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ORIGINAL ARTICLE

Use of Exclusive Enteral Nutrition Is Just as Effective as Corticosteroids in Newly Diagnosed Pediatric Crohn's Disease

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Abstract
Background The efficacy of exclusive enteral nutrition (EEN) in induction of remission in pediatric Crohn's disease (CD) is reported to be equivalent to that of corticosteroids (CS).
Aims Our objective was to compare the efficacy of EEN and CS in inducing remission in pediatric onset CD and the effects of the treatment on nutritional status and bone mineral density (BMD).
Methods Medical charts were retrospectively studied for patients diagnosed with CD between 2000 and 2010 at the Stollery children's hospital in Edmonton, Alberta. Anthropometric and dual-energy X-ray absorptiometry (DXA) data were collected to assess effects of therapy; clinical remission, relapse, and severity were defined on the basis of the pediatric Crohn's disease activity index.
Results To induce remission at first presentation, 36 patients (mean age 12.9 years) received EEN and 69 (mean age 11.2 years) received CS. Remission (88.9 % in the EEN group versus 91.3 % in the CS group ($p = 0.73$) at 3 months) and relapse (40.6 vs. 28.6 %, respectively ($p = 0.12$) over 12 months) were similar in both treatment groups. Thirty-four patients had paired DXA scans at the time of diagnosis and one year later: 16 given EEN and 18 given CS. Change in BMD spine z-scores based on bone age adjusted for height and chronological age was greater for EEN patients but not statistically significant (Δz-score 0.30 vs. 0.03, $p = 0.28$).
Conclusions EEN has similar efficacy to corticosteroids; however, EEN may lead to better BMD accrual. EEN should be preferred to corticosteroids as first-line therapy for induction of remission in pediatric CD.

Keywords Pediatric · Crohn's disease · Nutritional therapy · Corticosteroids · DXA

Abbreviation

BA	Bone age
BMC	Bone mineral content
BMD	Bone mineral density
BMAD	Bone mineral apparent density
CD	Crohn's disease
CS	Corticosteroids
DRIs	Dietary reference intakes
DXA	Dual-energy X-ray absorptiometry
EEN	Exclusive enteral nutrition
IBD	Inflammatory bowel disease
PCDAI	Pediatric Crohn's disease activity index

Introduction

Crohn's disease (CD) is a lifelong chronic inflammatory condition of the gastrointestinal tract. Childhood onset of CD is often accompanied by severe nutritional and metabolic implications [1]. At diagnosis, approximately 85 % of CD patients present with weight loss, and up to 15–40 % of this population experience growth failure [2, 3]. The purpose of therapeutic strategies is to achieve clinical remission and to maintain intestinal mucosal healing. In

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addition, management of CD in pediatric patients requires a greater emphasis on achieving optimum growth and pubertal development [4].

Corticosteroids (CS) are regarded as efficacious therapy for inducing remission among patients with active CD. However, this medication has significant side effects, especially with long-term use, and does not heal mucosal inflammation [5, 6]. Many pediatric gastroenterologists find CS therapy an even less attractive option for childhood-onset CD because of the risk of reduced bone mineral density (BMD) and growth impairment, often already adversely affected by the disease [7, 8]. Prolonged use of high-dose corticosteroids has been associated with both irreversible growth failure and rapid bone loss [9, 10].

Exclusive enteral nutrition (EEN) is reported to have many advantages beyond nutritional benefits alone, and these advantages persist beyond the initial duration of EEN itself [11, 12]. Several studies have supported a primary role EEN in the treatment of active CD, including achieving mucosal healing, improving gut permeability, promoting immune modulation, sustaining remission, and stimulating growth [13–15]. Patient adherence to consuming large volumes of formula every day for several weeks is recognized as a concern affecting efficacy. Despite these challenges, EEN is still recommended by physicians and selected by families because of its safety profile (i.e. rare adverse effects) and potential advantages to growth and improvement of bone mass [16].

In our IBD clinic the use of EEN is strongly advocated to induce remission, on the basis of long-term nutritional advantages, including reducing the effect of CD on adolescent bone accrual. The purpose of this study was to observe the efficacy of EEN and document its effect on disease activity, growth, and BMD in comparison with CS for newly diagnosed pediatric CD patients.

