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Walker K. Carson

Joseph L. Baumert

Jennifer Clarke

Jacques Izard

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Walker K Carson,[1,2] Joseph L Baumert,[1] Jennifer L Clarke,[3] Jacques Izard [1,2]

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[1]Department of Food Science and Technology, University of Nebraska-Lincoln, Lincoln, Nebraska, USA
[2]Nebraska Food for Health Center, University of Nebraska-Lincoln, Lincoln, Nebraska, USA
[3]Department of Statistics, University of Nebraska-Lincoln, Lincoln, Nebraska, USA

Correspondence to
Dr Jacques Izard;
izard@izard.org

ABSTRACT

Objective The effects of food sensitivity can easily be masked by other digestive symptoms in ostomates and are unknown. We investigated food-specific-IgG presence in ostomates relative to participants affected by other digestive diseases.

Design Food-specific-IgG was evaluated for 198 participants with a panel of 109 foods. Immunocompetency status was also tested. Jejunostomates, ileostomates and colostomates were compared with individuals with digestive tract diseases with inflammatory components (periodontitis, eosinophilic esophagitis, duodenitis, ulcerative colitis, Crohn's disease and appendicitis), as well as food malabsorption due to intolerance. A logistic regression model with covariates was used to estimate the effect of the experimental data and demographic characteristics on the likelihood of the immune response.

Results Jejunostomates and ileostomates had a significant risk of presenting circulating food-specific-IgG in contrast to colostomates (OR 12.70 (p=0.002), 6.19 (p=0.011) and 2.69 (p=0.22), respectively). Crohn's disease, eosinophilic esophagitis and food malabsorption groups also showed significantly elevated risks (OR 4.67 (p=0.048), 8.16 (p=0.016) and 18.00 (p=0.003), respectively), but not the ulcerative colitis group (OR 2.05 (p=0.36)). Individuals with profoundly or significantly reduced, and mild to moderately reduced, levels of total IgG were protected from the formation of food-specific IgG (OR 0.09 (p=<0.001) and 0.33 (p=0.005), respectively). Males were at higher risk than females.

Conclusion The strength of a subject's immunocompetence plays a role in the intensity to which the humoral system responds via food-specific-IgG. An element of biogeography emerges in which the maintenance of a colonic space might influence the risk of having circulating food-specific-IgG in ostomates.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Ostomates must control their diet while managing symptomatology related to food intake.
⇒ Food-specific-IgG-based elimination diets have been shown to be effective at reducing symptoms in some digestive diseases.
⇒ Food sensitivity is a complex phenomenon that is still misunderstood.

WHAT THIS STUDY ADDS?

⇒ A first analysis food-specific-IgG presents across digestive diseases or resections.
⇒ The impact of hypogammaglobulinaemia on circulating food-specific-IgG presentation.
⇒ Uncover a potential biogeography implication on food-specific-IgG risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH AND CLINICAL PRACTICE?

⇒ These findings broaden our understanding of risk of presenting circulating food-specific-IgG in digestive diseases.
⇒ Further studies need to investigate the impact of colon resection on the immune system.
⇒ Food-specific-IgG-based elimination diet might be an option for ostomates to improve quality of life outcomes.

INTRODUCTION

From the moment that a patient undergoes digestive tract-resection surgery leading to an ostomy, they are faced with a multitude of challenges and often experience a significantly reduced quality of life.[1 2] The needs for surgery are diverse and include escalation of gastrointestinal disorders such as Crohn's disease and ulcerative colitis, cancer and associated treatment, or traumatic abdominal injury. For jejunostomates, ileostomates and colostomates, adjustments in day-to-day living must also be made in order to manage food intake linked to aspects of stoma output like volume, consistency, gas release and frequency.[1 2] This activity balances nutritional intake, nutrient absorption, hydration and quality of life. Many aspects of managing output also affect the psychological well-being of ostomates, and can be amplified by personal circumstances, such as marital status or religion.[1–3]

While no current guidelines encourage the exclusion of specific foods from the diets of

ostomates, there are recommendations for managing the volume, consistency and gas release of stomas.[4] Individuals with jejunostomies and ileostomies can frequently have issues surrounding dehydration and electrolyte imbalance due to the loss of water that is normally reabsorbed in the colon.[5] Deficiencies of vitamin B_{12}, iron and zinc have also been observed in ileostomates and are associated with reduced quality of life.[1] These observations extend beyond minerals and vitamins to include short chain fatty acids and polyphenols, for example.[6 7] In the midst of the many issues that ostomates can face, there have been no studies on the presence of food sensitivity in ostomates.

Outside of the studies of food allergies that are, by definition, IgE mediated, the inconsistency of keywords between authors has been detrimental to a greater understanding of IgG, immune and non-immune-mediated food sensitivity and intolerance as well as food-related inflammation. These mechanisms of delayed symptomatology of food sensitivity and intolerance can also modify output characteristics. The mechanisms leading to the presence of food-specific-IgG are still under investigation in the larger context of immunotolerance, oral tolerance, inflammation, intestinal permeability, leaky gut and temporary or more long-term mucosal damage. Two challenges face us all: the difficulty to pinpointing the delayed effects of foods associated with the sensitivity process and the large amount of confusion surrounding definitions and symptomatology descriptions.

