OPEN ACCESS
Freely Available Online

INTERNATIONAL JOURNAL OF NUTRITION
ISSN NO: 2379-7835

Research

DOI: 10.14302/issn.2379-7835.ijn-20-3181

Implementation of an Elemental Diet in Five Children Diagnosed with Autism Spectrum Disorder Presenting with Gastrointestinal Disease: A Brief Report

Kelly Barnhill[1,2,*], Alan Gutierrez[1,3], Amy Potts[1,4], Morgan Devlin[1], Wendy Richardson[1], Laura Hewitson[1]

[1]The Johnson Center for Child Health & Development
[2]Certified Clinical Nutritionist
[3]Registered Dietitian
[4]Physician's Assistant

Abstract

Autism Spectrum Disorder (ASD) is a developmental disorder characterized by impaired communication and social interaction. Children with ASD are frequently diagnosed with gastrointestinal (GI) issues, including inflammatory bowel disease (IBD), gastroesophageal reflux, abdominal pain, diarrhea, and constipation, although the association between ASD and GI conditions is unclear. Underlying nutritional deficiencies are more common in children with ASD, and increase the risk of them developing medical conditions secondary to the behavioral diagnosis. This objective of this study was to examine the use of an elemental diet (ED) in the treatment of gastrointestinal disease in 5 children with ASD ages 2-21 years of age. In the study participants, the ED was well-tolerated with improvements in anthropometric measures, nutritional markers, and/or GI functioning reported after 12 weeks of intervention. Further research to advance the development of specific evidence-based guidelines in the management and treatment of gastrointestinal concerns in the ASD population is warranted.

Corresponding author: Kelly Barnhill, Certified Clinical Nutritionist, The Johnson Center for Child Health & Development, 1700 Rio Grande Street, Austin TX 78701. Ph: 512-732-8400. Fax: 512-732-8353.

Citation: Kelly Barnhill, Alan Gutierrez, Amy Potts, Morgan Devlin, Wendy Richardson et al. (2020) Implementation of an Elemental Diet in Five Children Diagnosed with Autism Spectrum Disorder Presenting with Gastrointestinal Disease: A Brief Report. International Journal of Nutrition - 5(2):01-14. https://doi.org/10.14302/issn.2379-7835.ijn-20-3181

Keywords: nutrition, elemental diet, autism spectrum disorder, gastrointestinal, anthropometrics, pediatric, intervention

Received: Jan 17, 2020 **Accepted:** Feb 06, 2020 **Published:** Feb 11, 2020

Editor: Ayse Yesim Gocmen, Bozok University School of Medicine, Biochemistry Department, Yozgat, Turkey.

Introduction

ASD is a complex pervasive developmental disorder characterized by impairments in social interaction, with deficits in verbal and non-verbal communication and/or restricted, repetitive and stereotyped patterns of behavior and interests [1]. There is increasing evidence of an involvement of gastrointestinal (GI) issues in children with ASD [2-4], with a potential secondary impact on behavior [5, 6]. Documented GI symptoms in ASD include eosinophilic esophagitis [7], gastroesophageal reflux (GERD), and abdominal pain, constipation and/or diarrhea [8-12]. Furthermore, a subset of ASD children with GI symptoms have an inflammatory mucosal pathology [2, 11, 13, 14].

Associated functional GI abnormalities in children with ASD include low activities of disaccharidase enzymes [15], defective sulfation of ingested phenolic amines [16], bacterial overgrowth with greater diversity and number of clostridial species [17], and increased intestinal permeability [18]. Dietary restrictions and problem feeding behavior, nutrient malabsorption, and increased intestinal losses in children with ASD can compromise dietary intake and cause nutritional depletion. For example, in a study of 36 children with ASD, essential amino acid deficiencies indicative of poor protein intake occurred more frequently than in controls regardless of whether the diet was restricted or unrestricted [19]. A compromised nutritional status negatively impacts growth velocity and increases the risk of developing medical conditions secondary to the primary diagnosis of ASD [20]. While general recommendations for symptomatic management have been developed [9], there are no evidence-based guidelines for therapy to address GI symptoms specific to children with ASD.