Methods

Chart Review

Study patients were identified using the pediatric inflammatory bowel disease (IBD) clinic database at Stollery Children's Hospital. This multidisciplinary IBD clinic is the major tertiary referral center for children with IBD in northern Alberta. All study patients were diagnosed with CD between January 2000 and July 2010 on the basis of acceptable clinical criteria, including endoscopic, histological, and/or radiological findings. The data extracted were: patient identifier, gender, birth date, diagnosis, site and severity (radiology and endoscopy); major presenting signs and symptoms (e.g. abdominal pain, fever, diarrhea); treatments administered; duration of disease pre-diagnosis; extra-intestinal manifestations of CD; serial weight, height, weight, and height *z*-scores (calculated by use of Epi Info Version 3.4.3 downloaded from the Centre for Disease control); and laboratory investigations.

Inclusion and Exclusion

To be included, study patients must have had a follow-up period with the IBD Clinic of at least 12 months. Patients were determined to be in the EEN group when they were given EEN as primary therapy to induce remission of their CD, at or near diagnosis. Data on the nutritional formula, calorie provision, and mode of administration (nasogastric vs. oral) were collected. Patients were determined to be in the CS group when they were given corticosteroids as primary therapy to induce remission of their CD, at or near diagnosis. This included different types of steroid (budesonide, methylprednisone, prednisone); data on dosages, weaning schedules, and modes of administration were collected. The choice of EEN versus CS was based on the patients' and treating physicians' preference. Although there is evidence suggesting little effect of disease phenotype on variation of response to EEN, the physicians in our practice favor treating small bowel or ileocolonic CD with EEN [17, 18]. In contrast patients with strictly colonic CD are more often recommended to receive CS.

Data Analysis

To comparatively assess the efficacy of CS and EEN, clinical remission, relapse, and severity were defined by use of the pediatric Crohn's disease activity index (PCDAI). At each clinic visit the physicians routinely completed a structured history and physical examination sheet that provides the clinical data required to calculate the PCDAI. Moderate to severe disease was defined as $\geq$30, mild or moderate disease was defined as $>$10 and $<$30, and remission was defined as $\leq$10. A relapse was documented as occurring when patients achieved remission (score of $\leq$10) and then on a subsequent clinic visit were assessed as having a PCDAI $>$10 [19]. Anthropometric data, also, were collected to assess effects of treatment on growth. Remission was calculated three months post therapy and relapse information was gathered for up to 12 months.

The effect of CS and EEN on bone status was evaluated by dual-energy X-ray absorptiometry (DXA) of the lumbar spine (L1–L4, inclusive) at or near the time of diagnosis and after 12–18 months of follow-up. BMD was converted to *z*-scores adjusted for bone age (BA) and height [20]. Furthermore, because two-dimensional DXA measurements do not take into account bone depth, hence do not provide an accurate value for volumetric bone density, an

estimate of volumetric bone density, bone mineral apparent density (BMAD), was determined by use of the method of Carter et al. [21]. To compare the effect of the two types of therapy on the change in BMD data between DXA scans, children with a history of corticosteroid use for reasons other than CD, those with other diagnoses which could affect BMD, or those on a mixed treatment regimen (EEN and CS) within the 12–18 month period were excluded.

Data Statistics

Statistical analysis was performed by use of Systat (Version 12.0 for Windows). Parametric values were compared by use of the *t* test method, whereas the chi-squared test was used for categorical variables. Ninety-five percent CI was calculated and statistical significance was considered to have been reached if the calculated two-tailed *p* value was less than 0.05.