There is a growing body of evidence correlating food-specific IgG and disease or comorbidities associated with bearing an ostomy. These comorbidities include Crohn's disease, ulcerative colitis, inflammatory bowel disease, headaches and anxiety.[8–11] An IgG-guided elimination diet has shown to partially alleviate the symptoms. The designed diet can affect faecal output, digestive symptoms and quality-of-life measurements.[12–15]

The present work investigates food sensitivity, as defined by the presence of circulating IgG against food antigens, in participants with different digestive disorders. The rates of positivity as well as the relative intensity of response toward food antigens in ostomates were compared with samples associated with diagnostic codes of inflammatory diseases identified along the digestive tract as well as food malabsorption due to food intolerance.

METHODS

Study population

Biobank samples were originally collected with the consent of Nebraska Medicine patients and consist of remaining donated blood samples from scheduled laboratory tests. The inclusion criteria for the request were for deidentified sera from individuals over the age of 19, the age of adulthood in Nebraska, with specific medical diagnoses affecting the digestive tract as described below. The exclusion criteria included the presence of a urostomy and that no two samples from the same individual were to be included. A total of 198 deidentified serum samples were acquired with the following diagnoses: appendicitis (n=18), colostomy (n=18), Crohn's disease (n=18), duodenitis (n=25), eosinophilic esophagitis (n=15), food malabsorption due to intolerance (n=18), ileostomy (n=31), jejunostomy (n=22), periodontitis (n=18) and ulcerative colitis (n=15). Specific ICD-10 codes (International Classification of Diseases version 10) can be found in online supplemental table 1. Eosinophilic esophagitis served as positive controls based on prior knowledge.[16]

The public involvement, prior to this research, was done through informal discussions with the ostomate community regarding the diverse symptoms observed with different food intake. Ostomates, ostomy nurses and advocates have expressed interest in disseminating the published findings.

ELISA-based testing

Serum food-specific-IgG were evaluated using the Eagle Biosciences IgG (109 foods) ELISA Assay Kit (Catalogue number: CNS14M; Eagle Biosciences, Amherst, NH). This is a 96 well-based ELISA kit with a few related foods pooled into single wells, such as lemon and lime (online supplemental table 2). For further analysis, tested foods were placed into 16 groups according to the US Department of Agriculture Food Data Central database (online supplemental table 3). The ELISA plates were read using a BioTek Synergy H1 plate reader (BioTek, Winooski, VT). As per manufacturer protocol, a categorical score was assigned from zero to three based on the strength of response. The categorical sum was calculated as the sum of all assigned scores to each food for each individual. The number of foods positive was calculated as the sum of different food recognised by each individual.

Total IgG-based evaluation was performed using Human IgG ELISA assay (Catalogue number: EGG39-K01; Eagle Biosciences). The mean absorbance of duplicate standards and samples was calculated. For analysis, the data was used as continuous or categorised as per strength of immune competency.[17–19] Individuals with total IgG level <299 mg/dL, 299–599 mg/dL, 600–1600 mg/dL and >1600 mg/dL were classified as 'profoundly or significantly reduced', 'moderately reduced', 'normal' and 'elevated', respectively.

Total IgA-based evaluation was performed using Human IgA ELISA assay (Catalogue number: HUG39-K01; Eagle Biosciences). Samples and standards were run in duplicate. For analysis, the data were used as continuous or categorised as per strength of immune competency.[19 20] Individuals with total IgA level <7 mg/dL, 7–60 mg/dL, 61–356 mg/dL and >356 mg/dL were classified as 'deficient', 'reduced', 'normal' and 'elevated', respectively.

Serum calprotectin was quantified using Calprotectin ELISA kit (Catalogue number: ab267628; Abcam, Cambridge, UK). Samples and standards were run in duplicate. Serum calprotectin was used to evaluate both systemic and digestive tract inflammation at the time of sampling. For analysis, the data were used as

continuous data or the calprotectin and associated levels of inflammation were categorised.[21] Individuals with serum calprotectin level <215 ng/mL, 215–3800 ng/mL and >3800 ng/mL were classified as 'low', 'normal' and 'high', respectively.

Statistical analysis

All analyses were performed using the statistical environment R (V.4.0.3) using the Integrated Development Environment RStudio for mac OS (V.1.4.1103). All standard curves were plotted on a semilog graph, with the concentration plotted logarithmically and the optical density plotted linearly, using the R package 'drc'.[22] The best-fit line was calculated using a four-parameter logistics curve.

Statistical differences between groups (ICD-10 or categorical classification for total IgG, IgA and calprotectin) were analysed using a Kruskal-Wallis analysis of variance (ANOVA) and Dunn's test, using the ggpubr package. Typically, when performing a Dunn's test, a multiple testing correction is applied to the resulting p values in order to avoid an inflated type 1 error level. These adjustments are quite conservative due to the large number of groups being tested, hence p values for the Dunn's test presented in the results section are unadjusted unless otherwise specified. Wilcoxon rank-sum test was used to assess differences in the number of foods present, categorical sum, total serum IgG, total serum IgA and total serum calprotectin.

To further investigate the possible factors (ie, covariates) impacting response, a logistic regression model was used to assess the impact of total serum IgG, total serum IgA and ICD-10 of selection on the presence of food-specific IgG while controlling for age and body mass index (BMI). The likelihood of food-specific IgG presence was used as the dependent response variable. The logistic regression model was used to estimate the degree to which ICD-10, gender, total IgG and total IgA impact the likelihood of response. Because some BMI measurements were missing from the metadata (n=46), values have been imputed for analysis using k-nearest neighbours methodology by using the kNN function of the VIM package (k=6).[23] All statistical significance was determined at $p<0.05$.

