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ORIGINAL ARTICLE

Oral exclusive enteral nutrition induces mucosal and transmural healing in patients with Crohn's disease

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Abstract

Background and aims: Mucosal healing is regarded as a clinical endpoint of Crohn's disease (CD), and transmural healing is correlated to the concept of deep remission. Current therapies to induce mucosal and transmural healing in CD are not satisfactory. Exclusive enteral nutrition (EEN) is underestimated therapy and its value has not been fully evaluated. Our aim was to investigate the efficacy of oral EEN for inducing mucosal and transmural healing in CD patients.
Methods: This was a prospective, single-center, open-label study including diagnosed CD children and adults conducted between January 2015 and December 2016 in the Sixth Affiliated Hospital of Sun Yat-sen University. All patients were treated with oral EEN and underwent paired assessment at baseline and completion using C-reaction protein, erythrocyte sedimentation rate, platelets, hemoglobin, body mass index, CD activity index, simple endoscopic score for CD and bowel sonography. Azathioprine was combined to prevent relapse.
Results: In this prospective observational study, 29 CD patients with an average age of 28.9 years were identified. After oral EEN treatment, 23 patients (79%) achieved complete mucosal healing, and the mean time to reach mucosal healing was 123 days (ranged from 50 to 212 days). Although only five patients (17%) achieved transmural healing, a significant reduction was observed in bowel-wall thickness (9.41 ± 3.06 vs 4.97 ± 1.76 mm, $P < 0.001$) and a significant improvement was observed in complications (including fistulas, abscess, ascites, stricture) assessed by bowel sonography (all $P < 0.05$).
Conclusions: Oral EEN therapy is highly effective for inducing mucosal healing in CD patients. Both CD patients at active stage and those at clinical remission show excellent clinical response to oral EEN.

Key words: Crohn's disease; oral exclusive enteral nutrition; mucosal healing; transmural healing

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Introduction

Crohn''s disease (CD) is an incurable inflammatory bowel disease (IBD) characterized by chronic destructive inflammation of the gastrointestinal tract and progressive transmural bowel damage leading to complications, such as strictures, fistulae and abscesses, which frequently require surgical treatment. It is characterized by periods of remission and relapse [1, 2]. With the development of economy and the changes in living habits, the morbidity of CD has increased rapidly in recent years [3]. Until now, there has been no known cure. The traditional goals in the management of CD are to induce clinical remission and maintain long-term remission [4, 5]. However, the traditional goals of CD therapy have not clearly changed its natural history. Researchers have begun to focus on mucosal and transmural healing in CD more frequently. Mucosal healing (MH), which is defined as the complete absence of blood, friability, erosion and ulcerative lesions in all segments of the gut [6, 7], is regarded as a clinical endpoint [8]. Emerging evidence suggests that achieving and maintaining MH may alter the natural history of CD, as it has proved to be associated with more sustained clinical remission, reduced rates of hospitalization and surgical resection, improved quality of life and an increase in work productivity [9–11]. The most profound impact on MH in CD has been shown with biological drugs. Several studies had demonstrated that the MH rate of infliximab ranged from 22 to 60% [12–15]. Steroids do not effectively induce MH [16, 17]. Furthermore, CD is a transmural disease. Intestinal wall thickening with fibrosis, penetrating complications, mesenteric hypertrophy with fat accumulation and hypervascularization are characteristic features of CD. Transmural healing (TH) of CD is a still unexplored and interesting outcome correlated to the concept of deep remission. A complete TH treated with anti-tumor necrosis factor (TNF) agents was found in only 14% patients of complete MH [18]. Another study found that, when treated with anti-TNFs, TH can be achieved in about 25% of CD patients, as shown by bowel sonography and magnetic resonance enterography (MRE) [19].

The value of exclusive enteral nutrition (EEN) therapy in CD has attracted more and more attention in recent years. EEN provides a liquid provision with 100% nutritional requirements for a person from a liquid-nutrition formula either taken orally or via a feeding tube. It is recommended as a first-line therapy instead of corticosteroid therapy to treat active CD in children [20, 21]. Grover *et al.* [22] found that EEN induced early clinical MH and TH in pediatric CD. Treatment with EEN is more effective in achieving clinical remission in children with IBD than in adults [23, 24]. A meta-analysis of clinical trials indicated that the efficacy of EEN might be comparable to that of corticosteroid therapy [25]. Poor compliance is the major cause that leads to EEN treatment failures [26]. At present, enteral nutrition is often delivered via a nasogastric or nasointestinal tube, which causes pharyngeal discomfort, regurgitation and unaesthetic effects, and influences patients'' daily lives. Oral EEN can solve these problems, but its value has not been fully evaluated. EEN is usually provided for 6–8 weeks and then the usual diet is gradually reintroduced [27]. Short-term therapy induces clinical remission rather than MH, which may be blamed for the relapse of CD.

