IGG FOOD ANTIBODY GUIDED ELIMINATION-ROTATION DIET WAS MORE EFFECTIVE THAN FODMAP DIET AND CONTROL DIET IN THE TREATMENT OF WOMEN WITH MIXED IBS – RESULTS FROM AN OPEN LABEL STUDY

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Abstract

Background
Irritable bowel syndrome (IBS) is a chronic disease with recurrent abdominal pain, disturbed bowel emptying and change in stool consistency. We compared the effectiveness of dietary treatment of three different diet plans (G1-FM-low FODMAP diet, G2-IP IgG based elimination-rotation-diet, and as control group, G3-K control diet recommended by an attending gastroenterologist) in treating patients diagnosed with mixed irritable bowel syndrome.

Methods
73 female patients diagnosed with mixed form of irritable bowel syndrome (IBS-M) were enrolled in the study. The diet of each patient in group 1 (G1-FM) and 2 (G2-IP) was determined individually during a meeting with dietitian. Patients from group 3 (G3-K) received nutrition advice from a gastroenterologist.

Results
Significant differences in reduction of IBS symptoms were found between the groups. IBS symptoms as well as comorbid symptoms significantly improved or disappeared completely in the G2-IP group, while in the G1-FM group, some of the IBS symptoms significantly improved. In group G3-K no significant improvement was seen.

Conclusion
Based on the results of this open study it was found that the different dietary intervention in the treatment of patients with IBS-M was unlikely effective. The G2-IP IgG based elimination-rotation-diet demonstrating a significant overall superior result compared to the others.

Trial registration
The clinical trial was retrospective registered at ClinicalTrials.gov, March 12, 2020, ClinicalTrials.gov ID: NCT04307368, (date of first registration 25.02.2020).

Keywords
Irritable bowel syndrome (IBS), IgG food hypersensitivity, elimination-rotation diet, low-FODMAP diet, classic dietary recommendation, calprotectin

Introduction

Irritable bowel syndrome (IBS) is a chronic gastrointestinal condition. It is characterized by abdominal pains of different intensity, located usually on the left side of lower abdomen, combined with changes in stool consistency and/or bowel movements [1, 2]. Treating IBS patients is a difficult and complex clinical problem; however, it appears that adequate dietary modifications can comprise an independent element of treatment. Some patients state that nutrition is an important factor influencing clinical symptoms of irritable bowel syndrome [3-5]. This view is supported by reports indicating that from 20% to 67% of IBS patients reported symptoms occurring after food intake. IBS patients often eliminate some food products from their diet. Results of numerous studies indicate that FODMAP carbohydrates (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) in diet cause or intensify symptoms of irritable bowel syndrome, and that in contrast a low FODMAP diet gives relief to patients with IBS [6-10]. It has been shown that low FODMAP diet was effective in treating functional symptoms of gastrointestinal conditions in comparison to diet plan consistent with recommendations of the UK National Institute for Health and Clinical Excellence (NICE) [9].

In recent years, hypothesis that IBS symptoms may also result from the IgG-dependent food hypersensitivities gains more and more supporters. In contrast to the FODMAP diet, IgG guided diets implicate the immune system of each individual. Atkinson et al [11] and Dixon [12] noted that elevated IgG food antibody concentrations in the serum can be a marker of immune activation and a manifestation of delayed food hypersensitivity. They could show that the elimination-rotation diet can be an effective way to alleviate the symptoms of IBS patients and other symptoms of delayed food hypersensitivities. Other researcher showed that IgG titers to food antigens were higher in patients with IBS than in subjects without IBS [13]. Significant improvements were obtained in a study by avoiding selected IgG positive foods for 6 months [14]. The Guidelines from German Society of Digestive and Metabolic Diseases (DGVS) and German Society of Neurogastroenterology and Motility (DGNM) state that elimination diet based on high titers of IgG food antibodies can be worth trying in cases of IBS [15]. Other studies showed significant improvement of IBS symptoms together with reduced activity in comorbidities such as migraine [16, 17]. IgG guided diets may provide an individualization of the diet according to individual IgG results, which may increase the effectiveness compared to other diets, where the focus is mainly on the nature of the food, not the response from the patient. Some studies [11-14, 16-20] have proven the beneficial effect of a change of diet based on IgG antibodies to food not only in case of IBS, but also in other pathologies [21-23].

The aim of this report was to compare the effectiveness of 8 weeks with dietary treatment of three different diet plans (low FODMAP diet, elimination-rotation diet based on IgG-dependent food hypersensitivity test, and a classic diet recommended by an attending gastroenterologist) in treating patients diagnosed with IBS-M.