An elemental diet (ED) is an easily-digestible, liquid diet typically used for patients who have compromised digestive systems [20], and is used to treat a number of conditions including small intestinal bacterial overgrowth (SIBO)[21], Crohn's disease [22], and eosinophilic esophagitis [23]. EDs are composed of oligopeptides and amino acids, disaccharides or partially hydrolyzed starch, and minimal fat, thus requiring minimal digestion. By providing dietary components in a readily assimilable form, there is low stool volume and minimal stimulation of bile and pancreatic secretions [24]. Clinical indications for the use of EDs include short gut syndrome, malabsorption syndromes, IBD, gastrointestinal fistulas, and nonspecific maldigestive and malabsorptive states [20, 25-27]. EDs are generally well-tolerated. Though the mechanism of action is not well defined, published clinical trials in pediatric populations diagnosed with active Crohn's disease demonstrate that ED as sole first-line therapy is as effective as corticosteroids in inducing remission in this pathology [28-30]. Malnourished children presenting with Crohn's disease suffer fewer side effects with enteral nutrition when compared to the alternative of steroid therapy [31]. In Japan, ED is the primary intervention for active IBD [32, 33]. Several studies have concluded that ED is an efficacious intervention for eosinophilic esophagitis, an inflammatory disease characterized by upper intestinal symptoms and the finding of more than 15 or 20 eosinophils in the esophageal epithelium [23, 34-37]. In a retrospective study, researchers assessed 381 children with eosinophilic esophagitis over a 10-year period and found that 98% of children who received ED had a significant improvement in clinical symptoms and esophageal histology [38].

Based on the above manifestations and clinical experience in treating the above symptoms with ED, the purpose of this investigation was to evaluate the tolerability and efficacy of ED in the amelioration of GI symptoms in children ages 2-21 years, with documented GI dysfunction, including duodenitis, ileitis, and/or colitis, and an ASD diagnosis.

Methods

Participants

This study was approved by the appropriate Institutional Review Board in accordance with local regulations and informed consent/assent was obtained from the subjects and/or their legal guardians after the nature of the procedures had been explained.

Male and female children (n = 5) aged 9-14 years, diagnosed with Autism Spectrum Disorder (ASD) and meeting the inclusion criteria below, were recruited sequentially through an out-patient clinic. If the caregiver expressed interest in their child participating in

the study, the consent form was reviewed with the family and informed consent and assent (if applicable) obtained. Inclusion criteria were as follows: 2-21 year-old males and females with ASD with a diagnosis of inflammatory bowel disease. The participant had to be under the care of a caregiver.

Willing to participate in the study by attending regularly scheduled appointments and completing the necessary measures, and be accessible to a research staff member via phone or in-office on a weekly basis throughout the study intervention period. Exclusion criteria were as follows: pregnant or nursing females up to 21 years of age; requirement of receiving any nutrition via enteral or parenteral routes; infectious colitis, metabolic disorders such as phenylketonuria, leukodystrophy, lysosomal disorder, Wilson's disease, and other concurrent physical or mental disorders that preclude participation in assessment procedures. Concurrent medications, dietary restrictions, and/or therapies were not exclusions to participation. However, concurrent interventions could not change during the period of the trial, unless there was a clear medical indication to do so.

Study Design

Enrolled participants received total elemental nutrition for 12 weeks under the guidance of a registered dietitian and a clinician. Anthropometric measurements were collected at baseline, 4, 8, and 12 weeks, and at two follow-up appointments conducted at 6 and 12 months. Biochemical markers and dietary analysis were monitored throughout the study, and caregivers participated in weekly phone or in-office visits to address any concerns raised by the clinician, dietitian and/or caregiver.

Study Measures and Assessments

The study procedures performed during each phase are summarized in Table 1.

Biochemical Markers

Biochemical markers of nutritional status, including albumin and hematocrit, were attained through a comprehensive metabolic panel and complete blood count. A lactulose-mannitol (L/M) recovery test for intestinal permeability was undertaken to examine intestinal integrity [39]. Fasting blood samples were analyzed by Clinical Pathology Laboratories, LabCorp or Quest Diagnostics.

Anthropometric Measurements

A physical exam was performed at each study visit during which, height and weight were recorded. If participants were unable to travel to the clinic for each scheduled visit, they were able to work with an approved, local dietitian/clinician to obtain measurements. Height and weight were compared with the standards for linear growth derived from the Centers for Disease Control-National Center for Health Statistics Growth Charts [40] and body mass index (BMI) including percentiles and Z-scores calculated.