Cross-sectional imaging modalities, such as computed tomography enterography (CTE), MRE and bowel sonography, are essential to monitor the progress of structural bowel damage in CD, providing information on both luminal and transmural disease, and extramural complications [28]. These tools have a high and comparable diagnostic accuracy in CD [29, 30], although the choice largely depends on the local availability and expertise. Bowel sonography is a non-invasive, non-radiation and broadly available method to assess disease activity in IBD patients [31]. Several reports have demonstrated the value of this method in the disease management of CD because of its accurate localization and characterization of inflammatory lesions and parietal abnormalities [32]. Bowel sonography could be used as the first cross-sectional procedure to detect TH. In a multicenter prospective study, Castiglione *et al.* [19] found that ultrasonographic examination could be used to monitor disease activity in patients with active CD and bowel sonography seemed to be an ideal follow-up method to evaluate early transmural changes in response to medical treatment.

The aim of this prospective observational study was to explore whether oral EEN could induce good MH and TH, assessing by colonoscopy and bowel sonography, respectively.

Patients and methods

Patients and study design

This was a prospective, single-center, open-label study including diagnosed children and adults with CD conducted between January 2015 and December 2016 in the Sixth Affiliated Hospital of Sun Yat-sen University. Institutional ethics approval was granted. All patients were fully informed and agreed to receive the oral EEN therapy and written consent was obtained from all subjects.

The diagnosis of CD was performed by the combination of the patient''s history, physical and laboratory examinations, bowel sonography, CTE, esophagogastroduodenoscopy and colonoscopy with histology, and imaging of the small bowel. Indeterminate colitis, infections, intestinal tuberculosis, Behcet's disease and other recognized causes of intestinal inflammation were excluded by appropriate investigations [33]. After confirming the diagnosis of CD, clinical disease type was classified according to the Montreal classification of IBD [34]. All patients clearly diagnosed of CD were included in the trial. Patients who previously used corticosteroids, immunosuppressive drugs or biologics were also included and stopped the previous therapy before undergoing oral EEN.

All enrolled patients underwent a comprehensive assessment including routine blood tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), conventional stool and occult blood, and body mass index (BMI). These parameters were collected before and after EEN regularly. CTE, bowel sonography and colonoscopy were all taken at baseline to confirm transmural and endoscopic inflammatory. Clinical disease activity was assessed at diagnosis by using the Crohn''s disease activity index (CDAI) scores and divided into two groups (a CDAI score <150 was defined as clinical remission and ≥ 150 was active stage). If clinical parameters became normal, colonoscopy and bowel sonography were taken to assess MH and TH.

Oral EEN

We used the commercial products Ensure® (Total Protein Enteral Nutritional Powder, Abbott, America: 450 kcal per 100 grams containing 60.7 grams of glucose, 15.9 grams of protein) and Peptisorb® (Short Peptide Enteral Nutrition Powder, Milupa GmbH, German: 400 kcal per 100 grams containing 71.5 grams of glucose, 14.7 grams of protein). Peptisorb is short peptide enteral nutrition, which is recommended to mix with total protein enteral nutritional powder Ensure at a ratio

of 3–4:1. To induce remission, enteral nutrition was given at 35–40 kcal/kg according to patients'' conditions. During this period, oral enteral nutrition was given as the sole nutritional source. The total daily calorie goal was achieved gradually by the first 3–4 days. After colonoscopy showed MH, EEN was turned into partial enteral nutrition (PEN) (400–800 kcal/day), while a normal diet was reintroduced gradually according to order of carbohydrate, fruit and vegetables, protein and fat. During the remission phase, no dietary restrictions were recommended. At the beginning, azathioprine was added to prevent relapse. After MH, azathioprine maintained the original amount.

Patients first tried oral EEN for 3–7 days. Patients who were unable to consume an adequate volume of the formula, or took other food during the EEN period, were defined as having non-adherence to enteral nutrition and excluded. All patients visited the hospital at regular follow-up periods to check their adherence and they underwent regular assessment.