Material and methods

Participants

Study material comprised of IBS-M patients diagnosed by an attending physician (gastroenterologist) based on the Rome III criteria with no other digestive tract conditions (e.g., coeliac disease, gastroesophageal reflux disease) that might influence results of this study.107 adults applied to be a part of the study. Patients who were using strong opioid or psychotropic drug and patients who participated in other clinical studies on digestive tract conditions or using dietary treatment during 90 days before including in this study, was excluded from the study. Hence 73 female patients completed the study. The study was an open-label trial comparing

three different dietary treatment of IBS-M. Due to their small number, the group of men was excluded from the study and 17 women did not agree to be a part of this study, no reasons given.

Patients included in the study were allocated in 3 groups. GROUP 1 (G1-FM) consisted of 26 patients who during the 1st appointment was given a diet plan low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) for 8 weeks. Each patient received individual dietary advice, materials with an example menu written for 7 days (energy value of the diet – 1800 – 2300 kcal) and a table of products recommended and contraindicated in the FODMAP diet. GROUP 2 (G2-IP) consisted of 21 patients who during the 1st appointment had their IgG antibody titers tested in response to certain foods in order to find food hypersensitivities. After receiving the results of the test, nutritional counseling regarding the use of elimination-rotation and exemplary menu (energy value of the diet – 1800 – 2300 kcal) were given to each patient for 8 weeks. IgG positive foods were eliminated from the diet. All IgG negative foods were allowed in a rotation diet. 26 patients were classified to the GROUP 3 - THE CONTROL (G3-K) and was advised to receive a dietary treatment by their attending gastroenterologist for 8 weeks. These patients were given an easily digestible diet consisting in the modification of rational nutrition of healthy people, covering the energy needs and providing the same amount of nutrients as a normal diet and during periods of diarrhea, an easily digestible low-fat diet with lower amounts of dietary fiber (especially its insoluble form). During periods of constipations, a high-fiber diet (30 – 50g of fiber daily) was prescribed.

The study was conducted between April 2016 and December 2018. The study was conducted in accordance with the guidelines set out in the 1964 Helsinki Declaration, and all procedures involving patients were approved by the Bioethics Committee of the Medical University of Bialystok (Poland), approval No. R-I-002/389/2015.The clinical trial was registered at ClinicalTrials.gov, (date of issue: March 12, 2020; date of first registration 25.02.2020), ClinicalTrials.gov ID: NCT04307368.

Methods of laboratory testing

Determination of specific IgG antibodies titers against selected foods (GROUP 2 - G2-IP)

Venous blood serum was collected from the patients. Specific IgG antibodies titers were determined using the ImuPro Complete test (enzyme-linked immunosorbent assay (ELISA) (RIDASCREEN® R-Biopharm) according to the manufacturer's recommendations. 269 foods and IgG antibodies were tested for every patient. Individual tested antibodies and distribution are presented in Table 1. Obtained values were interpreted based on concentrations of antibodies expressed in μg/ml: < 7.5 – not elevated specific IgG concentration, ≥ 7.5 – elevated specific IgG concentration and ≥ 20.0 – highly elevated specific IgG concentration. Foods that generated elevated and highly elevated IgG concentrations were eliminated from the patient's diet plan for 8 weeks.

Table 1. Presence of specific IgG_{1-4} antibodies in response to 269 foods among women of the group G2-IP (n-21).

Foods	Response level <7.5 μg/ml IgG not elevated	Response level ≥7.5 μg/ml IgG elevated	Response level ≥20.0 μg/ml IgG highly elevated
Vegetables			
Aubergine	90.5%	9.5%	0.0%
Bamboo shoots	100.0%	0.0%	0.0%