RESULTS

To investigate the risk of food sensitivities in ostomates, we compared 198 samples from jejunostomates, ileostomates, colostomates and other diseases localised along the digestive tract. These include, per positioning along the digestive tract, periodontitis, eosinophilic esophagitis, duodenitis, Crohn's disease of the small intestine, appendicitis, ulcerative colitis and food malabsorption due to intolerance. The sample was composed of 52.5% females and 47.5% males, with a mean age of 49.70±17.50 years (online supplemental table 4). Eighty-three per cent of serum samples originated from Caucasian individuals, 11% from African Americans, 2% from Native Americans, 1% from Asian individuals and 3% from individuals of unspecified race.

The top 10 most prevalent food antigens detected within the samples were cow's milk (55.56%), egg white (50.00%), wheat (36.36%), goat's/sheep's milk (35.35%), egg yolk (32.83%), beer yeast (28.28%), peanut (19.19%), bread yeast (18.69%), gluten (14.65%) and soybean (14.14%). A total of 55 out of 109 foods were detected, with 31 of them detected in at least 5% of the population.

The top five food categories detected were milk (55.56% of the individual tested positive for at least one product), eggs (51.52%) cereals grains and pasta (43.43%), legumes and legumes products (32.32%) and yeast (28.28%). At the exception of cereals grains and pasta, in the other four categories, all members of the category have been detected. Of note, no antigens were detected in the dark green vegetables and poultry categories. The remaining categories had only a subset of the foods detected (online supplemental table 2 and 5).

The distributions of positive foods across the different groups are similar; few foods are being shared by a significant proportion of individuals (like the most prevalent foods above mentioned) with a quick decrease in prevalence (online supplemental figure 1). Due to the overrepresentation of IgG against milk and egg categories in healthy individuals, they were excluded from the statistical analysis.[11 24–27]

The number of foods positive present in each diagnostic group was examined. There was a significant difference across the 10 ICD-10 groups (p=0.015), as shown by a non-parametric one-way Kruskal-Wallis ANOVA. To confirm this result, a Dunn's test was performed post hoc. It indicated a significantly larger number of positive foods for those with jejunostomy vs individuals diagnosed with periodontitis (p=0.002), duodenitis (p=0.006) or appendicitis (p=0.048). Similar observations were made for ileostomates vs individuals diagnosed with periodontitis (p=0.007), or duodenitis (p=0.017), and for colostomates vs individuals diagnosed with periodontitis (p=0.023). Significance values of all pairwise Dunn's test comparisons are presented in table 1.

Similarly, the relative intensity of response to all foods was investigated using the categorical sum of response for each food per individual, in each category. A significant difference in the categorical sum per diagnostic category was observed using a Kruskal-Wallis ANOVA (p=0.013). A Dunn's test indicated that there was a significant difference in the categorical sums of those with jejunostomy versus individuals diagnosed with periodontitis (p=0.003), or duodenitis (p=0.007); ileostomates versus individuals diagnosed with periodontitis (p=0.006), or duodenitis (p=0.014); and colostomates vs individuals diagnosed with periodontitis (p=0.029) (table 2).

The strength of the humoral response was tested by quantifying both total serum IgG and IgA antibodies. Total serum IgG was first analysed as a continuous variable and compared with the categorical sum of

Table 1 Dunn's test pairwise comparisons between diagnostic categories of interest and the number of foods positive

	Appendicitis	Colostomy	CD	Duodenitis	EE	FM	Ileostomy	Jejunostomy	Periodontitis
Colostomy	0.182								
CD	0.135	0.423							
Duodenitis	0.253	0.050	0.032*						
EE	0.079	0.293	0.359	0.016*					
FM	0.020*	0.125	0.169	0.002*	0.291				
Ileostomy	0.109	0.417	0.496	0.017*	0.341	0.139			
Jejunostomy	0.048*	0.237	0.305	0.006*	0.457	0.311	0.277		
Periodontitis	0.138	0.023*	0.014*	0.304	0.007*	0.001*	0.007*	0.002*	
UC	0.492	0.199	0.151	0.258	0.091	0.026*	0.127	0.059	0.145

*Indicates p≤0.05.
CD, Crohn's disease; EE, Eosinophilic esophagitis; FM, Food malabsorption; UC, Ulcerative colitis.

food-specific IgG. A linear regression indicated a strong positive correlation (p<0.001). Classifying the same data into medically relevant groups enabled us to also show a difference between the ICD-10 groups, using a Kruskal-Wallis ANOVA (p=0.002) (figure 1). A post hoc Dunn's test was performed, and significant pairwise differences were observed between elevated and mild-moderately reduced (p=0.03), mild-moderately reduced and normal (p=0.04), elevated and profoundly or significantly reduced (p=0.014), and normal and profoundly or significantly reduced (p=0.019). P value adjustments were made using the Benjamini-Yeukateli adjustment.

Similarly, total serum IgA was quantified and analysed first as a continuous variable. A Kruskal-Wallis test indicated that there were no significant differences in the levels of total serum IgA between ICD-10 groups tested (p=0.74). After classifying the same data into medically relevant groups, a Kruskal-Wallis ANOVA was performed and indicated that there were no significant differences between the groups (p=0.56).