Colonoscopy and MH

Colonoscopy was performed by the same operator, who was blinded with respect to the outcome of the other diagnostic procedures, using a conventional colonoscope (Olympus Exera CV-260) after standard bowel cleansing using a 2 –L solution of polyethylene glycol (PEG). Endoscopic diagnosis of CD was made in accordance with current European Crohn''s and Colitis Organization (ECCO) guidelines [35]. All patients received colonoscopy at baseline and after clinical parameters became normal, and some of them had this repeated more than twice until MH. The endoscopic activity of CD and the occurrence of MH after EEN treatment were assessed using the simple endoscopic score for Crohn's disease (SES-CD) [36]. MH was defined in the absence of ulcerations in bowel segments (SES-CD $\leq$1) (2–10 is mild active stage, 11–19 is moderate active stage and >19 is severe active stage) [37].

Bowel sonography and TH

At each study visit, all large bowel segments and small intestine were examined by bowel sonography. Increased wall thickness (>3 mm) was measured in transverse and longitudinal sections. Loss of bowel-wall stratification was documented, as well as other complications (prestenotic dilatations, bowel strictures, fistulae, mesenteric fibrofatty proliferation and/or masses, abscesses, mesenteric lymphadenopathy, ascites and Limberg score). Bowel sonography examinations were performed using the same equipment (LOGIQ E9; GE Healthcare, Milwaukee, WI, USA) with a high-frequency linear probe (9 L, frequency range 6.0–9.0 MHz). All examinations were performed by the same radiologist, with rich experience in bowel sonography. Patients fasted overnight before the examination. Each patient was required to drink 2000 mL of a warm water solution with mannitol (containing approximately 250 mL of mannitol) in 45 minutes (consuming 500 mL every 15 minutes). There was no accepted standard for defining TH. We defined TH based on literature [38, 39] and our experience [40]: TH during bowel sonography as a bowel-wall thickness $\leq$3 mm and normalization of the other bowel sonography parameters after EEN.

Statistical analysis

The data were analysed using SPSS 19.0. Qualitative variables were expressed as numbers and percentages, whilst the continuous variables were expressed as medians ± standard deviation. T text, analysis of variance and Wilcoxon rank sum test were used to assess the impact of clinical disease and treatment variables on MH and TH. The significance level was set at $P < 0.05$.

Results

Characteristics of the patients

A total of 30 patients participated in the oral EEN induction course and 29 completed it (Figure 1). Some patients had diarrhea or abdominal distension in the beginning and these symptoms began to ease up after 3–4 days as they were advised to drink more slowly. No other adverse effects were reported.

Table 1 shows the baseline characteristics of these 29 patients. The majority (22 individuals) were males. The average age was 28.9 ± 10.1 years. Of these 29 patients, 11 were ileal type, 1 colonic and 17 ileo-colonic. Four suffered from upper gastrointestinal ulcers, seven had perianal disease, seven had intestinal penetrations and five had intestinal stenosis. Assessed by the CDAI scores, 18 patients were in the active stage and 11 were in clinical remission. Assessed by the SES-CD scores, 6 patients were in the severe endoscopic active stage, 13 were moderate and 10 were mild.

All patients received assessment of clinical, biochemical, endoscopic at baseline and after EEN regularly; and each patient had assays multiple times that included routine blood tests, CRP, ESR, conventional stool and occult blood, and BMI at different time points. All patients received paired endoscopy and bowel sonography, and some of them had bowel sonography multiple times until TH.

Ability of EEN to induce MH

Significant improvements were observed in SES-CD, CRP, ESR, platelets and hemoglobin (all $P < 0.05$), when compared with data at baseline and after treatment (Table 2). CRP became normal first. However, BMI was showed no significant difference ($P = 0.196$) and did not become normal even in patients with complete MH. After completion of EEN, 23 patients (79%) achieved complete MH (Figure 2). Blood, friability, erosion and ulcerative lesions were completely absent in all segments of the gut (Figure 3). The MH rate was 91% for the clinical remission group, while 72% for the active group. However, the difference was not statistically significant ($P = 0.362$).

The mean time to reach MH was 123 days (ranging from 50 to 212 days). There was no statistical significance when data were grouped by course of disease, disease location, disease behavior, clinical disease severity, endoscopic disease severity and whether patients had received therapies before EEN (Figure 4).