Results

Study Population

The pediatric IBD database contained data for 250 patients; 154 of those were diagnosed with CD and 126 met inclusion criteria based on duration of follow up. Of the 28 patients excluded, 12 were lost to follow-up (i.e. patients' data were insufficient characterize their disease) and 16 were diagnosed before 2000. Of the 126 patients, 21 (mean age 12.9 years) were given other therapy; there was no statistical difference between this group and the treatment group ($n = 105$). Clinical and demographic data for CS and EEN patients ($n = 105$) are summarized in Table 1. Those on CS therapy ($n = 69$) were given 1 mg/kg/day prednisone to a maximum dose of 50 mg/day, for four weeks and then weaned over the next 6–8 weeks. Those on EEN therapy ($n = 36$) were given polymeric ($n = 33$, 91.7 %) or semi-elemental ($n = 3$, 8.3 %) formula, exclusively, for six weeks and then partially over the next two weeks depending on patient compliance. Most patients were treated with Nutren 1.5; Peptamen 1.5 was used when the disease was more severe and required a more broken down formula (i.e. stricture, intolerance of Nutren 1.5). Ideal body weight rather than actual body weight was used for patients with weight loss; activity factor or stress factor based on the patient's activity level or disease severity was taken into account. Patients were followed up after two weeks by a GI registered dietitian. Further increases in kcal (i.e. usually by one can formula or 375 kcal) were recommended when the expected weight gain was not observed. Seven patients were found to have mixed therapy (both EEN and CS) at diagnosis and so were not included in analysis of the BMD data; they were, however, still included in analysis of the efficacy of CS.

At the time of diagnosis, the two groups (EEN and CS) were not statistically different on the basis of the variables: height *z*-score, weight *z*-score, PCDAI, and duration of disease before diagnosis. Average age at diagnosis was older in the EEN group (12.9 vs. 11.2 years, $p = 0.005$). Most EEN patients had ileal and ileocolonic disease, on the basis of endoscopic and radiologic findings, whereas most CS patients had ileocolonic and colonic disease. Antibiotics were given to 22 out of 36 (61.1 %) EEN patients but only 19 out of 69 (27.5 %) CS patients. Of interest is that 29/36 (80.6 %) EEN patients were prescribed azathioprine (1–3 mg/kg/day) as maintenance therapy whereas only 43/69 (62.3 %) in the CS group were given azathioprine; $p = 0.06$. Patients were routinely prescribed vitamin D, 400–1,000 IU/day, and calcium supplementation, up to 1.5 g/day; the dose of each supplement was prescribed at the discretion of the treating physician.

Comparison of Efficacy

In terms of primary remission and subsequent relapse, within one year, the two treatment groups were not found to significantly differ. In the EEN group, 32/36 patients (88.9 %) achieved remission within the 12-month follow-up period; 13/32 (40.6 %) patients achieved remission and then relapsed. In the CS group, 63/69 patients (91.3 %) achieved remission within the 12-month follow-up period; 18/63 patients achieved remission and then relapsed (28.6 %). Time to relapse was not statistically different between treatment groups (Table 1). Patients who relapsed after gaining remission while on EEN ($n = 13$) were managed with biologics ($n = 3$), increased dose of azathioprine ($n = 4$) or switch from azathioprine to methotrexate ($n = 3$), addition of antibiotics ($n = 3$), and corticosteroids ($n = 4$). In comparison, patients who relapsed in the steroid group ($n = 18$) were managed with biologics ($n = 2$), initiation of azathioprine ($n = 5$) or methotrexate ($n = 1$), increased dose of azathioprine ($n = 7$), and reinitiating a steroid course ($n = 17$). The average number of steroid courses among the CS patients who relapsed was 2.7.

Comparison of Nutritional Status

Compared with CS treatment, a significant positive change in weight *z*-score for age was observed for EEN patients at 12 months of follow-up, 0.80 versus 0.48 ($p = 0.04$), whereas change in height for age was not significantly different (0.04 vs. −0.05, $p = 0.22$). Data on both efficacy and nutritional status by treatment group have been summarized in Table 1.

Table 1 Comparison of clinical and demographic data at diagnosis, and response, at follow-up (F/U), of the treatment groups to the induction therapy