To test that there was no digestive and/or systemic inflammation at the time of sampling, serum calprotectin was quantified. A Kruskal-Wallis test indicated that there were no significant differences in the levels of serum calprotectin between groups tested (p=0.72). After classifying the same data into medically relevant groups, a Kruskal-Wallis ANOVA was performed and indicated that there were no significant differences between the groups (p=0.081). As calprotectin is a measure of a transient inflammatory event, the measurement was not included in the next analysis.

To better understand the impact of demographics (age, BMI and sex), adaptive response (total serum IgG and IgA and food-specific IgG) and ICD-10 on the risk of food sensitivity, a logistic regression model was used (table 3). In this model, jejunostomates and ileostomates were, respectively, 12.70 and 6.19 times more likely to have at least one food sensitivity compared with individuals diagnosed with periodontitis. In contrast, colostomates had an OR of 2.69 and the test was shown to be not statistically significant. Interestingly, individuals with Crohn's disease of the small intestine had an OR of 4.67, reaching statistical significance, while those with ulcerative colitis had a non-significant lower OR. Food malabsorption due to intolerance group, as well as our positive control group, eosinophilic esophagitis, showed statistical significance and large ORs. Individuals with profoundly or significantly reduced and mild-moderately reduced levels of

Table 2 Dunn's test pairwise comparisons between ICD-10 groups of interest and categorical sum

	Appendicitis	Colostomy	CD	Duodenitis	EE	FM	Ileostomy	Jejunostomy	Periodontitis
Colostomy	0.261								
CD	0.110	0.278							
Duodenitis	0.200	0.063	0.015*						
EE	0.107	0.263	0.470	0.017*					
FM	0.031*	0.110	0.261	0.002*	0.296				
Ileostomy	0.131	0.343	0.398	0.014*	0.372	0.164			
Jejunostomy	0.073	0.216	0.433	0.007*	0.467	0.307	0.321		
Periodontitis	0.105	0.029*	0.007*	0.306	0.007*	0.001*	0.006*	0.003*	
UC	0.409	0.201	0.081	0.290	0.079	0.022*	0.095	0.052	0.167

*Indicates p<0.05.
CD, Crohn's disease; EE, eosinophilic esophagitis; FM, food malabsorption; UC, ulcerative colitis.

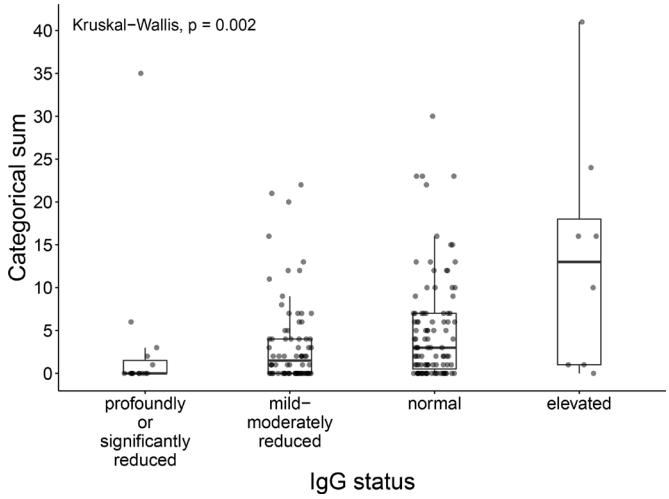

Figure 1 Significant differences were observed between the IgG overall response and the categorical sum of IgG food-specific response for each individual.

serum total IgG were less likely relative to the normal and elevated groups to develop food-specific IgG, with ORs of 0.09 and 0.33, respectively. Total IgA levels categories did not reach significance.

DISCUSSION

In this cross-sectional analysis, food-specific IgG was evaluated for 198 participants for a panel of 109 foods using deidentified biobank clinical serum samples. Ostomates with jejunostomy and ileostomy showed a significant risk of presenting circulating food-specific IgG in contrast to colostomates. In addition, ileostomates and jejunostomates had significantly higher categorical sums and numbers of foods positive relative to colostomates, as compared with each other or in the context of inflammatory disease groups. To the best of our knowledge, this is the first study to link the type of digestive resection in ostomates with the risk of having circulating food-specific IgG. These findings may improve dietary management while also managing symptomatology related to food intake.

The proposed link between food-specific IgG and ostomy management is based on the effect of directed elimination diets on digestive parameters. In particular, food-specific-IgG-based elimination diets have been shown to be effective at reducing symptoms in individuals with Crohn's disease and ulcerative colitis, as well as in people with irritable bowel syndrome.[12–15 28] These designed diets affect faecal output, digestive symptoms and quality-of-life measurements.

In absence of an easily detectable issue like a food allergy, confirmed by IgE detection, identifying which food could be causing the symptoms can be a long and complex process that includes the elimination of specific foods or food ingredients, while monitoring symptoms. Faecal output appearance and consistency are important semiological descriptors for self-care and clinical management. However, until recently, there has been a lack of any

Table 3 OR and 95% CI for the parameters included in the logistic regression model

