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ORIGINAL ARTICLE

Partial enteral nutrition induces clinical and endoscopic remission in active pediatric Crohn's disease: results of a prospective cohort study

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Abstract

The aim of this study was to evaluate rates of clinical remission, endoscopic remission, and mucosal healing after a 6-week treatment period with partial enteral nutrition (PEN) and to compare them to those obtained by standard exclusive enteral nutrition (EEN) treatment in children with active Crohn's disease (CD). Twenty-five patients with active CD (median age 13.6 years, range 3.6–18.0) were recruited to either PEN ($n = 12$) or EEN ($n = 13$) treatment groups. The PEN group received 75% of their dietary needs from a polymeric formula plus one meal per day from an anti-inflammatory diet (AID). Patients were assessed at weeks 0, 1, 3, and 6 using clinical and laboratory parameters. Endoscopic assessment was performed at induction and week 6. On intention to treat analysis, clinical remission (Pediatric CD Activity Index < 10) was achieved in 69.2% and 75.0% of EEN and PEN patients, respectively ($p = 0.999$). The endoscopic remission (Simple Endoscopic Score for CD (SES-CD) ≤ 2) rates were 45.5% in both groups, while mucosal healing rates (SES-CD = 0) were 45.5% with EEN and 27.3% with PEN ($p = 0.659$).

Conclusion: The results of our prospective pilot study suggest that PEN, allowing one meal from AID, could be as effective as EEN in inducing clinical and endoscopic remission in children with active CD. However, larger randomized controlled studies are warranted to confirm our findings.

Trial registration: This clinical trial was registered under the number *ClinicalTrials.gov identifier: NCT03176875*.

What is Known:
- *Exclusive enteral nutrition is a first-line treatment in active pediatric Crohn's disease; however, patients often find it difficult to adhere to.*
- *Exclusive enteral nutrition is more effective than corticosteroids in achieving mucosal healing.*

What is New:
- *This is the first prospective study on partial enteral nutrition in active pediatric Crohn's disease, evaluating not only clinical, but also endoscopic remission.*
- *A novel approach of partial enteral nutrition that allows one meal per day from an anti-inflammatory diet was as effective as exclusive enteral nutrition in inducing clinical and endoscopic remission in active Crohn's disease.*

Keywords Crohn's disease · Children · Exclusive enteral nutrition · Partial enteral nutrition

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Abbreviations

AID-CD	Anti-inflammatory diet for CD
CD	Crohn's disease
CRP	C-reactive protein
EEN	Exclusive enteral nutrition
FC	Fecal calprotectin
IBD	Inflammatory bowel disease
MH	Mucosal healing
PCDAI	Pediatric CD Activity Index
PEN	Partial enteral nutrition
SES-CD	Simple Endoscopic Score for CD

Introduction

Numerous clinical studies have confirmed that exclusive enteral nutrition (EEN) is as effective as corticosteroids (CS) for induction of remission in active pediatric Crohn's disease (CD) [1–4]. Moreover, EEN was shown to be more effective than CS in achieving mucosal healing (MH) [5–7]. Consensus guidelines of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and European Crohn's Colitis Organization (ECCO) recommend EEN as a first-line therapy in children with active CD, including those with colonic involvement [4]. Despite strong evidence showing the benefits of EEN, this treatment approach is still underused in many pediatric inflammatory bowel disease (IBD) centers [8]. The most important barriers to its use are the repetitive and poor taste of enteral formulas and the heavy dietary restriction EEN places on patients, as they are not allowed to consume any other food over a long period of time. The latter is likely the main reason that EEN therapy is not well received or adhered to in many patients. To improve compliance, it seemed beneficial to allow patients to consume some whole food alongside the enteral formula, thus introducing the idea of treatment with partial enteral nutrition (PEN).

The first randomized controlled trial on PEN (50% elemental formula + unrestricted diet) found that it was not sufficiently efficacious in inducing remission in active pediatric CD. Clinical remission was observed only in 15% of patients on PEN compared with 42% on EEN [9]. In accordance with the results of this well-designed study, interest in PEN had then declined for some years. In recent years, however, interest in PEN has begun to rise again, as newer studies have indicated that PEN might be effective in inducing remission in active pediatric CD. The studies to date on PEN, although still scarce and heterogenous in design, seem to point to an efficacy that is higher than was first published, with some showing remission induction rates above 70%, especially when PEN was combined with a specific exclusion diet [10–13].