Broad bean	95.2%	4.8%	0.0%
Chard	100.0%	0.0%	0.0%
Broccoli	85.7%	14.3%	0.0%
Rutabaga	95.2%	4.8%	0.0%
Brussels sprout	81.0%	14.3%	4.8%
Beetroot	85.7%	14.3%	0.0%
Onion	90.5%	9.5%	0.0%
Chickpea	90.5%	4.8%	4.8%
Courgette	85.7%	14.3%	0.0%
Pumpkin	100.0%	0.0%	0.0%
Mung bean	100.0%	0.0%	0.0%
Common bean	90.5%	9.5%	0.0%
Pea	90.5%	9.5%	0.0%
Kale	95.2%	4.8%	0.0%
Jute	100.0%	0.0%	0.0%
Cauliflower	100.0%	0.0%	0.0%
Kohlrabi	90.5%	9.5%	0.0%
White cabbage	90.5%	9.5%	0.0%
Red cabbage	76.2%	23.8%	0.0%
Chinese cabbage	100.0%	0.0%	0.0%
Savoy cabbage	100.0%	0.0%	0.0%
Artichoke	100.0%	0.0%	0.0%
Fennel	100.0%	0.0%	0.0%
Carrots	85.7%	14.3%	0.0%
Cucumber	95.2%	4.8%	0.0%
Okra	100.0%	0.0%	0.0%
Olive	95.2%	4.8%	0.0%
Chilli Cayenne	100.0%	0.0%	0.0%
Chilli Habanero	100.0%	0.0%	0.0%
Chilli Jalapeno	100.0%	0.0%	0.0%
Sweet pepper	81.0%	19.0%	0.0%
Parsnip	95.2%	4.8%	0.0%
Tomato	90.5%	9.5%	0.0%
Leek	95.2%	4.8%	0.0%
Radish	90.5%	9.5%	0.0%
Celeriac	85.7%	14.3%	0.0%
Celery	100.0%	0.0%	0.0%
Lentils	95.2%	4.8%	0.0%
Soybean	95.2%	0.0%	4.8%
Asparagus	100.0%	0.0%	0.0%
Spinach	100.0%	0.0%	0.0%
Potatoes	90.5%	9.5%	0.0%
Cereals containing gluten			
Gluten	23.8%	52.4%	23.8%
Barley	85.7%	14.3%	0.0%
Kamut	90.5%	4.8%	4.8%
Oats	81.0%	9.5%	9.5%
Wheat	52.4%	33.3%	14.3%

Spelt	61.9%	28.6%	9.5%
Rye	61.9%	23.8%	14.3%
Gluten-free cereals and alternatives			
Amaranth	100.0%	0.0%	0.0%
Buckwheat	90.5%	4.8%	4.8%
Carob (St John's bread)	100.0%	0.0%	0.0%
Chestnut	95.2%	4.8%	0.0%
Quinoa	95.2%	0.0%	4.8%
Maize	100.0%	0.0%	0.0%
Lupine	95.2%	4.8%	0.0%
Cassava	100.0%	0.0%	0.0%
Arrowroot	100.0%	0.0%	0.0%
Teff	100.0%	0.0%	0.0%
Fonio	100.0%	0.0%	0.0%
Millet	100.0%	0.0%	0.0%
Rice	95.2%	4.8%	0.0%
Sweet potato	95.2%	4.8%	0.0%
Jerusalem artichoke	100.0%	0.0%	0.0%
Tapioca	100.0%	0.0%	0.0%
Algae			
Red algae (nori)	81.0%	14.3%	4.8%
Spirulina	71.4%	28.6%	0.0%
Fruit			
Gooseberry	100.0%	0.0%	0.0%
Ananas	85.7%	14.3%	0.0%
Watermelon	85.7%	14.3%	0.0%
Avocado	100.0%	0.0%	0.0%
Banana	85.7%	9.5%	4.8%
Lingonberry	95.2%	4.8%	0.0%
Blueberry	95.2%	4.8%	0.0%
Peach	95.2%	4.8%	0.0%
Lemon	95.2%	4.8%	0.0%
Date	100.0%	0.0%	0.0%
Fig	100.0%	0.0%	0.0%
Pomegranate	100.0%	0.0%	0.0%
Grapefruit	100.0%	0.0%	0.0%
Pear	95.2%	4.8%	0.0%
Guava	100.0%	0.0%	0.0%
Apple	100.0%	0.0%	0.0%
Blackberry	100.0%	0.0%	0.0%
Kiwi	81.0%	14.3%	4.8%
Lychee	100.0%	0.0%	0.0%
Lime	90.5%	9.5%	0.0%
Raspberry	100.0%	0.0%	0.0%
Tangerine	90.5%	9.5%	0.0%
Mango	95.2%	4.8%	0.0%
Honeydew melon	100.0%	0.0%	0.0%
Yellow plum	85.7%	9.5%	4.8%