	EEN	CS
N	36	69
Sex (M, %)	21 (58 %)	43 (62 %)
Age, years (range)*	12.9 (7.4–16.2)	11.2 (2.4–16.8)
Height *z*-score (mean ± S.D.)	−0.354 ± 1.002	−0.147 ± 1.16
Weight *z*-score (mean ± S.D.)	−1.183 ± 1.37	−0.729 ± 1.27
PCDAI (at diagnosis, mean ± S.D.)	37.9 ± 15.6	35.6 ± 13.9
Mild–Moderate (PCDAI 11–30)	15 (42 %)	20 (29 %)
Severe (PCDAI > 30)	21 (58 %)	47 (68 %)
ESR (mm/h, at diagnosis, mean ± S.D.)	33.5 ± 20.0 ($n = 35$)	28.6 ± 16.6 ($n = 64$)
CRP (mg/L, at diagnosis, mean ± S.D.)	36.5 ± 56.4 ($n = 35$)	26.7 ± 31.2 ($n = 49$)
Disease location		
Upper GI	8 (22.2 %)	22 (31.9 %)
Lower GI		
Ileum*	13 (36.1 %)	9 (13.0 %)
Ileocolonic	22 (61.1 %)	35 (50.1 %)
Colonic*	1 (2.8 %)	22 (31.9 %)
Perianal	12 (33.3 %)	14 (20.3 %)
Duration of disease before diagnosis (wks, mean ± S.D.)	72.5 ± 152.1	55.1 ± 87.9
Concurrent treatment		
5-ASA*	23 (63.9 %)	59 (85.5 %)
Azathioprine (1–3 mg/kg/day)	29 (80.6 %)	43 (62.3 %)
Response		
Remission at 3 months	32 (88.9 %)	63 (91.3 %)
Relapse over 12 months	13/32 (40.6 %)	18/63 (28.6 %)
Average no. of relapses (/year)	1.23 ($n = 13$)	1.61 ($n = 18$)
Efficacy		
Time to relapse (days, $n = 13$)	154.8 ± 135.1	133.4 ± 118.4
Inflammatory markers at F/U[§]		
ESR (mm/h, mean ± S.D.)	14.0 ± 10.2 ($n = 34$)	16 ± 16.2 ($n = 60$)
CRP (mg/L, mean ± S.D.)	6.7 ± 5.8 ($n = 34$)	12.8 ± 25.6 ($n = 50$)
Nutritional status at 12 months F/U		
Change in wt. *z*-score*	0.80 ± 0.90	0.48 ± 0.67
Change in ht. *z*-score	0.04 ± 0.27	−0.05 ± 0.43

Data are expressed as number (%) of participants and mean ± standard deviation

*Age, disease location, concurrent 5-ASA use, and nutritional status were significantly different between CS and NT patients; $p < 0.05$. PCDAI was used to define clinical remission (score ≤ 10) and relapse (score > 10 after achieving remission)

[§] ESR and CRP values were recorded at 12 months for patients in remission and at the time of exacerbation for those patients who relapsed

Comparison of Bone Accrual

Thirty-four patients underwent a DXA scan at diagnosis and approximately one year later. There was likely to be a physician bias regarding request for DXA, because these patients presented with significantly lower height *z*-scores at diagnosis. Sixteen of these patients were given EEN, eighteen were given CS therapy. As shown in Table 2 the two groups were not statistically different in terms of baseline height *z*-score, weight *z*-score, PCDAI at time of diagnosis, chronological or bone age, and time between DXA scans. In the EEN group, 87.5 % of patients were given concurrent azathioprine treatment, compared with only 66.7 % of the CS group (Table 2). Mean serum 25-hydroxyvitamin D levels were not significantly different between the two groups (EEN, $n = 14 = 69.4$ nmol/L vs. CS, $n = 12 = 63.3$ nmol/L). While not reaching statistical significance, the change in bone density spine *z*-scores based on bone age, corrected for height and chronological age, were greater for patients given EEN than for those given CS (0.30 ± 0.60 vs. 0.03 ± 0.80, $p = 0.28$). This is likely to be of clinical significance, given that the change was close to zero for the steroid treated group, in this growing adolescent population. The change in BMAD, was close to zero for the EEN group, but negative for the CS group. The paired samples *t* test (baseline and endpoint) for

Table 2 Baseline and change in bone density values for patients with DXA follow-up