In all previous studies investigating PEN, only clinical remission rates and laboratory parameters have been evaluated after a course of PEN treatment, with fecal calprotectin levels used as a surrogate marker of mucosal inflammation [10–13]. However, in recent years, the primary endpoint of clinical trials has shifted from clinical remission towards endoscopic remission with the final goal of achieving complete mucosal healing [14–16].

Therefore, the primary aim of our study was to evaluate and compare the rates of clinical and endoscopic remission as well as mucosal healing rates after 6 weeks of treatment with either PEN or EEN in children with active CD. Secondary aims were to determine and compare changes in Pediatric CD Activity Index (PCDAI), Simple Endoscopic Score for CD (SES-CD), and laboratory and anthropometric parameters. We hypothesized that clinical and endoscopic remission rates after a 6-week period of PEN (+ one meal per day from anti-inflammatory diet for CD (AID-CD)) would not differ from those observed with EEN in treatment of active CD.

Materials and methods

Patients

From June 2017 to the end of February 2019, all pediatric patients with active CD (newly diagnosed and those with exacerbations), treated in a single tertiary center, who fulfilled inclusion criteria for enteral nutrition (EN) treatment, were prospectively included in the study. All patients were diagnosed according to the revised Porto criteria [17].

The inclusion criteria were clinically and endoscopically active CD (Pediatric CD Activity Index (PCDAI) > 10, Simple Endoscopic Score for CD (SES-CD) > 3, age ≤ 18 years, and no changes in maintenance treatment in the last 3 months.

The exclusion criteria were PCDAI ≤ 10, SES-CD ≤ 3, penetrating disease (abscess or fistula), active perianal disease or extra-intestinal disease, fixed strictures or small bowel obstruction, changes in maintenance treatment, or having received steroids in the last 3 months prior to inclusion.

Initially, patients were to be randomized to receive either EEN or PEN therapy; however, many of them did not agree with randomization. Thus, all eligible patients were recruited into either group by their selected choice.

Dietary therapy

Patients in the EEN group were treated according to the standard EEN protocol of our tertiary center, with oral polymeric formula (Alicalm, Nutricia, Netherlands) serving as the sole source of nutrition during the 6-week treatment period. The volume of daily prescribed formula was determined by a clinical dietitian, according to the calculated estimated average daily requirement (EAR) based on age, gender, height, weight, and assumption of daily physical activity (basal caloric

requirements + additional needs—20% caloric needs—for catch-up growth). EAR was calculated based on Central European (German (D), Austrian (A), and Swiss (CH); D-A-CH) recommendations [18]. Ninety-five percent of expenses for Alicalm are covered by Slovenian health insurance.

Patients in the PEN group were treated with enteral formula (Alicalm, Nutricia, Netherlands) that covered 75% of their daily caloric requirements, and lunch or dinner from an anti-inflammatory diet for CD (AID-CD). With the intention of making this new treatment regimen simple and patient-friendly, patients were encouraged to consume the same amount of food per meal as they were accustomed to before inclusion in the study, but they had to strictly adhere to the diet. The AID-CD made for the purpose of this study was based on the CD Exclusion Diet (CDED), which was grounded on recent scientific findings from epidemiological and animal model studies [12]. It excludes dietary components that negatively affect either intestinal permeability, the microbiome, or the innate immune system that are presumed to be involved in CD pathogenesis [12, 19–24]. The most important feature of CDED and our AID-CD is the exclusion of processed foods with additives, animal fat, sugar, dairy products, and gluten [19–24]. Unlike CDED, the AID-CD is based on Slovenian local and traditional cuisine (for more information on the diet used, see supplemental digital content 1). The difference between the CDED and the AID-CD is that CDED allows fried foods while AID-CD does not [25]. Additionally, only regionally grown fruits and vegetables and locally and ecologically sourced white meat or fish are allowed. Cooking or baking using olive oil is desirable [26].

In newly diagnosed patients, with moderate to severe disease activity, thiopurines were introduced according to standard clinical practice, at either the 1st- or 3rd-week visit with intention of maintenance therapy. The dose of azathioprine was gradually increased, aiming for a dose of 2–2.5 mg/kg/day at the end of the study protocol. Patients included into the study due to an acute exacerbation of CD continued their maintenance treatment for the entire study period without change.