Characteristic	OR	95% CI	P value
(Intercept)	0.36	0.04 to 2.82	0.330
Age	1.01	0.99 to 1.04	0.197
BMI	1.03	0.97 to 1.10	0.285
Sex			
Female	1.00	—	
Male	2.39	1.19 to 4.97	0.017**
ICD-10 based categories*			
Periodontitis	1.00	—	
Ulcerative colitis	2.05	0.45 to 10.10	0.360
Duodenitis	2.46	0.59 to 11.00	0.224
Appendicitis	2.50	0.59 to 11.40	0.222
Colostomy	2.69	0.57 to 13.60	0.216
Crohn's disease	4.67	1.06 to 23.20	0.048**
Ileostomy	6.19	1.58 to 27.00	0.011**
Eosinophilic esophagitis	8.16	1.58 to 49.80	0.016**
Jejunostomy	12.70	2.71 to 71.60	0.002**
Food malabsorption	18.00	3.09 to 160.00	0.003**
Total IgG status			
Normal	1.00	—	
Profoundly or significantly reduced	0.09	0.02 to 0.33	<0.001**
Mild-moderately reduced	0.33	0.15 to 0.70	0.005**
Elevated	4.09	0.59 to 83.10	0.219
Total IgA status			
Normal	1.00	—	
Deficient	1.38	0.11 to 33.90	0.819
Reduced	0.33	0.06 to 1.87	0.198
Elevated	0.41	0.16 to 1.05	0.064

AIC=245.70.
*ICD-10 ordered by increasing OR value.
**Indicates p<0.05.
BMI, body mass index.

output quality evaluation scale, an equivalent to a Bristol stool form scale, to monitor these signs overtime in relation to any food, medication or hydration regiment.[29 30] The daily constraints associated with stoma maintenance and nutritional management may be reasons for overlooking symptoms associated with specific food intake. The recognition of specific foods that could potentially trigger symptoms could be beneficial for quality-of-life management.

There are multiple factors that may explain the observed discrepant responses between the diverse groups and ostomates. Regarding oral tolerance, antigen sampling along the digestive tract is not homogeneous or equivalent. It involves different gut-associated lymphoid tissues including Peyer's patch and SM-ILF that are expressed at different density along the biogeography

of the digestive tract, as well as variations in the tolerogenic liver environment.[31–33] Individuals lacking a colon may be at a higher risk of developing food-specific IgG due to missing component of the immune system postsurgery. Alternatively, maintenance of long-term chronic digestive-tract inflammation in the ileal conduit could impact the antigen sampling process and lead to differences in response to food antigens depending on the cause of ostomy. These considerations underline that biogeography, long-term inflammation and immune tolerance sampling sites may play major roles. These hypotheses could not be further investigated due to the nature of the available samples (deidentified samples from a biobank).

The importance of general humoral immunocompetence as an indicator of food intolerance risk was supported by our results as individuals with higher levels of total IgG tended to correspond to higher levels of overall reactivity to food-specific antigens, as observed via categorical sum. In contrast, the individuals with profoundly or significantly and mild-moderately reduced levels of total IgG had significantly protective ORs of presenting circulating food-specific IgG. The total intake of a particular food may also impact the level of detectable IgG,[26] however, our findings show an impact across the panel of foods included in the test.

Additional findings include the strength of the food-specific IgG response in individuals with food malabsorption due to intolerance, in categorical sum, diversity of food antigens detected and ORs. Also, individuals with Crohn's disease of the small intestine had significantly higher numbers of foods positive and levels of overall reactivity than individuals with ulcerative colitis, duodenitis and periodontitis. Further, in the logistic regression a diagnosis of Crohn's disease was a predictive factor for the presence of food-specific IgG.

What to think if I am an affected patient? While few foods seem to have a broad and communally shared impact on the presence of food-specific IgG (online supplemental table 5) and (online supplemental figure 1), the IgG pattern is rather scattered and personalised. Implementing an overly restrictive diet as a way to mitigate symptoms of food-related inflammation—while appealing—might likely result in undernutrition that would be significantly detrimental. The role of food-specific-IgGs testing in routine clinical practice in those undergoing ostomy surgery and in most of the disease groups mentioned is at this stage unknown yet clearly worth of investigation.

The strengths of this study reside in the choice of target groups for the analysis that comprised inflammatory diseases from the oral cavity to the colon. Eosinophilic esophagitis provided a true positive control group as the disease is well known to have an IgG component.[16] We were also able to control for a range of important potential confounders, (eg, BMI, age, sex and immunocompetency), which were not included in previous analyses of food-specific IgG.

Our study also had several limitations. As the samples were deidentified, we were not able to investigate past medical history, including the main medical reason for ostomy surgery, medication intake that might influence immunocompetency, or past dietary intake. Per the design of a cross-sectional study, we do not have presurgical and postsurgical samples for the ostomates, thus, we are unable to identify if the food sensitivities were present prior to surgery. However, the needs of ostomates regarding food intake management do increase significantly postsurgery, and any tools provided to the community to improve management output are of significant importance. Lastly, for a panel of food antigens spanning 16 food categories, there is no available kit working with limited serum supplies to test IgG subtype or other classes of immunoglobulin.

In conclusion, food sensitivity risk is increased significantly in the ostomate population, and the risk is associated with the type of overall resection observed. The strength of the subject's immunocompetence seems to play a great role in the intensity to which the humoral system responds via food-specific IgG. An element of biogeography emerges where the maintenance of a colonic space or ileal chronic inflammation influences the risk of having circulating food-specific IgG. Questions related to the effect of the immune tolerance biogeography, the strength of the adaptative immunity on food sensitivity, and the potential impact of elimination diet on the health and wellness of ostomates still need to be answered.

