
	Diet-2	. . . .days/10 days					
Diarrhea, Constipation	Pretreatment	0	1	2	3	4	5
	Diet-1	0	1	2	3	4	5
	Diet-2	0	1	2	3	4	5
Quality of life (at work, family, social) (best 5, worst 0)							
	Pretreatment	0	1	2	3	4	5
	Diet-1	0	1	2	3	4	5
	Diet-2	0	1	2	3	4	5

No of Defecation in a week: Pretreat:. . . ./a week Diet-1:. . . ./a week Diet-2:. . . ./a week
Please give points between 0 and 5 (0 for no complaint, 5 for worst complaint)
Pretreat Urgency for bowel movement ( ) Fecal incontinence ( ) Straining ( ) Incomplete evacuation ( )
Diet-1 Urgency for bowel movement ( ) Fecal incontinence ( ) Straining ( ) Incomplete evacuation ( )
Diet-2 Urgency for bowel movement ( ) Fecal incontinence ( ) Straining ( ) Incomplete evacuation ( )
Stress at work: Yes No Little
Personality: Meticulous Emotional Stressful Ambitious Relaxed Normal

Happy at work	Pretreatment	0	1	2	3	4	5
Diet-1		0	1	2	3	4	5
Diet-2		0	1	2	3	4	5

Absence from work; how many days in last 1 month
Pretreatment (. . .days) Diet-1 (. . .days) Diet-1 (. . .days)

Happy at home	Pretreatment	0	1	2	3	4	5
	Diet-1	0	1	2	3	4	5
	Diet-2	0	1	2	3	4	5
Fear of having a serious illness	Pretreatment	0	1	2	3	4	5
	Diet-1	0	1	2	3	4	5
	Diet-2	0	1	2	3	4	5
Do you believe that your disease can be cured/relieved?							
	Pretreatment	0	1	2	3	4	5
	Diet-1	0	1	2	3	4	5
	Diet-2	0	1	2	3	4	5
Are you satisfied with the treatment?	Diet-1	0	1	2	3	4	5
	Diet-2	0	1	2	3	4	5