The primary outcome measures were clinical remission (PCDAI < 10) [27], endoscopic remission (defined by a SES-CD ≤ 2) [15], and mucosal healing (defined as complete lack of endoscopically visible inflammation (SES-CD = 0)) [15, 16].

Secondary outcomes were clinical response (PCDAI reduction of ≥ 15), endoscopic response (decrease in SES-CD from baseline of at least 50%), changes in PCDAI and SES-CD, changes in laboratory data (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), thrombocytes, serum albumin, fecal calprotectin), and anthropometric parameters (body weight and body mass index (BMI)). Fecal calprotectin (FC) concentration was analyzed at baseline and week 6, using a commercial Calprest assay (Eurospital, Trieste, Italy). The kit test range was 15.6–500 mg/kg.

The patients were seen by a consultant gastroenterologist (D.U) and a clinical dietitian (E.B) at weeks 0, 1, 3, and 6. At each visit, response and compliance to EN treatment were assessed and a physical examination was performed, along with PCDAI scoring and measurements of anthropometric and laboratory parameters (at weeks 3 and 6).

Ileocolonoscopies (complete colonoscopies with ileal intubation) were performed at baseline and at the end of the study period by trained pediatric endoscopists, who calculated the SES-CD score. SES-CD scoring was again reviewed, with central reading of the video recording of the procedures done by two experienced endoscopists, at the time unaware of the specific patients' treatment.

The volume of daily enteral formula intake and the type and amount of food consumed in the permitted meal per day were assessed by our clinical and research dietitian (E.B). Both the dietitian (E.B) and gastroenterologist (D.U) were always available for questions regarding nutritional treatment and the AID-CD by phone or e-mail. The patients and their parents were encouraged to call at any time, if they had any trouble or questions regarding the nutritional treatment in order to immediately offer them support and motivation to continue with treatment. During the visits, at weeks 1, 3, and 6, patients were additionally assessed regarding their adherence.

Statistical analysis

Baseline demographic and clinical data are presented as median with minimum and maximum values if numeric, and as frequencies and percentages if categorical. Comparisons of numeric variables between the two patient groups were performed using the Mann-Whitney *U* test, while chi-squared test or Fisher's exact test was used for assessing difference in distribution of categorical variables. A two-way repeated analysis of variance (ANOVA) was conducted to test whether there is a significant change in outcome variables (anthropometric and laboratory data, PCDAI, and SES-CD) over weeks of treatment between EEN and PEN patient groups. Main effects, i.e. the outcome measure and the weeks of treatment, and their interaction were included in the model. The results are presented as estimated means with standard errors. The statistical model used did not account for confounders that are present (such as age, sex, disease phenotype, disease duration, or adherence). Statistical analysis was performed with SPSS 20 software (SPSS Inc., Chicago, IL, USA) and with R language for statistical computing (R version 3.4.4). *p* values less than 0.05 were considered statistically significant.

Results

From June 2017 to February 2019, 37 pediatric patients with clinically (PCDAI > 10) and endoscopically active disease (SES-CD > 3) were identified. Nine patients were excluded according to the exclusion criteria (Fig. 1). Twenty-eight patients fulfilled inclusion criteria, but three chose CS; therefore, only 25 could be included in the study. Of those, 13 were recruited in the EEN and 12 in the PEN study group. In the PEN group, one patient withdrew from the study due to nausea and non-adherence. In the EEN group, two patients withdrew from the study, the first patient due to vomiting and the second patient because he could not tolerate the taste of Alicalm; he was changed to another polymeric formula and was thus also excluded from the study (Fig. 1).

Twenty-two patients completed the 6-week study protocol, 11 in the PEN group and 11 in the EEN group. Only one patient, a 4-year-old boy, could not complete EN treatment via the oral route, instead he received EEN via a nasogastric tube.

Baseline characteristics of the patients who completed EN treatment are presented in Table 1.

Primary aims

On intention to treat analysis, clinical remission (PCDAI < 10) was observed in 9 out of 12 patients (75.0%) in the PEN and in 9 out of 13 (69.2%) patients in the EEN group ($p = 0.999$). On per protocol analysis, clinical remission was achieved in 9 out of 11 patients (81.8%) in the PEN group as well as in 9 out of 11 patients (81.8%) in the EEN group.