Dietary Analysis

Caregivers were given standardized written instructions and measurement guidelines to record all food and beverage intake for two weekdays and one weekend day that they considered typical for their child (Three-Day Food Diary, Supplementary Figure S1). Homemade recipes, brand names of packaged products and restaurant information of foods consumed were required. Food records were analyzed using Food Processor SQL (version 10.3.0, 2008, ESHA, Salem, OR;

Table 1. Timing of ED study measures and assessments

Study Assessments	Baseline	4 Weeks	8 Weeks	12 Weeks	6 Months	12 Months
Biochemical Markers	X			X	X	X
Anthropometrics	X	X	X	X	X	X
Dietary Analysis	X			X		X
Clinical Evaluation	X			X		X

Supplementary Figure S2). Supplement data was not included in the nutrient analysis for an accurate assessment of dietary nutriture. Ideal body weight (IBW) was calculated as the appropriate weight for height according to the CDC growth charts. Estimated energy requirement for each patient was derived from height, weight, and a moderate physical activity level using the formulas developed by the Institute of Medicine [41].

Clinical Evaluation

A clinical evaluation was performed at baseline and at the completion of the study to assess the health and well-being of participants. Participants were also monitored throughout the study to assess actual elemental nutrition intake and tolerance, and to ensure that caloric intake was adequate, hydration status normal, and nutritional goals were achieved and maintained. Caregivers were given a standard weight scale and received training on proper use in order to track weight outside of the clinic. Greater than 5% weight loss in one month was considered abnormal, and would either result in the clinician either changing the dosing of the elemental formula or withdrawing the participant from the study. Gastrointestinal tolerance was also assessed weekly using the Gastrointestinal Symptoms Rating Scale (GSRS) [42], which document issues with diarrhea, indigestion, constipation, abdominal pain, and GERD on a scale of 0-3. Severe side effects, such as an allergic reaction, severe abdominal pain, vomiting, aggression and/or hyperactivity interfering with daily functioning, or significant alterations in white blood cell count, or liver or pancreatic enzymes, would have resulted in the elemental formula being withdrawn.

Application of Elemental Nutrition

Total daily nutrition was provided by elemental formulas that were provided at no cost to study participants. Three options for elemental nutrition were offered to the participants and their caregivers: two flavored powdered elemental formulas, Ross Nutricia Neocate and Elecare, and the ready-to-drink elemental formula, Neocate EO28 Splash. The powered formulas were prepared to provide appropriate caloric density to meet estimated energy requirements for weight maintenance or weight gain if indicated. Neocate EO28 Splash required no additional preparation. Two participants favored the ready-to-drink formula, while the other three chose the powdered formula. Formula was prescribed by the clinician and caregivers received sufficient formula for the 3 months study intervention period. Verbal and written instructions on titration and maintenance dose administration was provided to the caregiver under the guidance of a registered dietitian. Each participant received the optimal amount of formula appropriate for their daily energy and nutrient needs. Feedings occurred at meal or snack time, or ad libitum.

A daily food (formula) diary was maintained by the caregiver to record: i) all feedings with the elemental formula consumed on a daily basis, including documentation of any missed feedings and reasons for feedings being missed; ii) any ingested foods and beverages that were not allowed in the dietary intervention; and iii) suspected adverse diet-related events including the nature, severity and duration of such events. The daily food diaries were discussed during the weekly study appointments. At the end of 12 weeks, the clinician and dietitian reviewed all the study data and subsequently recommended that either the participant continue with elemental nutrition (outside of the study) or they begin the process to reintroduce solid foods, done under the guidance of a registered dietitian for a period of 4 weeks. In all cases, whether ED was continued or discontinued, follow-up assessments at 6 and 12-months were scheduled although not all families provided additional data past the study intervention period.

Assessment of Study Outcomes

Primary outcomes examined the efficacy of the elemental formula, as evidenced by the improvement in bowel symptoms and height/weight gain. Secondary outcomes included assessments of nutritional status and nutrient intake based on measurements of blood concentrations of total protein, albumin, pre-albumin, ferritin, C-reactive protein, RBC, MCV, MCHC, AST and alkaline phosphatase. Vitamin and minerals that were assessed included: sodium, potassium, chloride, magnesium, calcium, phosphorous, zinc, vitamin D, E, and K and folate. Nutrient intake was assessed by comparing submitted 3-Day food diaries with baseline data.