Seven patients had intestinal fistula and peritoneal abscess. After treatment, bowel sonography showed the abscess was absorbed gradually and finally the fistula healed, while colonoscopy confirmed MH. As for five patients with stenosis, no obstructive symptoms occurred after MH. Among seven patients with perianal fistula, six showed a turn for the better, but one needed further treatment due to the unclosed fistula.

Ability of EEN to induce TH

Transmural disease activity was assessed by bowel sonography. We compared the bowel sonography of baseline and after treatment for 29 individuals. Figure 5 showed a series of bowel sonography images of a patient. At baseline, there were extensive

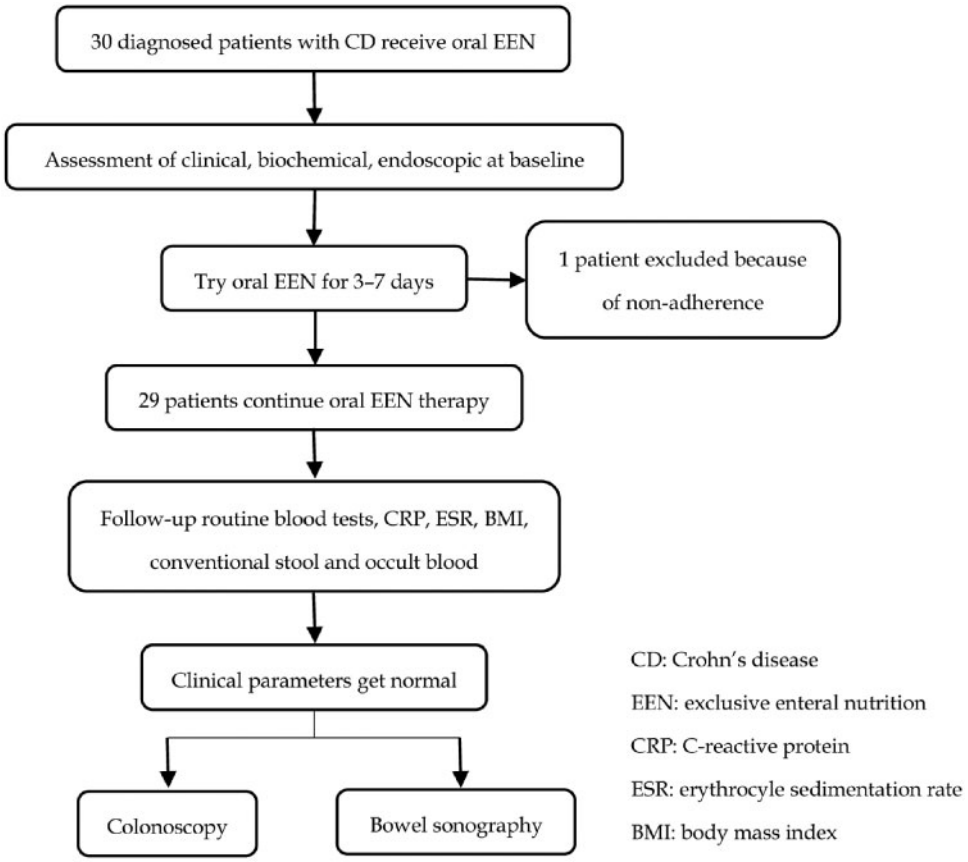

Figure 1. Flow chart of oral exclusive enteral nutrition (EEN) treatment and assessment for Crohn's disease (CD).

bowel-wall incrassation and fistulas. Abscesses and ascites showed as a hypoecho band and liquid dark area, respectively. After oral EEN treatment for 20 days, abscesses and ascites were absent. Significant reduction was observed in bowel-wall thickness and fistulas closed after another 20-day treatment. Three months later, bowel sonography showed the maximum bowel-wall thickness was 3 mm, and no fistulas, abscess and ascites relapsed. After oral EEN treatment, significant reduction was observed in bowel-wall thickness (9.41 ± 3.06 vs 4.97 ± 1.76 mm, $P < 0.001$). All the positive rates of bowel sonography parameters declined and fistulas, abscesses and ascites were absent (Table 3). However, there were still 13 patients (44.8%) who had mesenteric fibrofatty proliferation and only 5 patients (17%) reached TH. Moreover, some bowel sonography parameters still remained abnormal in patients who had confirmed MH.