Endoscopic remission (SES-CD ≤ 2) was found in 5 out of 11 patients (45.5%) in both groups. All patients in the EEN group who achieved endoscopic remission also achieved complete mucosal healing (MH). MH was observed more often with EEN than PEN (45.5% vs 27.3%); however, the difference between groups did not reach statistical significance ($p = 0.659$) (Table 2).

Secondary aims

Clinical response (PCDAI decrease ≥ 15) was found in all PEN and in 10/11 (90.9%) patients on EEN. Endoscopic response (decrease in SES-CD from baseline of at least 50%) was observed in all but one PEN patient, a 17-year-old girl with severe CD on maintenance therapy with vedolizumab (Paris L2L4a). However, she did achieve clinical response and improvement of laboratory parameters. In the EEN group, four patients did not achieve endoscopic response, but clinical remission was observed in three of them.

Mean PCDAI and SES-CD scores decreased significantly in both groups from baseline to the end of the study (Table 3). Changes in PCDAI and SES-CD scores did not significantly differ between groups ($p = 0.778$ and $p = 0.113$, respectively) (Table 3). A significant decline by week 6 was observed in both groups for mean ESR, CRP, number of thrombocytes, and FC, whereas changes in mean weight, body mass index

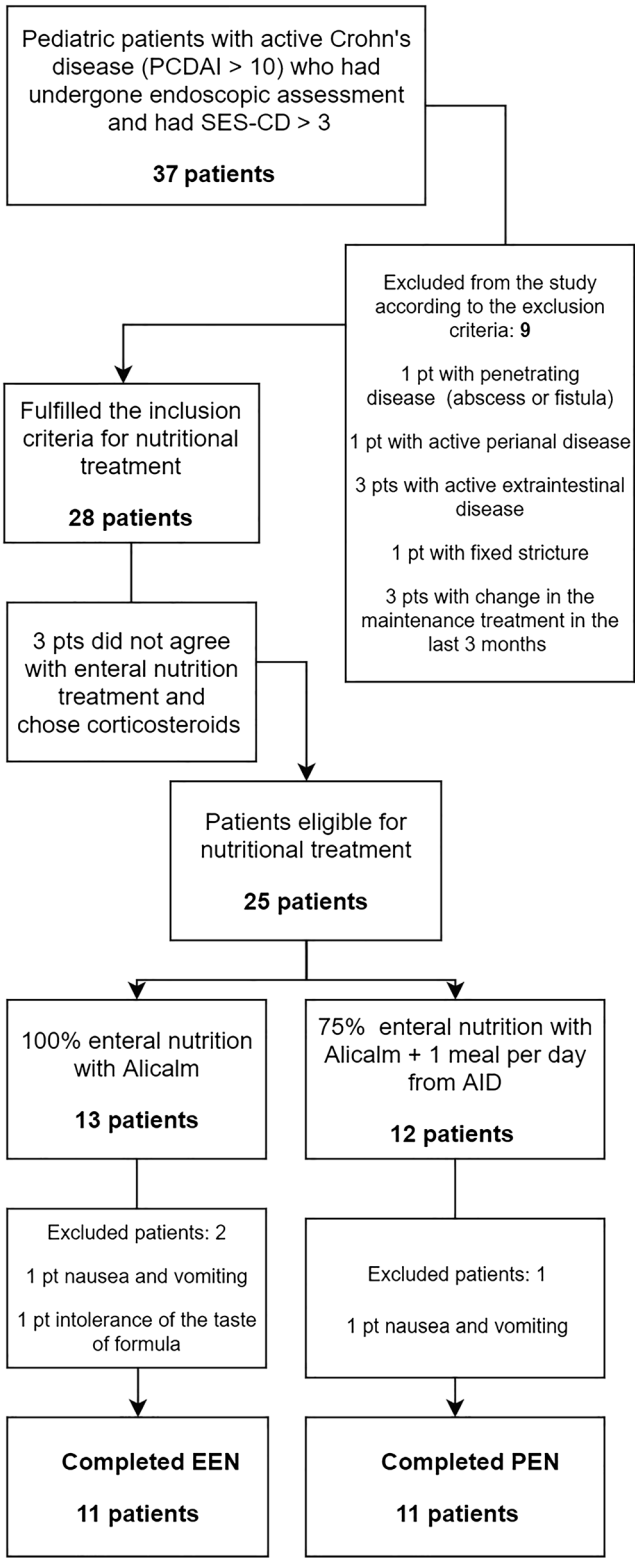

Fig. 1 Flowchart of patients throughout the study

Table 1 Baseline characteristics of patients treated with exclusive and partial enteral nutrition