Results

Participant 1

A 14-year old boy with Crohn's disease presented with abdominal pain, frequent daily loose stools, and low muscle tone. BMI was <1st percentile. Following the 12-week intervention, the participant reported a reduction in abdominal pain and improvement in stool consistency and frequency. Although there was a small overall loss in body weight from 94.5 lbs to 89 lbs from baseline to 12 weeks, this subject reported a 34% weight gain at the 6-month follow-up appointment (Table 2). Height remained unchanged during this time. BMI remained in the <1st percentile from baseline to 12 weeks but increased to 23rd percentile at 6 months. Intestinal permeability (L/M recovery test) remained within normal limits throughout the study. CRP decreased from a baseline value of 4.4 mg/dL (high) to <0.5 mg/dL (reference range <0.8mg/ml) and was within normal limits (WNL) at 12 weeks, although it increased to 1.7 and 3.0 mg/dL at the 6- and 12-month follow-up appointments, respectively. Vitamin D status increased from a baseline level of 17 ng/mL (insufficient reference range: <20ng/ml) to 61 ng/mL (optimal reference range: 30-100ng/ml) at 12 weeks, but decreased to 28 and 20 ng/mL (suboptimal reference range: 20-29 ng/ml) at the 6- and 12-month follow-up appointments, respectively. All other blood work remained WNT throughout the study. Nutrient intake was reported as 2631 total kCal, 362g total carbohydrates, 82g total fat and 36g total protein at baseline. After the 12-week study intervention period, nutrient intake was reported as 2000 total kCal, 210g total carbohydrates, 95g total fat and 60g total protein. GSRS analysis reported a total score of 13 at baseline and 1 at 12 weeks. This was attributed to a decrease in the pain and diarrhea domains after the 12-week study intervention. The caregiver also reported that the participant had no abdominal pain and "stool were daily and formed". Although there were no formal behavioral assessment of the participants who were included in the study, a parental caregiver reported anecdotes of increased levels of physical activity, and improved socializing with peers. Solid food was re-introduced at 12 weeks as per recommendations but no nutrient intake data was provided at follow-up appointments. Following the re-introduction of solid food, the participant's weight increased to 120lbs by the 6-month appointment and remained unchanged at the 12-month appointment.

Participant 2

An 11-year old boy diagnosed with gastropathy and enteritis and a history of pica presented with chronic constipation cycling with diarrhea, consistent abdominal pain prior to defecating, and chronic eructation. Weight, height and BMI were considered to be in a healthy range at baseline. After the 12-week study intervention, caregivers and/or participants reported improvements in GI symptoms and reduction in pain. The participant showed a consistent increase in body weight from 85.2 lbs at baseline to 93 lbs at 12 weeks, representing an increase of 7.8 lbs (Table 3). At the 6- and 12-month follow-up appointments, his weight was 88.25 and 92 lbs, respectively. Height increased slightly during the intervention period from 59 to 61.5 in but had not increased further at follow-up. BMI remained relatively steady throughout the study (Table 2). Lab values assessing nutrition and inflammation remained WNL except for vitamin D, which was considered suboptimal at 29 ng/mL at the 12-month follow-up appointment. Nutrient intake was reported as 2489 total kCal, 251g total carbohydrates, 126g total fat and 98g total protein at baseline. After the 12-week study intervention period, nutrient intake was reported as 2060 total kCal, 204g total carbohydrates, 92g total fat and 58g total protein. The participant's mother reported some dietary infractions during the study, as well as periods of hyperactivity, visual stimming, bedwetting, and daytime incontinence. Pica (with items such as rocks, playground bark, and leaves) was also reported during the first month of intervention. The participant was subsequently diagnosed with round worms and began a parasite protocol under the care of his PCP. Treatment was completed half way through the ED intervention period. Follow-up nutrient analysis demonstrated an increase in total calories, with macronutrients reported as similar to baseline levels (data not shown). GSRS analysis reported a small improvement in GI symptoms with a score of 6 at baseline and 4 at 12 weeks. While the diarrhea domain score had decreased, the constipation domain score had increased. Anecdotal reports from a parental caregiver described a reduction of abdominal pain after the intervention period, but bed-wetting was still a frequent problem. Solid food was re-introduced at 12