Contributors Study concept, design and guarantor: JI. Acquisition of data: WKC. Analysis and interpretation of data: all coauthors. Drafting of the manuscript: WKC, JI. Critical revision of the manuscript for important intellectual content: all coauthors. Statistical analysis: WKC, JC. Obtained funding: JI. Administrative, technical or material support: JI. Study supervision: JI.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Deidentified serum samples were acquired from the Nebraska Biobank (RRID: SCR_021024; University of Nebraska Medical Center, Omaha, NE). The Institutional Review Board (IRB) of the University of Nebraska-Lincoln made the determination that this project and the use of samples did not meet the definitions of human subject research under regulatory requirements at 45 CFR 46.102 and the project did not require IRB approval (FWA00002258).

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Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iD

Jacques Izard http://orcid.org/0000-0002-5904-5436

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Supplemental material

Ileostomate and jejunostomate are at higher risk of circulating food-specific-IgG than other participants with digestive illness including colostomates

Walker K. Carson[1, 2], Joseph L. Baumert[1], Jennifer L. Clarke[1, 2,3], and Jacques Izard[1, 2, 4, *]

[1] Department of Food Science and Technology, University of Nebraska-Lincoln, Lincoln, NE

[2] Nebraska Food for Health Center, Lincoln, Nebraska, USA
[3] Department of Statistics, University of Nebraska-Lincoln, Lincoln, NE
[4] Fred and Pamela Buffet Cancer Center, Omaha, Nebraska, USA

Supplemental Tables 1 to 5

Supplemental Figure 1

Supplemental Table 1. Number of sera samples acquired per diagnostic group (n=198).

ICD-10[1]	ICD-10 Code Description	Number of samples[2]
Z93.4	Jejunostomy present	**22**
Z93.3	Colostomy in place	**18**
Z93.2	Ileostomy present	**31**
K50.0*	Crohn's Disease	**18**
K50.00	Crohn's disease of small intestine without complication	7
K50.012	Crohn's disease of small intestine with intestinal obstruction	3
K50.013	Crohn's disease of small intestine with fistula	1
K50.018	Crohn's disease of small intestine with other complication	3
K50.019	Terminal ileitis with complication	4
K35.*	Acute appendicitis	**18**
K35.20	Acute appendicitis with generalized peritonitis	1
K35.32	Acute appendicitis with rupture	2
K35.80	Acute appendicitis, unspecified acute appendicitis type	8
K35.30	Acute appendicitis with localized peritonitis	7
K29.80	Duodenitis	**25**
K51.0*	Ulcerative colitis	**15**
K51.00	Ulcerative pancolitis without complication	12
K51.011	Ulcerative pancolitis with rectal bleeding	3
K20.0	Eosinophilic esophagitis	**15**
K90.49	Food Malabsorption due to intolerance	**18**
K05.30	Periodontitis	**18**

[1] The codes represent the selected diagnostic groups using International Classification of Diseases, Tenth Revision (ICD-10). Asterisks represent that the preceding alphanumeric sequence may be further broken down into subcategories of the selected ICD-10 code.
[2] Bolded numbers refer to the total number of samples received in each diagnostic category. Non-bolded numbers are the breakdown of the number of samples received from each subcategory.

Supplemental Table 2: Food tested in this investigation organized by USDA categories in decreasing order of frequency of positive rate within the population tested.

Category [1]	Foods [2]
Milk	Cow's Milk*, Goat's/Sheep's Milk*
Eggs	Egg White*, Egg Yolk*
Cereal grains and pasta	Wheat*, Gluten*, Corn (Maize)*, Barley*, Buckwheat*, Rice*, Rye*, Oat, Durum Wheat
Legumes and legume products	Peanut*, Soybean*, Pea*, Chickpea*, Haricot/Kidney Bean*, Lentil*
Yeast	Yeast (beer)*, Yeast (bread)*
Nuts and seeds	Pistachio*, Almond*, Hazelnut*, Chestnut*, Pine Seed, Sunflower Seed, Sesame Seed, Cola Nut, Walnut, Cocoa Bean
Fruit	Lemon/Lime*, Melon*, Orange/Tangerine*, Pineapple*, Apricot/Peach*, Cherry*, Banana*, Olive*, Plum, Strawberry*, Kiwi Fruit, Apple, Pear, Grape Black/White, Watermelon, Fig
Spices, Herbs, and Sweets	Mustard*, Black/White Pepper*, Basil, Caper, Honey
Shellfish	Oyster/Clam*, Sepia/Calamar/Octopus*, Mussel*, Prawn/Shrimp, Crab/Lobster
Beverages	Coffee*, Tea
Other vegetables	Garlic*, Chilli*, Courgette (Zucchini)*, Onion*, Artichoke, Aubergine (Eggplant), Fennel, Mushroom, Cauliflower/Cabbage, Chicory, Lettuce, Cucumber, Parsley, Potato, String Bean (Green Bean)
Finfish	Tuna*, Cod*, Sardine/Anchovy, Sole, Trout/Hake, Sea Bass, Salmon
Red meat	Rabbit*, Pork, Lamb, Beef
Red and orange vegetables	Tomato*, Pumpkin, Carrot, Peppers/Capsicum
Dark green vegetables	Broccoli, Spinach
Poultry	Chicken, Turkey

[1] Food categories based on U.S. Department of Agriculture, Agricultural Research Service. FoodData Central, 2019. fdc.nal.usda.gov.
[2] Food listed in the Eagle Biosciences IgG (109 foods) ELISA Assay Kit
* Food tested positive for at least one individual

Supplemental Table 3. Food tested by the Eagle Biosciences IgG (109 foods) ELISA Assay Kit, with associated USDA categories and FoodData Central ID.