	Exclusive enteral nutrition (n = 11)	Partial enteral nutrition (n = 11)	p
Age at inclusion (years)	13.8 (3.6 to 18.0)	13.4 (9.8 to 17.9)	0.949
Female, n (%)	8 (73)	5 (46)	0.387
Newly diagnosed, n (%)	9 (82)	4 (36)	0.080
Age at diagnosis (Paris), n (%)			0.999
A1a (< 10 years)	2 (18)	3 (27)	
A1b (10–17 years)	9 (82)	8 (73)	
A2 (> 17 years)	0 (0)	0 (0)	
Location (Paris), n (%)			0.999
L1 - ileal/ileocecal	0 (0)	1 (9)	
L2 - colonic	4 (36)	4 (36)	
L3 - ileocolonic	7 (64)	6 (55)	
L4a - gastroduodenal	9 (82)	10 (91)	
L4b - proximal ileum/jejunum	1 (9)	3 (27)	
L4ab - L4a+L4b	1 (9)	3 (27)	
Duration of EN treatment (days)	48 (39 to 54)	47 (42 to 52)	0.847
Maintenance therapy at baseline, n (%)			
IMM only	2 (18)	5 (45)	
Anti-TNF	0	1 (9)	
Vedolizumab	0	1 (9)	
Weight (kg)	45.4 (6.5)	49.7 (4.3)	0.588
BMI (kg/m^2)	18.9 (1.5)	19.8 (1.0)	0.614
Undernourished patients (z-score < − 2), n (%)	2 (18)	1 (9)	
Baseline PCDAI score	30.5 (3.6)	31.4 (3.2)	0.854
Baseline SES-CD score	10.7 (1.8)	13.5 (1.7)	0.293
ESR (mm/h)	37.1 (6.5)	38.5 (7.6)	0.893
CRP (mg/L)	16.5 (3.1)	18.4 (5.8)	0.774
Fecal calprotectin (mg/kg)	381.1 (37.3)	426.5 (31.8)	0.365

Data are reported as median with range; values of weight, BMI, PCDAI, SES-CD, ESR, CRP, and fecal calprotectin are presented as mean (standard error)

IMM immunomodulator, *Anti-TNF* anti-tumor necrosis factor, *BMI* body mass index, *PCDAI* Pediatric Crohn's Disease Activity Index, *SES-CD* Simple Endoscopic Score for Crohn's disease, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

(BMI), and hemoglobin levels were not statistically significant. As expected, mean albumin levels increased significantly in both groups (Table 3).

Discussion

To the best of our knowledge, this is the first study evaluating endoscopic remission rates and mucosal healing after a course of PEN treatment. Mucosal remission and mucosal healing are now considered as major treatment goals in clinical trials and clinical practice for patients with CD [14–16]. They are associated with sustained, steroid-free clinical remission, reduced rates of hospitalizations and surgery, and lower risk of fistulizing disease [28, 29].

We evaluated clinical and endoscopic remission rates and mucosal healing rates of PEN + one meal of AID per day and compared them to those obtained by EEN in children with active CD. We did not observe any difference between PEN and EEN regarding rates of clinical and endoscopic remission or mucosal healing.