Discussion

The choice of oral administration is made to avoid the constraints and psychological impact linked to the wearing of a feeding tube. This is particularly important, as compliance is the main factor that impairs the clinical response to EEN therapy [26]. A study to analyse the efficiency of EEN in inducing remission in children with CD found that there was no difference whether the EEN was administered orally or by continuous enteral feeding, apart from weight gain, which was greater with nasogastric continuous feeding [41]. In current study, we performed the long-term EEN therapy until MH, which is different from the previous studies with a short-term theray of 6–8 weeks. EEN presents excellent clinical response, biochemical remission and MH. The complete MH rate was 79%, which is superior to infliximab (22–60%) and short-term EEN (33–58%) [22, 42]. The high MH rate could be related to the duration of oral EEN.

CD patients with endoscopic inflammatory, both active stage and in clinical remission, had an excellent clinical response to EEN. The time to reach MH had no relationship with the baseline clinical disease severity ($P = 0.213$). Assessed by the SES-CD scores, endoscopic severity was not in accordance with clinical severity. Even patients who showed clinical remission could have severe ulcers and complications confirmed by colonoscopy and bowel sonography.

There is limited evidence suggesting that EEN therapy is more effective in newly diagnosed CD patients compared to patients with long-standing CD. The difference was not statistically significant in our study ($P = 0.358$). A study that investigated the efficacy of EEN in pediatric CD supported that patients with shorter time to diagnosis from the onset of first symptoms had good early endoscopic response [22]. In an Australian study in CD children, induction treatment with EEN was successful in 80% of newly diagnosed and 58% of long-standing CD patients [43]. Another pediatric study confirmed these results, showing a higher relapse rate after the second course of EEN (70%) when compared to the first one (67%) during a 1-year period of follow-up [44]. According to these findings, early EEN therapy is recommended.

Significant improvements were observed in CRP, ESR, platelets and hemoglobin (all $P < 0.05$). CRP became normal first. The mean time was 22 days, which was less than half the time for

ESR to become normal (59 days), since CRP correlated with clinical activity while ESR correlated well with endoscopic and histologic colitis [45]. Growing evidence has shown that increased platelets counts seemed to play a crucial role in determining the hypercoagulable state observed in CD [46]. With platelets decreased to normal, the hypercoagulable state was ameliorated in patients with CD. Anemia is a frequent extraenteric complication of CD. The main types are iron-deficiency anemia and anemia accompanying chronic diseases [47]. The improvement of anemia in CD is a slow process. Every patient put on weight under oral EEN therapy, but BMI was not significantly different when comparing data at baseline with data after treatment ($P = 0.196$). Our findings indicate that EEN had a direct anti-inflammatory action, as evidenced by a decrease in inflammatory cytokines and MH even before the nutritional benefits became apparent. The direct anti-inflammatory effect of EEN has also been demonstrated through the use of *in vitro* models [48].

There are few available data on the efficiency of EEN for the complications of CD. A systematic review suggested EEN can be beneficial in children with peri-anal disease and can be helpful in the management of enterovesical fistula [29]. In our study, the complications had significant changes, especially for intestinal fistula and peritoneal abscess.

Until now, only a few studies have investigated the effect of therapies on the transmural inflammation of CD. Mesenteric fat could result in cytokine production and induce intestinal inflammation, which is associated with active CD [49]. The frequency of fibrofatty proliferation is an indirect measure of mesenteric fat. Studies have shown that mesenteric fibrofatty proliferation is increased in patients with CD on cross-sectional imaging [50, 51]. In our study, nearly half of the patients (44.8%) with pair bowel sonography still showed mesenteric fibrofatty proliferation after treatment. This indicated that patients who were confirmed MH might still remain with transmural inflammation. However, mesenteric fibrofatty proliferation as a single distinguishing parameter is associated with a low diagnostic accuracy, as it is based on subjective assessment. A recent study by Ordas *et al.* [52] revealed that the achievement of endoscopic MH markedly correlated with resolution of the transmural inflammatory sonography changes, including bowel-wall thickness, hypervascularity and extramural alterations, such as the enlargement of lymph nodes and mesenteric fibrofatty proliferation. Interestingly, another study evaluated the efficacy of biologic therapy in inducing TH and found that 14% of 32 patients achieved TH, with a MH rate of 72% [18], which was in accordance with our findings. In our study, MH was not always associated with TH; more than half of the patients with complete MH still showed evidence of transmural inflammation, despite improvement in the US parameters. Our data suggest that a considerable number of patients still exhibit bowel sonography activity. Even in patients with complete MH, active transmural disease can persist. The existence of increased bowel-wall thickness may be relevant to the proliferation of fibrous tissue. The search aimed at promoting TH is a growing challenge for clinicians caring for patients with CD. Future studies will be focused on the clinical use of tools evaluating transmural inflammation and how to achieve TH after complete MH.