Table 2. Anthropometric data collected from baseline to 12 months for participant 1

	Baseline	*4 weeks EDS*	*8 weeks EDS*	*12 weeks EDS*	*6 month follow-up*	*12 month follow-up*
Age (yr)	14.82	14.92	14.99	15.07	15.30	15.92
Weight (lbs)	94.5	95.6	93.75	89	120.5	120
Percentile	6.81	6.3	4.85	1.92	37.83	25.46
Z score	-1.49	-1.53	-1.66	-2.07	-0.31	-0.66
Height (in)	68.0	68.0	68.0	68.0	68.0	68.0
Percentile	68.8	64.8	64.8	62.9	57.5	46.4
Z score	0.5	0.4	0.4	0.3	0.2	-0.1
BMI	14.4	14.5	14.3	13.5	18.3	18.2
Percentile	<1	<1	<1	<1	23	16
Z score	-3.33	-3.24	-3.57	-4.39	-0.73	-0.98

Abbreviations: BMI, body mass index; in, inches; lbs, pounds; Yr, Year.

Table 3. Anthropometric data collected from baseline to 12 months for participant 2

	Baseline	*1 month*	*2 months*	*3 months*	*4 months*	*12 months*
Age (yr)	11.72	11.81	11.88	11.96	12.28	12.73
Weight (lbs)	85.2	89	90	93	88.25	92
Percentile	47.6	54.38	52.79	59.1	40.52	38.97
Z score	-0.06	0.11	0.07	0.23	-0.24	-0.28
Height (in)	59	59.5	59.5	61.5	61.5	61.5
Percentile	63.7	67.4	64.8	83.9	75.5	61.8
Z score	0.3	0.5	0.4	1	0.7	0.3
BMI	17.2	17.7	17.9	17.3	16.4	17.4
Percentile	43	50	53	42	22	35
Z score	-0.18	0.01	0.07	-0.21	-0.77	-0.39

Abbreviations: BMI, body mass index; in, inches; lbs, pounds; Yr, Year.

weeks as recommended. Nutrient intake data provided at the 6- and 12-month follow-up appointments indicated that the participant was receiving appropriate nutrition and weight was stable over this time.

Participant 3

A 13-year old boy with a history of esophageal ulcers and lymphonodular hyperplasia of the terminal ileum presented with abdominal pain and diarrhea. Weight, height and BMI were considered to be in a healthy range at baseline. After the 12-week study intervention, the participant's weight increased from 104 lbs at baseline to 115.4 lbs at 12 weeks representing an increase of ~11 lbs during the intervention period (Table 3). At the 6- and 12-month follow-up visits, his weight had increased to 118 and 119 lbs, respectively. Height increased by 4 in during the intervention period (65.5 to 69.5 in) remaining the same at both follow-up visits (Table 4). BMI remained relatively stable, decreasing slightly at 12 weeks due to the gain in height. Intestinal permeability decreased from 0.18 (reference range: <0.1) to 0.05 after the 12-week intervention and remained WNL at follow-up. Hemoglobin and hematocrit values were slightly high at baseline but within range at all other timepoint measured. (data not shown) All other lab work remained WNL. Nutrient intake was reported as 2517 total kCal, 259g total carbohydrates, 108g total fat and 128g total protein at baseline. After the 12-week study intervention period, nutrient intake was reported as 2844 total kCal, 415g total carbohydrates, 100g total fat and 71g total protein. GSRS analysis did not highlight any specific GI symptoms at baseline or at 12 weeks. Solid food was re-introduced at 12 weeks as recommended. Nutrient intake data provided at the 6- and 12-month follow-up appointments indicated that the participant was receiving appropriate nutrition and weight had increased by 4lbs at the 6-month time point, remaining stable at the 12-month follow up.