EEN is very effective in inducing remission in active pediatric CD, with a reported clinical remission rate of 70–90% [1–4, 30–32]. Our results on clinical remission rates in the EEN group (81.9%) are comparable to those published in literature [7, 30–32]. However, in our PEN group, rates of clinical remission on per protocol analysis (81.9%) are higher than those reported in previous studies on PEN [9–13]. In the studies published by Gupta et al. [10] and Lee et al. [11], the reported clinical remission rates of PEN combined with an unrestricted diet were 65% and 50%, respectively. In both studies [10, 11], high volume of PEN was used as was in our case. However, in our study, PEN was combined with AID-CD. Therefore, it is plausible that PEN treatment

Table 2 Comparison of clinical and endoscopic outcomes between the two groups

Outcome at the end of the study (on per protocol analysis)	EEN group Completed EEN protocol (n = 11)	PEN group Completed PEN protocol (n = 11)	p
Clinical response (reduction of PCDAI ≥ 15)	10/11 (90.9%)	11/11 (100%)	0.999
Clinical remission (PCDAI < 10)	9/11 (81.8%)	9/11 (81.8%)	0.999
Clinical remission (PCDAI < 10)[a]	9/13 (69.2%)	9/12 (75.0%)	0.999
Endoscopic response (50% decrease in SES-CD)	7/11 (63.6%)	10/11 (90.9%)	0.311
Endoscopic remission (SES-CD ≤ 2)	5/11 (45.5%)	5/11 (45.5%)	0.999
Mucosal healing (MH) (SES-CD = 0)	5/11 (45.5%)	3/11 (27.3%)	0.659

[a] on intention to treat analysis

improves on efficacy when combined with a diet that excludes certain foods that promote gut inflammation in active CD. Indeed, in two recent Israeli studies [12, 13], where PEN (50%) was combined with CDED, the clinical remission rates on per protocol analysis were better than in studies using an unrestricted diet [10, 11]. However, our PEN treatment protocol consisted of 75% PEN and AID-CD. Our AID-CD does not differ significantly from the CDED; it avoids potentially harmful dietary components that increase intestinal permeability or negatively affect either the microbiome, metabolome, or other gut immune mechanisms involved in CD pathogenesis [19–24]. Therefore, our slightly higher clinical remission rate on per protocol analysis in the PEN group may be in part due to the higher amount of EN formula intake per day.

On intention to treat analysis, our results on clinical remission rates in PEN group are in accordance with those that have already been published by Levin et al. after a 6-week course of treatment [13]. This is the most recent prospective randomized controlled trial (50% PEN + CDED) where PEN was found to be as effective as EEN in inducing clinical remission on intention to treat analysis (75% vs 59%; p = 0.14), after 6 weeks of treatment. The study consisted of another 6-week period, immediately following the first one, where the PEN group received 25% PEN combined with CDED and the control group 25% PEN with a free diet. The PEN+CDED group achieved better remission rates at week 12. The authors concluded that these data support the use of CDED+PEN as a first-line therapy for children with luminal mild to moderate active CD [13]. However, their conclusion is not in accordance to the latest guidelines on nutrition in pediatric IBD of the Porto IBD group of ESPGHAN where exclusivity of enteral nutrition is still strongly recommended [33]. Additionally, their study lacks endoscopic evaluation, as nowadays clinical remission and changes in laboratory markers are not considered sufficient endpoints in CD, both in clinical trials and in real-life practice [14–16]. In our study, endoscopic remission (SES-CD ≤ 2) rates did not differ between the PEN and EEN groups (45.5% in both groups), and there was no significant difference in the observed mucosal healing between the two groups (45.5% with EEN and 27.3% with PEN (p = 0.659), however this may be due to the small sample size.

Indeed, several limitations to our study exist, the most important one being the small number of patients who completed the study protocol. Another limitation is the lack of randomization. Initially, the study was conceived as such, but most of our patients refused randomization, they wanted to select the type of nutritional treatment by themselves. Almost all children and adolescents wanted to choose PEN, that would allow them 1 meal per day, but some parents were discouraged by the non-standard PEN treatment and preferred the EEN protocol, as it is the one based on established guidelines [4]. This study carries a high risk of inherent biases. Patients reported about their own adherence to the prescribed volume of enteral formula and to AID and this introduces reporting bias. Furthermore, since the study was not randomized, a selection bias was also present. Moreover, the small sample size limits the power of the study. Therefore, the results should be interpreted with caution and further larger studies are needed to assess the rates of endoscopic remission and mucosal healing after PEN treatment, before any firm conclusions should be drawn.