In conclusion, long-term oral EEN therapy is highly effective for inducing complete MH in CD. All stages of CD patients show excellent clinical response to EEN. A complete TH is achieved only in a small percentage of patients with complete MH.

Table 1. Baseline characteristics of patients with Crohn's disease

Variables	$N = 29$
Age, years	28.90 ± 10.08
Sex (male/female)	22/7
Duration of symptoms before diagnosis	2 months to 20 years
Course of disease, *n* (%)	
<3 months	10 (34%)
3–12 months	7 (24%)
1–3 years	4 (14%)
>3 years	8 (28%)
Age at diagnosis, *n* (%)	
A1 (≤16 years)	3 (10%)
A2 (17–40 years)	22 (76%)
A3 (>40 years)	4 (14%)
Disease location, *n* (%)	
Terminal ileum (L1)	11 (38%)
Colon (L2)	1 (3%)
Ileocolon (L3)	17 (59%)
Disease modifier, *n* (%)	
Upper gastrointestinal (L4a + L4b)	4 (14%)
Perianal	7 (24%)
Disease behavior, *n* (%)	
Non-stricturing, non-penetrating (B1)	17 (59%)
Stricturing (B2)	5 (17%)
Penetrating (B3)	7 (24%)
Clinical disease severity, *n* (%)	
Remission (CDAI <150)	11 (38%)
Active (CDAI ≥150)	18 (62%)
Endoscopic disease severity, *n* (%)	
Mild (SES-CD 2–10)	10 (34%)
Moderate (SES-CD 11–19)	13 (45%)
Severe (SES-CD >19)	6 (21%)
Medication history, *n* (%)	16 (55%)
Intestinal surgery history, *n* (%)	3 (10%)

CDAI, Crohn's disease activity index; SES-CD, simple endoscopic score for Crohn's disease.

Table 2. Clinical parameters and endoscopic disease activity of 29 patients with Crohn's disease before and after oral exclusive enteral nutrition (EEN)

Parameters	Before oral EEN	After oral EEN	P-value	Mean days to become normal
Mean SES-CD	14.93 ± 8.64	0.93 ± 2.36	<0.001	122.55 ± 45.39
Mean CRP, mg/L	23.93 ± 21.23	3.32 ± 2.92	0.003	22.43 ± 23.96
Mean ESR, mm/h	43.70 ± 28.38	16.00 ± 7.06	<0.001	59.05 ± 49.13
Mean platelet, $\times 10^9$/L	412.54 ± 80.46	279.39 ± 50.17	<0.001	76.46 ± 58.48
Mean hemoglobin, g/L	105.14 ± 15.53	126.61 ± 4.64	0.018	99.57 ± 64.56
Mean BMI, kg/m^2	16.95 ± 2.43	17.65 ± 2.14	0.196	–

SES-CD, Simple Endoscopic Score for Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BMI, body mass index.

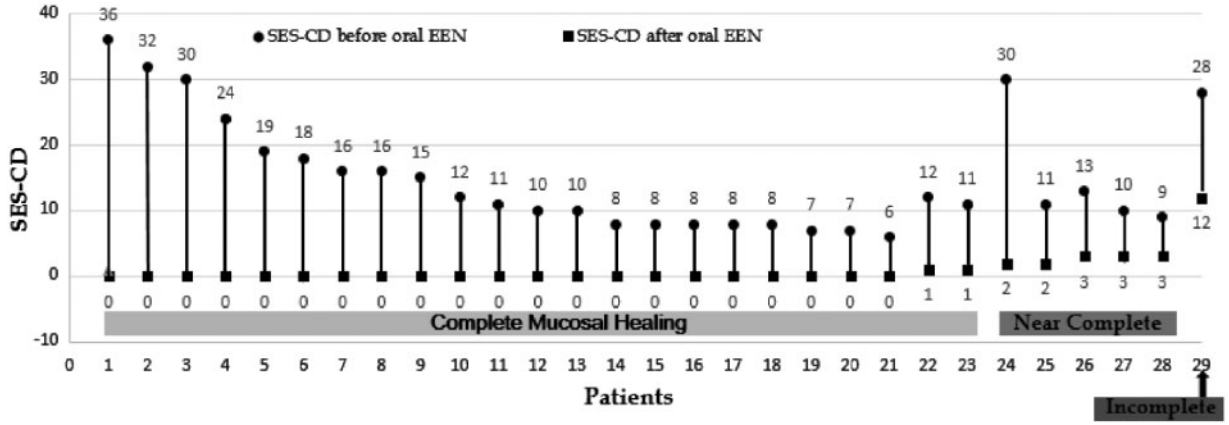

Figure 2. The paired simple endoscopic score (SES-CD) for Crohn's disease for each patient before and after oral exclusive enteral nutrition (EEN).