	EEN (mean ± S.D.); $N = 16$	CS (mean ± S.D.); $N = 18$	p Value (95 % CI)
Age, years (range)[a]	12.5 (9.9–16.1)	10.6 (3.96–14.9)	0.022 (−3.44 to −0.282)
Ht z-score	−0.65 ± 1.32	−0.85 ± 0.72	0.59 (−0.93 to 0.54)
Wt, z-score	−0.42 ± 0.99	−0.72 ± 0.81	0.33 (−0.93 to 0.32)
PCDAI (at diagnosis)	34.5 ± 12.6	38.5 ± 13.1	0.38 (−5.07 to 13.0)
Disease location			
Lower GI			
Ileum	2 (12.5 %)	3 (16.7 %)	0.73
Ileocolonic	14 (87.5 %)	15 (83.0 %)	0.73
Perianal	8 (50.0 %)	5 (27.8 %)	0.18
Medication			
5-ASA[a]	4 (25.0 %)	11 (61.1 %)	0.034
Azathioprine	14 (87.5 %)	12 (66.7 %)	0.082
Bone age			
Baseline	11.70 ± 2.25	10.2 ± 2.90	0.098 (−3.38 to 0.30)
Change	1.09 ± 0.60	1.27 ± 1.17	0.58 (−0.47 to 0.82)
25 Hydroxy Vit D (μmol/L)	69.4 ± 16.8 ($n = 14$)	63.3 ± 19.6 ($n = 12$)	0.41 (−20.8 to 8.72)
Difference in chronological age and bone age at or near diagnosis	0.96 ± 1.03	0.70 ± 0.99	0.48 (−0.96 to 0.46)
BMAD (= BMC/BA$^{1.5}$)			
Baseline	0.78 ± 0.16	0.99 ± 0.85	0.33 (−0.23 to 0.66)
Change	0.004 ± 0.09	−0.18 ± 0.74	0.33 (−0.56 to 0.19)
BMD (g/cm^2)			
Baseline	0.65 ± 0.14	0.62 ± 0.10	0.59 (−0.11 to 0.06)
Change	0.079 ± 0.057	0.054 ± 0.060	0.23 (−0.066 to 0.016)
Adjusted z-score[b]			
Baseline	−0.96 ± 1.01	−0.69 ± 0.78	0.38 (−0.35 to 0.90)
Final	−0.66 ± 0.89	−0.65 ± 0.77	0.98 (−0.57 to 0.59)
Change	0.30 ± 0.60	0.03 ± 0.80	0.28 (−0.77 to 0.23)

For all parametric variables, treatment groups were analyzed by use of Student's t test; chi-squared analysis was used for non-parametric data

[a] Age and concurrent treatments (5ASA)

[b] Spine z-score based on bone age adjusted for height and chronological age. No difference between treatment groups was found for gender, duration of disease before diagnosis, time between DXA, and change in bone area (BA) or bone mass concentration (BMC)

BMD was statistically significant for both groups ($p < 0.01$). However, the paired samples t test spine z-score based on bone age corrected for height and chronological age was closer to significance for EEN than for CS patients (0.30 ± 0.60, $p = 0.06$ vs. 0.03 ± 0.80, $p = 0.86$). Bone density data at baseline and the changes observed over time are summarized in Table 2.

Discussion

The objectives of therapy for pediatric CD include inducing remission, maintaining mucosal healing (i.e. preventing relapse), and promoting healthy growth including pubertal development [22, 23]. This study revealed similar efficacy and relapse between EEN and CS for inducing remission in pediatric CD. In terms of any advantage in managing CD severity and progress in the first year after diagnosis, there does not seem to be any benefit of CS over EEN. However, most CS patients who relapsed were treated with a subsequent course of steroids. On the other hand, it was difficult to convince EEN patients who relapsed to attempt a repeat of EEN as treatment for their exacerbation because of challenges such as palatability and financing. In terms of advantages for nutritional status and for bone development, this study shows EEN is a beneficial therapeutic alternative to CS. Considering that bone accrual is expected at this age/developmental stage and was not detected in the CS group is a notable physiological observation. The benefit of EEN over CS is bone accrual in children with CD, suggesting EEN may lead to positive changes in BMD z-score. Werkstetter et al. [16] report improved bone biomarkers, bone density, and overall nutritional status within three months after starting EEN.

The nutritional sequelae observed in growing children with CD can be related to a number of underlying mechanisms. Particularly relevant are: increased total energy requirements because of inflammation (increased tumor necrosis factor-α); loss of lean body mass (malabsorption and/or increased gut nutrient losses), and pubertal delay (as a consequence of protein energy malnutrition); inhibitory action of cytokines on bone turnover; and perturbations of the insulin-like growth factor 1-growth hormone axis [14, 24]. Additional factors that contribute to the metabolic bone disease in CD patients include calcium and vitamin D malabsorption and reduced exercise tolerance [25, 26]. We observed a positive increase in weight for age in each treatment group, but more so in the EEN group, and this is, therefore, independent of improved disease activity alone. Whitten et al. [27] reported similar increases in mean weight and change in weight *z*-score after EEN treatment of newly diagnosed pediatric CD patients. In addition, it is recognized that after a period of protein energy malnutrition, weight gain, in particular gain in lean mass, will benefit bone accrual during adolescence [28, 29].