In conclusion, while taking note of the limits of the study, our findings on PEN in achieving endoscopic and clinical remission suggest that PEN combined with AID-CD may be an effective therapeutic approach in active pediatric CD. The treatment strategy was made to be simple and patient-friendly and allows patients to consume 1 meal per day, consisting of whole food with minor restrictions. Enteral nutrition exclusivity presents a major challenge to many patients who cannot deal with the monotony of EN therapy. Allowing one meal per day can help patients remain adherent throughout the relatively long treatment period. Owing to the small sample size of our study, larger prospective studies are

Table 3 Changes in clinical, endoscopic, anthropometric, and laboratory parameters from baseline to the end of the study

	Week 0		Week 1		Week 3		Week 6		p^a		p
	EEN (n = 11)	PEN (n = 11)	EEN (n = 11)	PEN (n = 11)	EEN (n = 11)	PEN (n = 11)	EEN (n = 11)	PEN (n = 11)	EEN	PEN	EEN vs PEN
PCDAI score	30.5 (3.6)	31.4 (3.2)	17.1 (3.6)	15.0 (1.3)	8.2 (2.9)	7.0 (1.6)	6.1 (2.8)	4.1 (1.4)	< 0.001	< 0.001	0.778
SES-CD score	10.7 (1.8)	13.5 (1.7)	-	-	-	-	4.6 (1.6)	3.2 (1.0)	0.003	< 0.001	0.113
Weight (kg)	45.4 (6.5)	49.7 (4.3)	45.8 (6.3)	50.1 (4.3)	46.4 (6.4)	50.0 (4.3)	46.2 (6.1)	49.9 (4.2)	0.404	0.800	0.624
BMI (kg/m^2)	18.9 (1.5)	19.8 (1.0)	19.0 (1.5)	19.8 (1.0)	19.1 (1.4)	19.9 (1.0)	18.9 (1.4)	19.9 (0.9)	0.648	0.841	0.760
ESR (mm/h)	37.1 (6.5)	38.5 (7.6)	-	-	18.7 (3.9)	17.9 (2.8)	16.3 (3.6)	13.8 (1.4)	0.009	0.003	0.794
CRP (mg/L)[b]	16.5 (3.1)	18.4 (5.8)	-	-	8.3 (1.3)	7.9 (0)	8.8 (1.3)	7.9 (0)	0.008	0.007	0.881
Hemoglobin (g/L)	118.7 (3.5)	121.8 (3.1)	-	-	118.2 (4.2)	126.0 (2.1)	115.0 (4.9)	124.7 (2.3)	0.286	0.176	0.204
Platelets ($\times 10^9$/L)	438.4 (34.0)	435.7 (42.3)	-	-	388.4 (30.5)	385.8 (29.6)	344.9 (30.6)	370.6 (32.7)	0.017	0.003	0.697
Albumin (g/L)	40.0 (1.6)	39.8 (1.2)	-	-	42.7 (1.6)	42.9 (1.1)	43.2 (1.6)	43.3 (1.3)	0.049	0.012	0.882
Fecal calprotectin (mg/kg)[c]	381.1 (37.3)	426.5 (31.8)	-	-	-	-	206.9 (41.3)	138.2 (25.0)	0.009	< 0.001	0.064

Data are presented as mean (standard error)

[a] Comparisons of measured parameters in the EEN and PEN groups between the measured time points

[b] Negative CRP < 8 mg/L

[c] At week 6, there are three missing values in the EEN group and two in the PEN group

EEN exclusive enteral nutrition, *PEN* partial enteral nutrition, *PCDAI* Pediatric Crohn's Disease Activity Index, *SES-CD* Simple Endoscopic Score for Crohn's Disease, *BMI* body mass index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

warranted to fully assess not only the clinical, but endoscopic efficacy of PEN in combination with different anti-inflammatory diets. Further research should also focus on assessing quality of life, adherence rates, and patient's satisfaction as well as differences in long-term outcomes in both clinical and endoscopic remission rates between PEN and EEN treatment groups.

Authors' Contributions DU, EB, and RO designed the study; DU, JB, and RO enrolled the patients and performed endoscopies; EB and DU performed nutritional assessments; DU wrote the manuscript that was additionally contributed to and reviewed by all the authors. Statistical analysis was done by a professional statistician.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study received ethical approval from The National Medical Ethics Committee of Republic of Slovenia (approval number 0120-66/2016-2, KME 67/02/16). All participants received accurate information on the study. Informed consent was obtained from all individual participants included in the study (from one of the parents in case of children and in case of adolescents, both from one parent and the participating adolescent).

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