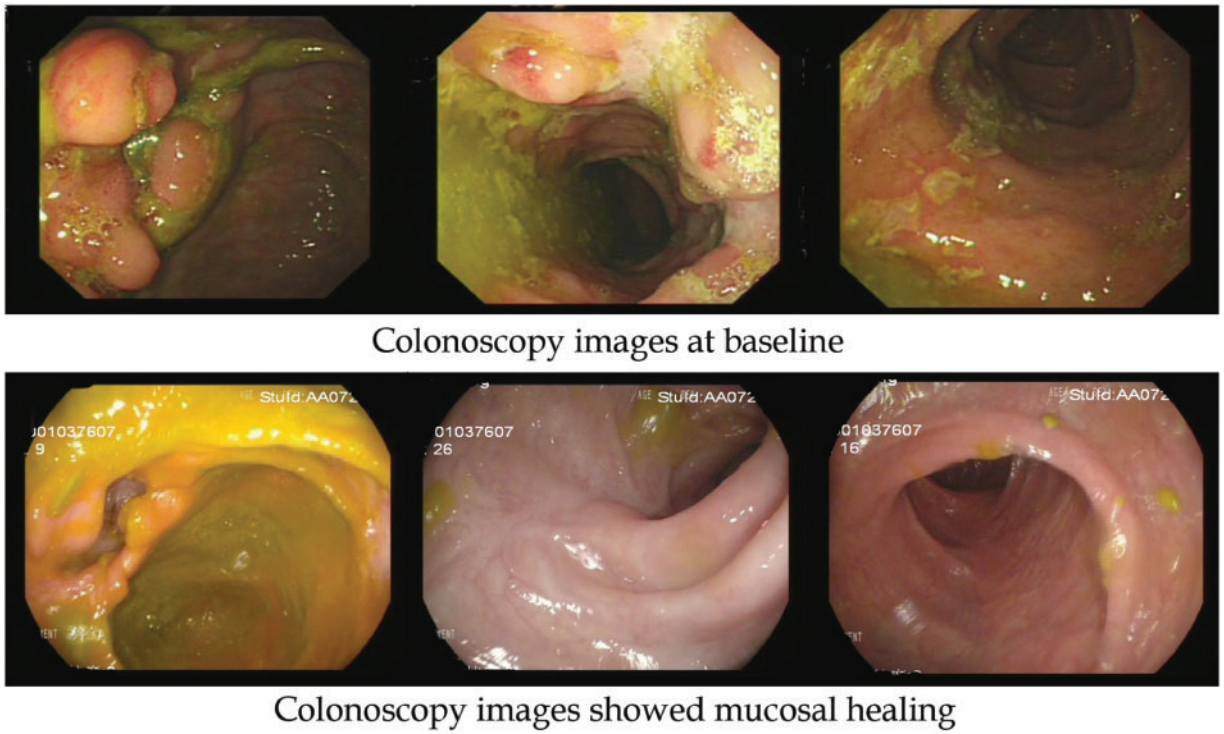

Figure 3. Paired colonoscopy images of a patient at baseline and at 20 weeks after oral exclusive enteral nutrition (EEN).