Apricot	100.0%	0.0%	0.0%
Nectarine	85.7%	9.5%	4.8%
Prickly pear	95.2%	4.8%	0.0%
Papaya	100.0%	0.0%	0.0%
Quince	100.0%	0.0%	0.0%
Orange	90.5%	4.8%	4.8%
Currants (red and black mixed)	100.0%	0.0%	0.0%
Rhubarb	100.0%	0.0%	0.0%
Sea buckthorn	100.0%	0.0%	0.0%
Plum	90.5%	9.5%	0.0%
Strawberry	90.5%	4.8%	4.8%
Grape	100.0%	0.0%	0.0%
Cherry	85.7%	14.3%	0.0%
Cranberry	95.2%	4.8%	0.0%
Yeast			
Yeast	71.4%	23.8%	4.8%
Spices			
Aniseed	95.2%	4.8%	0.0%
Basil	100.0%	0.0%	0.0%
Horseradish	90.5%	9.5%	0.0%
Cinnamon	100.0%	0.0%	0.0%
Savory	100.0%	0.0%	0.0%
Garlic	90.5%	4.8%	4.8%
Wild garlic	100.0%	0.0%	0.0%
Nutmeg	100.0%	0.0%	0.0%
Mustard seed	95.2%	4.8%	0.0%
Clove	100.0%	0.0%	0.0%
Ginger	85.7%	14.3%	0.0%
Juniper berry	100.0%	0.0%	0.0%
Capers	100.0%	0.0%	0.0%
Cardamom	100.0%	0.0%	0.0%
Caraway	100.0%	0.0%	0.0%
Coriander	100.0%	0.0%	0.0%
Dill	100.0%	0.0%	0.0%
Cumin	100.0%	0.0%	0.0%
Lavender	100.0%	0.0%	0.0%
Bay leaf	100.0%	0.0%	0.0%
Lovage	100.0%	0.0%	0.0%
Alfalfa	95.2%	4.8%	0.0%
Marjoram	100.0%	0.0%	0.0%
Lemon balm	100.0%	0.0%	0.0%
Oregano	100.0%	0.0%	0.0%
Paprika, spice	95.2%	4.8%	0.0%
Pepper, white	100.0%	0.0%	0.0%
Pepper, black	100.0%	0.0%	0.0%
Parsley	100.0%	0.0%	0.0%
Rosemary	100.0%	0.0%	0.0%
Cress	100.0%	0.0%	0.0%

Saffron	100.0%	0.0%	0.0%
Salvia	100.0%	0.0%	0.0%
Chive	100.0%	0.0%	0.0%
Chervil	100.0%	0.0%	0.0%
Thyme	100.0%	0.0%	0.0%
Vanilla	81.0%	14.3%	4.8%
Allspice	100.0%	0.0%	0.0%
Fish			
Anchois	95.2%	4.8%	0.0%
Patagonian toothfish	100.0%	0.0%	0.0%
Pollock	85.7%	14.3%	0.0%
Gilthead	100.0%	0.0%	0.0%
Codfish	100.0%	0.0%	0.0%
Plaice	95.2%	4.8%	0.0%
Halibut	95.2%	4.8%	0.0%
Lobster	100.0%	0.0%	0.0%
Squid	100.0%	0.0%	0.0%
Redfish	85.7%	9.5%	4.8%
Carp	100.0%	0.0%	0.0%
Shrimp	95.2%	4.8%	0.0%
Salmon	100.0%	0.0%	0.0%
Snapper	100.0%	0.0%	0.0%
Mackerel	100.0%	0.0%	0.0%
Swordfish	100.0%	0.0%	0.0%
Sea bass	95.2%	4.8%	0.0%
Blue mussels	100.0%	0.0%	0.0%
Octopus	100.0%	0.0%	0.0%
Oyster	85.7%	14.3%	0.0%
Panga (iridescent shark)	85.7%	14.3%	0.0%
Haddock	100.0%	0.0%	0.0%
Scallop	100.0%	0.0%	0.0%
Trout	90.5%	9.5%	0.0%
Crayfish	100.0%	0.0%	0.0%
Shark	100.0%	0.0%	0.0%
Zander	100.0%	0.0%	0.0%
Sardine	95.2%	4.8%	0.0%
Herring	90.5%	9.5%	0.0%
Sole	100.0%	0.0%	0.0%
Tuna	95.2%	4.8%	0.0%
Eel	95.2%	4.8%	0.0%
Angler	95.2%	4.8%	0.0%
Mushroom			
Oyster mushrooms	100.0%	0.0%	0.0%
Cep (boletus)	100.0%	0.0%	0.0%
Shiitake	100.0%	0.0%	0.0%
Meadow mushrooms	100.0%	0.0%	0.0%
Chanterelle	100.0%	0.0%	0.0%
Bay boletus	100.0%	0.0%	0.0%