Category [1]	Food [2]	FDC ID [3]	Category	Food	FDC ID
Beverages	Coffee	171890	**Nuts and seeds**	Pistachio	170184
	Tea	174155		Almond	170567
Cereal grains and	Wheat	169725		Hazelnut	170581
pasta	Gluten	168147		Chestnut	170164
	Buckwheat	170286		Cocoa Bean	169593
	Corn (maize)	170288		Cola Nut	169588
	Barley	170284		Pine Seed	170591
	Rice	168931		Sesame Seed	170150
	Rye	168884		Sunflower Seed	170562
	Durum Wheat	169721		Walnut	170187
	Oat	169705	**Other vegetables**	Chilli	170108
Dark green vegetables	Broccoli	787465		Courgette (Zucchini)	169291
	Spinach	787373		Onion	170000
Eggs	Egg White	172183		Garlic	169230
	Egg Yolk	172184		Artichoke	169205
Finfish	Cod	171955		Aubergine (Eggplant)	169228
	Salmon	175138		Cauliflower/Cabbage	169986, 169975
	Sardine/Anchovy	175139, 174182		Chicory	169992
	Sea Bass	175142		Cucumber	168409
	Sole	174196		Fennel	169385
	Trout/Hake	175153		Lettuce	169249
	Tuna	173706		Mushroom	169251
Fruit	Lemon/Lime	167746, 168155		Parsley	170416
	Melon	169092		Potato	170026
	Apricot/Peach	171697, 169928		String Bean	169961
	Orange/Tangerine	169919, 169105	**Poultry**	Chicken	171116
	Pineapple	169124		Turkey	171505
	Cherry	171719	**Red and orange**	Tomato	170457
	Olive	169094	**vegetables**	Carrot	170393
	Apple	171689		Peppers/Capsicum	787810
	Banana	173944		Pumpkin	168448
	Fig	173021	**Red meat**	Rabbit	174347
	Grape Black/White	174682		Beef	168608
	Kiwifruit	168153		Lamb	174370
	Pear	169118		Pork	167902
	Plum	169949	**Shellfish**	Oyster/Clam	171978, 782757
	Strawberry	167762		Sepia/Calamar/ Octopus	174215, 782743, 174218
	Watermelon	167765		Crab/Lobster	174204, 174208
Legumes and legume	Peanut	172430		Mussel	174216

products	Soya Bean	174270		Prawn/Shrimp	175179
	Pea	170419	**Spices, herbs, and**	Mustard	172234
	Lentil	172420	**sweets**	Basil	172232
	Chickpea	173756		Black/White Pepper	170931, 170933
	Haricot/Kidney Bean	175193		Caper	172238
Milk	Cow's Milk	781084		Honey	169640
	Goat's/Sheep's Milk	171278, 170882	**Yeasts**	Yeast (beer)	788564
				Yeast (bread)	175043

[1] Food categories based on U.S. Department of Agriculture, Agricultural Research Service. FoodData Central, 2019. fdc.nal.usda.gov.
[2] Food listed in the Eagle Biosciences IgG (109 foods) ELISA Assay Kit
[3] FoodData Central ID

Supplemental Table 4. Demographic table per total population examined and individual diagnosis.

ICD-10 diagnosis	N	Percent of total population	Percent in ICD-10 code	Mean age (years)
Population	**198**			
Female	104	52.53%	NA	50.10 (±18.00)
Male	94	47.47%	NA	49.20 (±17.00)
Appendicitis	**18**			
Female	6	3.03%	33.33%	35.17 (±12.92)
Male	12	6.06%	66.67%	51.00 (±16.71)
Colostomy	**18**			
Female	9	4.55%	50.00%	63.44 (±20.17)
Male	9	4.55%	50.00%	58.56 (±14.15)
Crohn's Disease	**18**			
Female	9	4.55%	50.00%	47.89 (±16.05)
Male	9	4.55%	50.00%	46.78 (±10.94)
Duodenitis	**25**			
Female	15	7.58%	60.00%	59.53 (±13.34)
Male	10	5.05%	40.00%	59.70 (±18.56)
Eosinophilic Esophagitis	**15**			
Female	10	5.05%	66.67%	36.40 (±14.42)
Male	5	2.53%	33.33%	38.20 (±14.48)
Food Malabsorption	**18**			
Female	9	4.55%	50.00%	51.11 (±13.78)
Male	9	4.55%	50.00%	47.11 (±17.97)
Ileostomy	**31**			
Female	15	7.58%	48.39%	53.27 (±14.35)
Male	16	8.08%	51.61%	52.25 (±15.03)
Jejunostomy	**22**			
Female	14	7.07%	63.64%	49.36 (±17.54)
Male	8	4.04%	36.36%	48.75 (±21.95)
Periodontitis	**18**			
Female	9	4.55%	50.00%	40.67 (±21.77)
Male	9	4.55%	50.00%	36.33 (±13.87)
Ulcerative Colitis	**15**			
Female	8	4.04%	53.33%	53.50 (±22.01)
Male	7	3.54%	46.67%	42.43 (±17.14)

Supplemental Table 5. Percent of population with food-specific-IgG, broken down by diagnostic category.