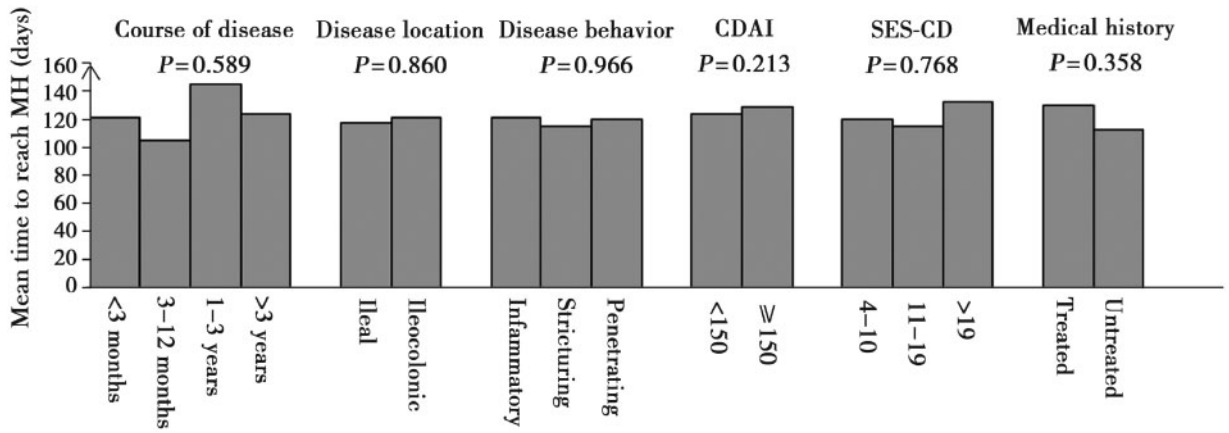

Figure 4. The mean time to reach mucosal healing (MH) for groups with different characteristics. CDAI, Crohn's disease activity index; SES-CD, simple endoscopic score for Crohn's disease.

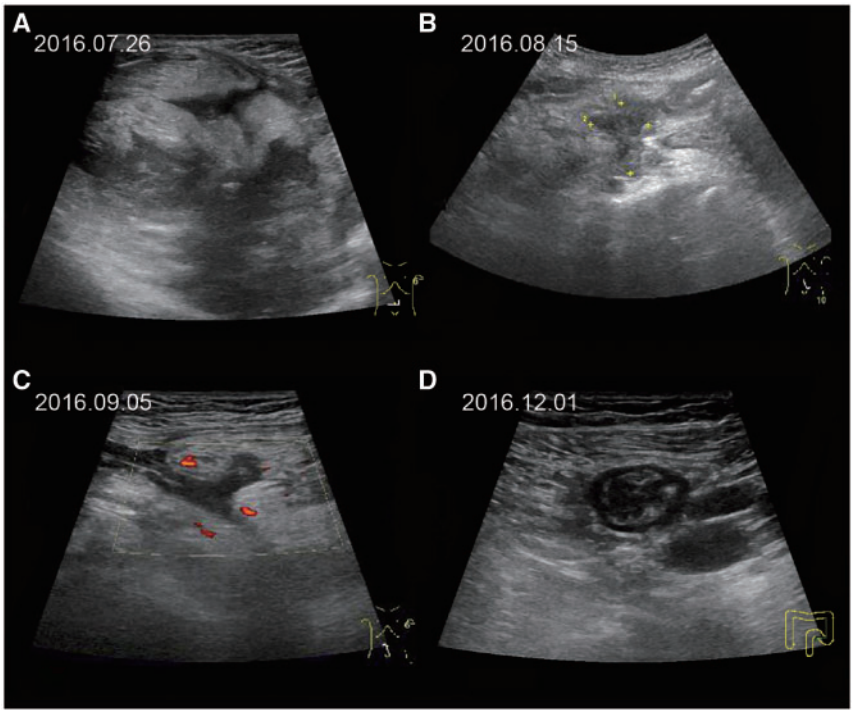

Figure 5. A series of bowel sonography images of a patient. **(A)** At baseline, there was extensive bowel-wall incrassation and fistulas; abscesses and ascites are shown as a hypoecho band and liquid dark area, respectively. **(B)** After taking oral exclusive enteral nutrition for 20 days, abscesses and ascites were absent. **(C)** Significant reduction was observed in bowel-wall thickness and fistulas closed after another 20-day treatment. **(D)** Three months later, bowel sonography showed the maximal bowel-wall thickness was 3 mm, and no fistulas, abscesses and ascites relapsed.

Table 3. The positive rate of bowel sonography parameters at baseline and after treatment ($N = 29$)

Bowel sonography parameters	Positive rate at baseline	Positive rate after treatment	*P*-value
Loss of bowel-wall stratification	76%	7%	<0.001
Mesenteric fibrofatty proliferation	97%	45%	<0.001
Lymph nodes	86%	21%	<0.001
Prestenotic dilation	38%	3%	0.001
Fistulas	21%	0%	0.031
Abscess	21%	0%	0.031
Ascites	31%	0%	0.004
Stricture	31%	3%	0.005
Limberg score[a]	90%	17%	<0.001

[a]Limberg score 3/4 being defined as positive.

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Conflict of interest

The authors declared no conflicts of interest relevant to this article.

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