Meat			
Veal	95.2%	4.8%	0.0%
Wild boar	95.2%	4.8%	0.0%
Goose	100.0%	0.0%	0.0%
Turkey	100.0%	0.0%	0.0%
Lamb	100.0%	0.0%	0.0%
Deer	100.0%	0.0%	0.0%
Duck	100.0%	0.0%	0.0%
Rabbit	95.2%	4.8%	0.0%
Chicken	95.2%	4.8%	0.0%
Goat meat	100.0%	0.0%	0.0%
Ostrich meat	100.0%	0.0%	0.0%
Quail	100.0%	0.0%	0.0%
Roe deer	100.0%	0.0%	0.0%
Pork	90.5%	4.8%	4.8%
Beef	90.5%	9.5%	0.0%
Hare	95.2%	4.8%	0.0%
Seeds and nuts			
Cacao bean	100.0%	0.0%	0.0%
Coconut	95.2%	0.0%	4.8%
Poppy seed	90.5%	4.8%	4.8%
Almond	95.2%	0.0%	4.8%
Sunflower seeds	90.5%	4.8%	4.8%
Cashews	95.2%	0.0%	4.8%
Brazil nuts	90.5%	4.8%	4.8%
Hazelnuts	95.2%	0.0%	4.8%
Macadamia nuts	95.2%	0.0%	4.8%
Walnut	100.0%	0.0%	0.0%
Pine nuts	100.0%	0.0%	0.0%
Peanuts	90.5%	9.5%	0.0%
Pumpkin seeds	95.2%	0.0%	4.8%
Pistachio nuts	90.5%	4.8%	4.8%
Sesame seeds	95.2%	4.8%	0.0%
Flax, linseed	71.4%	23.8%	4.8%
Eggs			
Chicken egg white	23.8%	23.8%	52.4%
Geese egg	57.1%	28.6%	14.3%
Quail egg	38.1%	47.6%	14.3%
Chicken egg yolk	38.1%	42.9%	19.0%
Additives			
Agar (E406)	81.0%	19.0%	0.0%
Aloe	100.0%	0.0%	0.0%
Aspergillus niger	90.5%	9.5%	0.0%
Sodium benzoate (E211)	100.0%	0.0%	0.0%
Guar gum (E412)	66.7%	28.6%	4.8%
Xantan gum (E415)	90.5%	4.8%	4.8%
Candied lemon zest	100.0%	0.0%	0.0%
Carrageen (E407)	100.0%	0.0%	0.0%

Curcumin (E100)	95.2%	4.8%	0.0%
Sorbic acid (E200)	100.0%	0.0%	0.0%
Vine leaves	100.0%	0.0%	0.0%
Pectins (E440)	95.2%	4.8%	0.0%
Tragacanth (E413)	100.0%	0.0%	0.0%
Milk products			
Kefir	57.1%	23.8%	19.0%
Mare’s milk	90.5%	9.5%	0.0%
Goat milk, goat cheese	76.2%	14.3%	9.5%
Cow's milk	28.6%	33.3%	38.1%
Cooked cow's milk	57.1%	23.8%	19.0%
Sheep's milk, sheep's cheese	85.7%	9.5%	4.8%
Camel’s milk	95.2%	4.8%	0.0%
Sour-milk products	38.1%	33.3%	28.6%
Halloumi	85.7%	14.3%	0.0%
Cow’s rennet cheese	85.7%	14.3%	0.0%
Ricotta cheese	47.6%	28.6%	23.8%
Lettuces			
Chicory	95.2%	4.8%	0.0%
Endive	100.0%	0.0%	0.0%
Radicchio	95.2%	4.8%	0.0%
Dandelion	100.0%	0.0%	0.0%
Lamb’s lettuce	90.5%	9.5%	0.0%
Arugula	100.0%	0.0%	0.0%
Iceberg lettuce	95.2%	4.8%	0.0%
Iceberg lettuce	100.0%	0.0%	0.0%
Lollo rosso	100.0%	0.0%	0.0%
Romaine lettuce	100.0%	0.0%	0.0%
Coffee, tea			
Rose hip	100.0%	0.0%	0.0%
Rooibos tea	100.0%	0.0%	0.0%
Tea, black	100.0%	0.0%	0.0%
Tea, green	100.0%	0.0%	0.0%
Coffee	100.0%	0.0%	0.0%
Peppermint	95.2%	4.8%	0.0%
Nettle	100.0%	0.0%	0.0%
Camomile	100.0%	0.0%	0.0%
Tannin	100.0%	0.0%	0.0%
Sweeteners			
Cane sugar	100.0%	0.0%	0.0%
Honey (mixed)	76.2%	14.3%	9.5%
Maple syrup	100.0%	0.0%	0.0%
Agave nectar	85.7%	14.3%	0.0%

Determination of fecal calprotectin concentration

In order to identify digestive tract inflammation, calprotectin concentration was determined in a stool sample. The test was conducted using the enzyme-linked immunosorbent assay (ELISA) (RIDASCREEN® Calprotectin R-Biopharm) according to manufacturer's recommendation. Values ≤50 mg/kg of stool were considered as normal values, values >50 mg/kg of stool are considered elevated values.

Statistical analyses

Significance of changes in the frequency of IBS symptoms before and after the prescribed diet plans was tested using the McNemar tests. In individual cases, when a certain symptom was not reported by the patients, it was not possible to conduct the test for numerical reasons.
Quantitative variables (i.e., calprotectin concentration) were analyzed using non-parametric tests, and verified using the Shapiro-Wilk test.

Results

Demographic characterization of the studied patients

Table 2. Demographic characterization of the patients.