Participant 4

A 9-year old boy, significantly underweight and diagnosed with gastropathy, esophageal ulcers, and aphthous ulceration of the rectosigmoid presented with abdominal distention and diarrhea. The participant's weight increased from 49.5 lbs at baseline to 52.8 lbs at the end of the 12-week intervention period representing an increase of ~3.5 lbs. Weight gain continued after transitioning back to solid food with a reported weight of 54.4 and 67 lbs at the 6- and 12-month follow-up

Table 4. Anthropometric data collected from baseline to 12 months for participant 3

	Baseline	*1 month*	*2 months*	*3 months*	*4 months*	*12 months*
Age (yr)	13.26	13.45	13.53	13.60	13.87	14.37
Weight (lbs)	104	111.4	116	115.38	118	119
Percentile	50	59.87	65.91	63.31	62.17	53.59
Z score	0	0.28	0.41	0.34	0.31	0.09
Height (in)	65.5	67.5	68.5	69.5	69.5	69.5
Percentile	84.4	93.1	95.7	97.5	95.8	90.3
Z score	1	1.5	1.7	2	1.7	1.3
BMI	17	17.4	17.4	16.8	17.2	17.3
Percentile	23	27	26	16	19	17
Z score	-0.74	-0.62	-0.64	-0.99	-0.86	-0.95

Abbreviations: BMI, body mass index; in, inches; lbs, pounds; Yr, Year.

appointments, respectively placing him at the 3.6th and 20th percentile, respectively (Table 5). Data for height, and therefore BMI, during the study was not available. All lab measures remained WNL throughout the study. Nutrient intake was reported as 1992 total kCal, 210g total carbohydrates, 91g total fat and 60g total protein at baseline. At the end of the 12-week study intervention period, nutrient intake was reported as 1659 total kCal, 242g total carbohydrates, 60g total fat and 42g total protein. GSRS analysis indicated a baseline score of 11 that was attributed to all 5 GI domains assessed. Unfortunately, a GSRS was not completed at 12 weeks, although data was available at 8 weeks, which indicated that GI symptoms were resolving: a score of 6 was reported primarily attributed to decreases in the pain and indigestion domains. Solid food was re-introduced at 12 weeks with no concerns. Nutrient intake data provided at the 6- and 12-month follow-up appointments indicated that the participant was receiving appropriate nutrition. Clinical follow-up to assess the status of previous gastrointestinal pathology after the study was not reported to study investigators.

Participant 5

A 9-year old boy with a history of enuresis, GERD, and lymphonodular hyperplasia of the terminal ileum and colon presented with abdominal pain, diarrhea, and vomiting. Weight, height and BMI were considered to be in a healthy range at baseline. There was no significant weight change over the 12-week intervention period however the child grew 1.25 inches (Table 6). Weight and height continued to increase at both the 6- and 12-month follow-up appointments with a final weight of 74 lbs and height of 57.5 in reported at the 12-months follow-up appointment. Lab values remained WNL throughout the study except for intestinal permeability, which decreased from 0.11 (reference range <0.10) to 0.06 after the 12-week intervention, and remained WNL at 6 months (a 12-month follow was not available). Nutrient intake was reported as 2662 total kCal, 299g total carbohydrates, 131g total fat and 93g total protein at baseline. After the 12-week study intervention period, nutrient intake was reported as 2133 total kCal, 312g total carbohydrates, 75g total fat and 54g total protein. GSRS analysis reported an improvement in stool consistency with a score of 22 at baseline and 8 at 8 weeks (a 12-week GSRS was not available). This was primarily attributed to decreases in the pain, reflux and indigestion domains. Parental caregiver reported initial concerns over pica (paper) when ED was started so gave ice-chips to provide a chewing sensation, which helped although the pica did not completely resolve during the study. Improved activity levels towards the end of the intervention period was reported, although enuresis did not resolve. Solid food was re-introduced at 12 weeks as recommended with no concerns reported. Nutrient intake data provided at the 6- and 12-month follow-up appointments indicated that the participant was receiving appropriate nutrition and their weight had increased by 4lbs.

Discussion

This is the first report describing the use of an ED in the treatment of IBD in children with ASD. In general, the ED was well-tolerated with improvements in clinical lab measures, and/or GI functioning reported by all 5 subjects after 12 weeks of intervention.