Although not demonstrated in our study, it is also recognized that CS can have a negative effect on linear growth, even when given in low systemic doses [30]. Growth failure is a recognized risk factor for reduced BMD and, furthermore, DXA measurements are, coincidentally, size-dependent [31]. In this study the observed reduction in BMD in CD patients on CS treatment is not simply a case of reduced bone size, because stature and BMAD did not differ between groups. Therefore it is likely to be a true reduction in bone mass and hence probably bone strength. This is supported by other studies that confirm osteopenia and osteoporosis, with fractures, among CD patients throughout the life span [32–34]. In addition, pediatric Crohn's patients develop malnutrition over a long period of time [35]. If the increased nutritional requirements are not met, a decrease in height velocity, weight loss, and increased risk of fractures from underlying osteoporosis is inevitable [36, 37]. Although we did not measure bone metabolism in this study, CS treatments are known to cause an early onset, extremely rapid, and severe loss of bone mass, because of increased bone resorption, that can lead to fractures [38]. Therefore, the risk of suffering a fracture is greater for those requiring corticosteroids for management [39].

Although our study does provide important support for considering EEN as primary therapy in pediatric CD, a number of limitations were inherent in the retrospective design. In particular it would have been ideal if all patients had DXA scans completed at two time points. In this regard selection bias could not be excluded. However, to limit further potential bias from missing data, a data-extraction procedure was developed and implemented. In addition, access to all IBD patients in the database ensured the review was as inclusive as possible.

Another limitation of our study conclusions is the greater use of concomitant immune modulator therapy with azathioprine in the EEN group, given the relevance of disease activity to the nutritional and metabolic complications of CD [40]. Although the results were not statistically significant, a trend towards greater disease activity was observed for EEN patients. These patients presented with higher PCDAI score, elevated ESR and CRP, increased amount of perianal involvement, greater duration of disease before diagnosis and/or initiation of disease-specific treatment, greater likelihood of being on azathioprine, and lower baseline height and weight *z*-scores. Of note, azathioprine therapy has not been shown to specifically reduce the risks of osteoporosis or to affect BMD directly [41]. The difference between treatment was likely to have been because of the treating physicians' bias toward use of EEN among those with small bowel CD and perianal CD. Fistulizing CD is less likely to develop complications from EEN, because worse outcomes, for example abscess formation and sepsis, have been reported for patients with abdominal mass treated with CS [42, 43]. In addition, treatment of large-bowel CD with EEN has been perceived to be less effective.

Finally in this single institution we were limited in the number of subjects who had EEN and follow up DXA scans. If the difference in the change in spine *z*-score of height and chronological age adjusted BMD is true between EEN and CS in our study (i.e. a change *z*-score of 0.28), then a sample size of approximately 70 in each group would be required to show statistical significance over one year. Despite this limitation our results are convincing as to the potential risk to bone mass inherent over time in adolescent IBD patients and should encourage a larger multicenter study to examine this issue in more detail.

In summary, despite similar efficacy to CS for inducing remission, EEN may lead to bone density improvement. On the basis of the objectives of treatment of pediatric CD, exclusive EEN is an optimum therapeutic choice as first-line therapy. We recognize there are limitations to the use of EEN from the perspective of both the patient and the health-care team that must be addressed to optimize the utility of this therapy. This is evident from the lower numbers of patients given EEN at our own institution, despite our preference for this treatment to be offered as first-line therapy. In addition, several limiting patient acceptability factors have been inadequately studied, including: formula palatability, tolerance for nasogastric feeding, financing, and the burden of not having additional food for six weeks. Furthermore, there are factors inherent to individual treating teams which might explain, in part, geographic variances in the use of EEN in the literature.

Not the least of these includes the need for additional nursing, dietetic support, and funding resources. We believe this study facilitates understanding of the unique role of EEN in pediatric CD by highlighting important benefits to bone health and promoting further investigation of the limiting factors.

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Conflict of interest None.

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