Selected demographic features	G1-FM, n= 26	G2-IP (n=21)	G3-K (n=26)	P
AGE				
mean age	42.70±16.70	40.60±14.50	41.70±13.40	0.931*
Median	46.00	46.00	43.50	
the total mean age	41.70±14.80			
LEVEL OF EDUCATION				
Vocational	2 (7.70%)	2 (9.50%)	2 (7.70%)	0.078**
Secondary	7 (26.90%)	11 (52.40%)	4 (15.40%)	
Higher	17 (65.40%)	8 (38.10%)	20 (76.90%)	
PLACE OF RESIDENCE				
Village	3 (11.50%)	3 (14.30%)	1 (3.80%)	0.155**
Town	0	3 (14.30%)	1 (3.80%)	
City	23 (88.50%)	15 (71.40%)	24 (92.30%)	
IBS DURATION				
<5 years	11 (42.30%)	12 (57.10%)	11 (42.30%)	0.849**
6 – 10 years	9 (34.60%)	5 (23.80%)	9 (34.60%)	
>11 years	6 (23.10%)	4 (19.00%)	6 (23.10%)	

p* Kruskal-Wallis test (comparison of groups regarding age)
p** Pearson's chi-square independence test
G1-FM – the FODMAP group
G2-IP – the elimination-rotation group
G3-K – the control group

Results

Tables 3, 4, and 5 present the presence of "typical" clinical symptoms, dyspeptic symptoms, and extra-intestinal symptoms in the female IBS-M patients before and after dietary treatment. Patients were asked a closed question of a single choice "yes", "no".

When comparing idiopathic abdominal pain, abdominal pain after a meal, abdominal pain during defecation and sensation of incomplete defecation before and after the diet plans, statistically significant differences were found only in the case of the group G2-IP. (Table 3).

During the 1st examination, mucus in stool was reported by 30.8% of the patients from the group G1-FM, 28.6% of the patients from group G2-IP, and 19.2% of the patients from group G3-K. During the final examination, significant improvement was found in the group G1-FM were only 7.7% (p=0.031) reported mucus in stool, and in G2-IP, no patient reported this symptom anymore. However, in the group G3-K the percentage of the patients reporting mucus in stool increased, but not significant. (Table 3). In the section concerning typical symptoms connected to digestive tract, patients were asked whether they experienced constipations, bloating, sensation of gurgling, and sensation of gastric fullness. The results proved significant reduction of these symptoms in the group G2-IP. Also, after 8 weeks with low-FODMAP diet, the percentage of patients reporting bloating, sensation of gurgling, and sensation of gastric fullness decreased statistically significant (Table 3). During the final examination, nausea disappeared in groups G1-FM and G2-IP, but not in the G3-K group (Table 4).

Extra-intestinal symptoms like tiredness and weakness, skin lesions and headaches/migraine were also evaluated before and after the dietary interventions (Table 5). Patients were asked a closed question of a single choice "yes", "no".

Table 3. Frequency of IBS symptoms in studied patients before and after dietary treatment.

Symptoms		G1-FM			G2-IP			G3-K		
		1st examination	2nd examination	P	1st examination	2nd examination	P	1st examination	2nd examination	P
Idiopathic abdominal pain	N	15	11	0.125	16	2	**0.000**	16	14	0.500
	%	57.7	42.3		76.2	9.5		61.5	53.8	
Abdominal pain after a meal	N	11	6	0.063	14	2	**0.000**	14	12	0.625
	%	42.3	23.1		66.7	9.5		53.8	46.2	
Abdominal pain during defecation	N	5	2	0.250	9	1	**0.008**	6	6	1.000
	%	19.2	7.7		42.9	4.8		23.1	23.1	
Sensation of incomplete defecation	N	13	10	0.250	13	2	**0.001**	14	15	1.000
	%	50.0	38.5		61.9	9.5		53.8	57.7	
Mucus in stool	N	8	2	**0.031**	6	0	*	5	6	1.000
	%	30.8	7.7		28.6	0.0		19.2	23.1	
Blood in stool	N	3	0	*	2	0	*	2	2	1.000
	%	11.5	0.0		9.5	0.0		7.7	7.7	
Difficulty to defecate (constipations)	N	11	7	0.219	14	4	**0.002**	19	17	0.500
	%	42.3	26.9		66.7	19.0		73.1	65.4	
Bloating	N	22	7	**0.000**	19	2	**0.000**	24	22	0.500
	%	84.6	26.9		90.5	9.5		92.3	84.6	
Gurgling sensation	N	17	4	**0.000**	18	2	**0.000**	21	19	0.500
	%	65.4	15.4		85.7	9.5		80.8	73.1	
Gastric fullness	N	15	3	**0.000**	19	2	**0.000**	22	19	0.250
	%	57.7	11.5		90.5	9.5		84.6	73.1	

McNemar p test
* conducting the test was impossible because the symptom was not reported by any patient during the 2nd examination
G1-FM – the FODMAP group

G2-IP – the elimination-rotation group
G3-K – the control group
N – number of patients

Table 4. Frequency of dyspeptic IBS symptoms in studied patients before and after dietary treatment.