Children with Crohn's disease, IBD and eosinophilic esophagitis are at high risk of nutrient malabsorption and weight loss, and in many cases, an ED may improve malabsorption and weight gain [29, 33, 34, 43]. In our study, we anticipated that initiating an ED might negatively impact BMI as the result of catch-up growth in either height or weight [37], especially in those participants that were underweight. Furthermore, caloric intake decreased during the intervention period due to the reliance on an elemental diet to provide all dietary nutriture. Regardless, BMI stayed relatively constant in four of the participants during the intervention period (this data was not available for participant 4). Interestingly, the height and weight of these four participants all increased over time. For some, this began immediately after starting the ED whereas in others, it was delayed or even decreased slightly during the intervention period but was followed by clear gains reported at the 6- and 12-month appointments. The latter may be indicative of the need for a period of gut 'rest' to improve nutritional status, as has been indicated in children with Crohn's disease [44].

Most of the clinical lab measures were within normal limits at baseline. CRP, a marker of active inflammation, was high in one participant at baseline but resolved following 12 weeks of ED intervention, as

Table 5. Anthropometric data collected from baseline to 12 months for participant 4

	Baseline	*1 month*	*2 months*	*3 months*	*4 months*	*12 months*
Age (yr)	9.58	9.71	9.79	9.95	10.13	10.8
Weight (lbs)	49.5	50	52.4	52.8	54.4	67
Percentile	1.7	1.54	3.29	2.87	3.67	20.61
Z score	-2.12	-2.16	-1.84	-1.9	-1.79	-0.82
Height (in)	50	n/a	n/a	n/a	n/a	n/a
Percentile	6.8					
Z score	-1.5					
BMI	13.9	n/a	n/a	n/a	n/a	n/a
Percentile	4					
Z score	-1.8					

Abbreviations: BMI, body mass index; in, inches; lbs, pounds; Yr, Year.

Table 6. Anthropometric data collected from baseline to 12 months for participant 5

	Baseline	*1 month*	*2 months*	*3 months*	*4 months*	*12 months*
Age (yr)	9.92	10.04	10.11	10.19	10.46	10.98
Weight (lbs)	69	70.8	70.4	70.4	73.2	74
Percentile	46.41	50	46.81	44.83	46.81	36.69
Z score	-0.09	0	-0.08	-0.13	-0.08	-0.34
Height (in)	54.5	55	55.75	55.75	55.75	57.5
Percentile	50	55.2	64.1	61.4	54.4	65.2
Z score	0	0.1	0.4	0.3	0.1	0.4
BMI	16.3	16.5	15.9	15.9	16.6	15.7
Percentile	44	45	33	33	43	21
Z score	-0.14	-0.12	-0.44	-0.44	-0.18	-0.79

Abbreviations: BMI, body mass index; in, inches; lbs, pounds; Yr, Year.

previously reported [45]. However, following the re-introduction of solid food, CRP levels in this participant were elevated at both the 6- and 12-month appointments suggesting that there was active inflammation. The L/M ratio was high (indicative of gastrointestinal permeability) in two participants at baseline but resolved following ED intervention and remained in range at the 6- and 12-month visits.

Assessing GI symptoms in children can be challenging [46] and this is further compounded when assessing children with ASD who may not be able to communicate or localize pain in typical ways due to impairments in social communication and sensory processing [47, 48] resulting in problem behaviors [5, 12]. Accurately capturing GI symptomatology in children with ASD has been hampered by the lack of an ASD-specific screening tool. The GSRS has been used in several studies of children with ASD [49] but the language used is complicated and overly clinical, and it was originally designed for use in adults to screen for irritable bowel syndrome and peptic ulcer disease [42]. However, at the time of study initiation, the GSRS was considered the best questionnaire available for capturing the anticipated five domains in GI symptomatology: abdominal pain, reflux, indigestion, diarrhea, and constipation and has since been used in a number of ASD studies [50-53]. Overall, GI symptoms improved over time in most of the participants. The greatest improvement in GI symptoms was seen in participant #1 whose baseline score of 13 was reduced to a score of 1 after the 12-week study intervention period. This was primarily attributed to a significant decrease in scores in the 'pain' and 'diarrhea' domains, with the participant's mother also reporting that the participant had "no abdominal pain" and "stool were daily and formed". GI improvements in other participants were subtle and therefore harder to quantify.