Food	Total	Appendicitis	Colostomy	CD[1]	Duodenitis	EE[2]	FI[3]	Ileostomy	Jejunostomy	Periodontitis	UC[4]
Wheat	36%	28%	33%	44%	16%	60%	44%	39%	41%	33%	33%
Yeast (beer)	28%	22%	22%	50%	16%	13%	50%	29%	50%	6%	20%
Peanut	19%	17%	28%	11%	12%	27%	33%	19%	23%	11%	13%
Yeast (bread)	19%	11%	6%	50%	8%	0%	22%	23%	41%	6%	13%
Gluten	15%	6%	11%	6%	4%	53%	17%	19%	14%	17%	7%
Soya Bean	14%	6%	17%	11%	8%	33%	17%	16%	18%	6%	13%
Pistachio	13%	11%	17%	6%	20%	13%	17%	19%	9%	0%	13%
Mustard	13%	11%	17%	17%	8%	20%	28%	6%	5%	6%	20%
Corn (Maize)	10%	0%	11%	22%	4%	13%	0%	10%	32%	0%	0%
Pea	9%	0%	22%	6%	4%	7%	11%	10%	18%	0%	7%
Oyster/Clam	9%	17%	17%	0%	4%	13%	22%	10%	0%	0%	7%
Lemon/Lime	9%	6%	22%	11%	0%	20%	22%	6%	0%	6%	0%
Barley	8%	0%	22%	11%	0%	13%	6%	13%	14%	0%	0%
Almond	8%	6%	6%	6%	4%	20%	17%	10%	5%	6%	7%
Chick Pea	6%	0%	6%	0%	0%	7%	17%	3%	18%	0%	13%
Buckwheat	6%	0%	11%	11%	0%	7%	6%	10%	14%	0%	0%
Hazelnut	6%	0%	11%	6%	0%	13%	6%	3%	9%	6%	7%
Sepia/Calamar/ Octopus	5%	6%	6%	0%	4%	7%	6%	10%	0%	0%	7%
Melon	5%	0%	11%	6%	0%	7%	6%	3%	14%	0%	0%
Haricot/Kidney Bean	4%	0%	6%	6%	0%	0%	11%	3%	14%	0%	0%
Lentil	4%	0%	0%	6%	0%	7%	6%	3%	14%	0%	0%
Rice	3%	0%	11%	0%	0%	13%	0%	0%	9%	0%	0%

Orange/ Tangerine	3%	0%	6%	6%	0%	7%	6%	3%	0%	0%	0%
Coffee	3%	6%	0%	6%	0%	7%	6%	3%	0%	0%	0%
Chestnut	2%	0%	0%	0%	0%	13%	6%	0%	5%	0%	0%
Garlic	2%	0%	0%	0%	0%	0%	6%	3%	5%	0%	0%
Apricot/Peach	2%	0%	6%	0%	0%	7%	6%	0%	0%	0%	0%
Cherry	2%	0%	6%	0%	0%	7%	6%	0%	0%	0%	0%
Pineapple	2%	0%	11%	0%	0%	0%	0%	0%	5%	0%	0%
Rabbit	2%	6%	6%	0%	0%	0%	0%	0%	0%	0%	7%
Tomato	1%	0%	6%	0%	0%	7%	0%	0%	0%	0%	0%
Rye	1%	0%	0%	0%	0%	7%	0%	0%	5%	0%	0%
Cod	1%	0%	6%	0%	0%	0%	0%	0%	0%	6%	0%
Banana	1%	0%	0%	0%	0%	0%	0%	0%	9%	0%	0%
Courgette	1%	0%	0%	0%	0%	0%	0%	3%	0%	0%	0%
Onion	1%	0%	0%	0%	0%	0%	0%	0%	5%	0%	0%
Chilli	1%	0%	6%	0%	0%	0%	0%	0%	0%	0%	0%
Blakc/White Pepper	1%	0%	0%	0%	0%	0%	6%	0%	0%	0%	0%
Olive	1%	0%	0%	0%	0%	7%	0%	0%	0%	0%	0%
Mussel	1%	6%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Tuna	1%	6%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Strawberry	1%	0%	0%	0%	0%	7%	0%	0%	0%	0%	0%

[1] Crohn's Disease
[2] Eosinophilic esophagitis
[3] Food intolerance
[4] Ulcerative Colitis

Supplemental Figure 1: Distributions of the percentage of the sample with food-specific-IgG across food types. Total sample distribution is followed by each ICD-10 group in order of decreasing odd ratio.

(see next page)


Perecent of population positive
Wheat
Yeast (beer)
Peanut
Yeast (bread)
Gluten
Soybean
Pistachio
Mustard
Corn (Maize)
Lemon/Lime
Oyster/Clam
Pea
Almond
Barley
Buckwheat
Chick Pea
Hazelnut
Melon
Sepia/Calamar/Octopus
Haricot/Kidney Bean
Lentil
Rice
Coffee
Orange/Tangerine
Chestnut
Apricot/Peach
Cherry
Garlic
Pineapple
Rabbit
Banana
Cod
Rye
Tomato
Black/White Pepper
Chilli
Courgette
Mussel
Olive
Onion
Strawberry
Tuna
Ulcerative colitis
Appendicitis
Ileostomy
Population
Periodontitis
Colostomy
Eosinophilic esophagitis
Food malabsorption
Duodenitis
Crohn's disease
Jejunostomy
Category
Yeast
Spices, herbs, and sweets
Shellfish
Red meat
Red and orange vegetables
Other vegetables
Nuts and seeds
Milk
Legume and legume products
Fruit
Finfish
Egg
Cereal grains and pasta
Beverages