Symptoms		G1-FM			G2-IP			G3-K		
		1st examination	2nd examination	P	1st examination	2nd examination	P	1st examination	2nd examination	P
Nausea	N	6	0	*	7	0	*	9	9	1.000
	%	23.1	0.0		33.3	0,0		34.6	34.6	
Heartburn	N	2	2	1.000	7	1	**0.031**	5	4	1.000
	%	7.7	7.7		33.3	4.8		19.2	15.4	
Belching	N	5	4	1.000	6	0,0	*	7	7	1.000
	%	19.2	15.4		28.6	0,0		26.9	26.9	

McNemar p test
*conducting the test was impossible because the symptom was not reported by any patient during the 2nd examination
G1-FM – the FODMAP group
G2-IP – the elimination-rotation group
G3-K – the control group

Table 5. Frequency of extra-intestinal symptoms in patients before and after dietary treatment.

Symptoms		G1-FM			G2-IP			G3-K		
		1st examination	2nd examination	P	1st examination	2nd examination	P	1st examination	2nd examination	P
Constant tiredness and weakness	N	5	4	1.000	7	1	**0.031**	9	8	1.000
	%	19.2	15.4		33.3	4.8		34.6	30.8	
Skin conditions	N	0	0	*	4	0	*	1	1	1.000
	%	0.0	0.0		19.0	0.0		3.8	3.8	
Headaches/migraines	N	3	3	1.000	3	0	*	5	4	1.000
	%	11.5	11.5		14.3	0.0		19.2	15.4	

McNemar p test
* conducting the test was impossible because the symptom was not reported by any patient during the 2nd examination
G1-FM - FODMAP group
G2-IP - the elimination-rotation group
G3-K - the control group

Discussion

IBS is a complex syndrome with probably different causes and a single or generalized treatment will not be efficient. It seems obvious that food plays a major role in development of IBS, either due to the nature of the food, the immune response from the host, or the microbiota present.

This report includes analysis of the frequencies of typical irritable bowel syndrome symptoms (e.g., idiopathic abdominal pain, abdominal pain after a meal, abdominal pain during defecation, sensation of incomplete defecation, mucus and blood in stool, and bloating), dyspeptic symptoms (nausea, heartburn, and belching), and non-bowel symptoms (constant tiredness, skin lesions, and headaches) occurring before the dietary treatment and after

implementing the 8-week elimination-rotation diet plan. After implementing the diet, among patients with IBS-M, statistically significant reduction of the frequency of the idiopathic abdominal pain was found. Strikingly, only in the G2-IP group a highly significant decrease or complete disappearance of dyspeptic IBS symptoms and comorbidities together with IBS symptoms could be seen, while no differences could be observed in G1-FM and G3-K.

For a long time, it has been known that low-FODMAP diet was effective in treating functional symptoms of digestive tract conditions in comparison to diet plan consistent with recommendations of the UK National Institute for Health and Clinical Excellence (NICE). [7-9,24-26]. Over 76% of patients reported improvement after introducing the low-FODMAP diet in comparison to 54% eating according to the NICE recommendations. In these studies, improvements were seen mainly for abdominal pain, abdominal cramps, diarrhea, gas and bloating. Other symptoms either weren't analyzed or didn't show any improvement. This seems logic, as the effect of FODMAPs is mainly excessive production of gas, leading to discomfort and pain and an increased osmotic effect leading to increased bowel movement and diarrhea. Nevertheless 30% of the affected patients still suffered from bloating on the FODMAP diet. Similar observations were found in this study except that both bloating, gurgling sensation and gastric fullness decreased significantly. Gurgling sensation decreased from 65% to 15%, and gastric fullness decreased from 58% to 11% of the patients on the low FODMAP diet. The patients on the elimination-rotation group had a decrease in bloating from 90% to 9%, in gurgling sensation from 85% to 9% and in gastric fullness from 90% to 9%. This study shows that a personalized dietary approach is more effective in treating IBS than generalized diet recommendations and even more effective than low FODMAP diet. Only the IgG elimination-rotation diet could demonstrate significant improvements in all monitored IBS symptoms.