Based on the case reports in our pilot study, it appears that 12 weeks of an ED intervention was a suitable timeframe to observe quantitative changes in laboratory measures, GI symptoms and/or anthropometric measures in most participants. In the clinical setting, a longer period of intervention may be required to see sustained effects.

Pica was a concern in two participants, which is more likely due to the need for a 'chewing' sensation than nutrient deficit. One participant was reportedly to occasionally eat mulch and leaves from the playground at school during the beginning of the study intervention. This child was subsequently diagnosed with roundworms requiring a parasite treatment protocol that lasted several weeks. It is not known how long the participant had roundworms, i.e. was this an underlying problem (the child had been treated for parasites before) or if this was the result of the pica, but it is highly likely that this may have affected nutritional and GI parameters during the ED intervention period. The participant's mother also reported that the child had periods of unusual hyperactivity, visual stimming, bedwetting, and daytime incontinence. It is well known that parasite infections can lead to a range of symptoms including those described above [54].

While an ED has not been used specifically in the ASD population before, it has been well documented in the pediatric population, especially for the treatment of Crohn's disease [29, 30], active inflammatory bowel disease [32, 33], and eosinophilic esophagitis [23, 34, 35, 37]. In children with ASD, there is mounting evidence that gastrointestinal dysfunction is highly prevalent [4] suggesting that they are at risk of nutrient malabsorption and growth impairment. Although this can often be attributed to specific behaviors such as food refusal, pica, food restriction, and/or sensory issues [55], in some cases there is an organic disease, which should be treated in the similar way to children without ASD.

However, the use of an ED is not risk free [56]. Nutritional deficiency, decreased quality of life, psychological impact, risk of developing eating disorders, increased cost and complexity are major drawbacks in diet therapy [57]. Patients on therapeutic diets should be closely monitored by a nutritionist to maximize the number of options available in the diet, and to avoid nutritional imbalances and accidental exposures [56]. Children's growth parameters and feeding behaviors should be closely monitored. All of the children in this study were monitored weekly by a dietitian and had a member of the clinical team available to them 24 hrs a day, 7 days a week.

There are a number of limitations of this study. Although this is a prospective study, there were only 5

participants and thus it is descriptive in nature. Due to the complexity of each participant's presentation, it is not possible to confer any specific benefits of the ED to the study group as a whole. Furthermore, some data were missing or not available and/or participants did not complete certain assessments at the required study visits. Controlling dietary infractions for the duration of the 12-week trial was challenging for some parents, especially for older children that attended school. One parent reported weekly food infractions, while two reported pica. Both food infractions and pica could impact the efficacy of the ED intervention but this could not be easily measured. While the inclusion criteria for this study required confirmed gastrointestinal diagnoses, this was identified from the patient's medical records and did not require confirmation from a gastroenterologist at the time of study initiation. In the absence of active inflammation, an ED may not be efficacious. The GSRS questionnaire that was used to capture GI symptoms is designed for adults and is difficult to complete in the pediatric populations, especially in children that are non-verbal and unable to communicate their specific GI concerns [47]. Since this study was concluded, two new pediatric questionnaires have been proposed for use in children with autism [47], which may provide better screening and assessment of GI symptomology in future studies. In hindsight, a behavioral assessment, such as the Vineland Adaptive Behavior Scales, would have been very helpful in identifying any behavioral changes throughout the study. In the absence of any standardized behavioral questionnaire, we reported anecdotal evidence provided by the primary caregiver when appropriate.

Conclusion

In conclusion, the ED was well tolerated in the participants in this study, all of who generally showed improvements in anthropometrics, clinical lab measures, and/or GI symptoms. Prospective longitudinal studies are needed to evaluate the effects of an ED on anthropometric measures, sleep, GI symptoms, and behavior in children with ASD and GI conditions to definitively determine the optimal treatment approach when an ED is warranted.

Acknowledgments

This study was funded by The Jane Botsford Johnson Foundation. We are very grateful to all the families that participated in this research study. We would also like to thank the staff at The Johnson Center for implementation of this study protocol. This study was approved by the Austin Multi-Institutional Review Board (AMIRB).

Conflict of Interest

The authors have no conflicts of interest to declare.

Ethical Board Approval

This study was approved by the appropriate Institutional Review Board in accordance with local regulations.

Supplementary Figures

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