IBS is often associated with extra-intestinal comorbid disorders such as migraine [27], asthma, food-, pollen- and animal allergies, psoriasis, and rheumatoid arthritis, as well as behavior disorders and depression. This provides evidence that different peripheral pathways may be involved in the pathogenesis of certain functional gastrointestinal disorders [28,29]. In recent years, there is increasing evidence that the irritable bowel syndrome symptoms are a low-grade inflammatory disease [30-32] and may result from or lead to IgG-dependent food hypersensitivities. Our data confirm previous results from different studies, showing the effectiveness of an IgG guided diet also in comorbid conditions such as fatigue, headache/migraine and skin conditions. Identical results were found by Aydinlar [17] who could show that migraine paralleled IBS improvements after a change of diet according to IgG findings. A recent paper [16] confirmed these findings and furthermore showed an increase of serotonin after the elimination diet. This could be an indication of lower inflammation in the gut. Wichers et al [33] showed that inflammation leads to the depletion of tryptophan via IDO (indole-amine dioxygenase) and thus to lower serotonin levels, promoting fatigue and depression. This confirms the hypothesis that apparently disparate conditions may operate through common pathways, and treatments used exclusively for one of these conditions may prove beneficial for the others [34].

There is still a controversial discussion about the use of IgG tests to detect delayed food sensitivities [35]. The IgG antibodies include 4 subclasses IgG_{1-4}. They efficiently opsonize pathogens enabling their absorption by phagocytes and activate the complement system, except IgG4 [36,37]. IgG_4 are antibodies released in response to IL-10 (anti-inflammatory cytokine), an antibody connected to Th2 immune response in the process of desensitization in type-I allergies (IgE-independent). Since the discovery of Th17 linage [38], IgG must be seen at a different angle

than before. IgG is not only the immunoglobulin that protects us against foreign infectious agents but is now also recognized as a mediator of inflammation and responsible for auto-immune diseases. The balance of Th17 and Treg is largely responsible for the pro-inflammatory conditions in our body. Both are expressed in peripheral tissue and in particular in the gut [39]. Alterations of the microbiome [40] and leaky gut induce the activation of Th17 mediated immune response and the production of pro-inflammatory IgG antibodies against food and other potential harmful antigens present in the gut [40]. The publication Jönnson et al [18] demonstrated the pathological pathways of IgG inducing an inflammatory reaction, via Platelet Activation Factor (PAF), with the participation of IgG receptors and neutrophils. They also showed and reproduced previous scientific findings [41-43] that IgG can be implicated in anaphylaxis.

It is difficult to assess low grade inflammation in the gut. Among the available diagnostic markers, calprotectin is currently one of the best-known markers indicating mucosa inflammation and changes in the inflammation intensity. In this paper it was assumed that serious intestinal inflammation was diagnosed at the fecal calprotectin concentration of >50 mg/kg of stool. During the 1st examination, no statistically significant differences were found in calprotectin concentrations between the compared groups of patients and the values were low. These findings suggest that the included patients suffered from low grade inflammation suitable for alteration of diet as the best choice of treatment.

The main limitations of this study are the open-labeled nature and the low number of participants in the study. Another weakness is that the patients consist of females only. Further, all patients were not tested for IgG food antibodies, only those in the G2 group. It would be helpful to compare common IgG food hypersensitivities between the groups. It would also be of interest to know which foods the patients were ingested before they entered in the study. These limitations can impact or influence the interpretation of the findings from our research.

Conclusions

This study shows that a personalized dietary approach is more effective in treating IBS, than generalized diet recommendations. Only the IgG elimination-rotation diet could demonstrate significant improvements in all monitored IBS symptoms as well as extra-intestinal symptoms. None of the diets have shown 100% effectiveness. By applying an IgG guided elimination diet, some FODMAPs are automatically removed as well, depending on which foods have to be avoided. One possible strategy could be to start with the elimination-rotation diet, as it was proved to be the more effective in this open study and in case of persistent symptoms to combine it with a low-FODMAP diet. Claims that IgG food antibodies are only revealing exposure to food not intolerance should be reinvestigated in larger double blinded studies.

Conflict of interests

D.W and L.O declare no conflict of interest. C.F.J.L, M.G. and A. B. are employees of the Institute of Microecology in Poznań, where the ImuPro tests were determined. D.T. is the Head of Laboratory and shareholder of Lab1 offering ImuPro tests in Norway.

Declaration

Ethics approval and consent to participate

The study was conducted in accordance with the guidelines set out in the 1964 Helsinki Declaration, and all procedures involving patients were approved by the Bioethics Committee of the Medical University of Bialystok (Poland), approval No. R-I-002/389/2015. All patients had signed informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DW collected and analyzed the data, wrote and conceptualized the manuscript. LO analyzed the data, wrote and conceptualized the manuscript. DW established the database, wrote and reviewed the manuscript. DW, LO, CFJL, MG, AB, DT reviewed and commented on the manuscript. DW, LO established the study, wrote and conceptualized the manuscript. All authors have read and approved the manuscript.

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Authors' information (optional)

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