The Crohn's disease exclusion diet for induction and maintenance of remission in adults with mild-to-moderate Crohn's disease (CDED-AD): an open-label, pilot, randomised trial

Henit Yanai, Arie Levine*, Ayal Hirsch, Rotem Sigall Boneh, Uri Kopylov, Hagar Banai Eran, Nathaniel A Cohen, Yulia Ron, Idan Goren, Haim Leibovitzh, Joram Wardi, Eran Zittan, Tomer Ziv-Baran, Lee Abramas, Naomi Fliss-Isakov, Barbara Raykhel, Tamar Pfeffer Gik, Iris Dotan†, Nitsan Maharshak†*

Summary

Background The Crohn's disease exclusion diet (CDED) with partial enteral nutrition is effective for induction of remission in children with mild-to-moderate Crohn's disease. We aimed to assess the CDED in adults with Crohn's disease.

Methods We did an open-label, pilot randomised trial at three medical centres in Israel. Eligible patients were biologic naive adults aged 18–55 years with mild-to-moderate Crohn's disease (defined by a Harvey–Bradshaw Index score of 5–14 points), a maximal disease duration of 5 years, with active disease on colonoscopy, or imaging with elevated inflammatory markers (C-reactive protein >5 mg/L or faecal calprotectin concentration >200 µ/g). Patients were randomly assigned (1:1) to CDED plus partial enteral nutrition or CDED alone for 24 weeks. Randomisation was via block randomisation (block sizes of six) using sealed, numbered, and opaque envelopes. Patients and investigators were aware of which group patients were assigned to due to the nature of the different interventions. The primary endpoint was clinical remission, defined as a Harvey–Bradshaw Index score of less than 5 at week 6. The primary endpoint was assessed in the intention-to-treat (ITT) population, which included all patients who used the dietary therapy for at least 48 h. We report results of the final analysis. This trial is registered with ClinicalTrials.gov, NCT02231814.

Findings Between Jan 12, 2017, and May 11, 2020, 91 patients were screened, of whom 44 were randomly assigned to the CDED plus partial enteral nutrition group (n=20) or CDED alone group (n=24). 19 patients in the CDED plus partial enteral nutrition group and 21 patients in the CDED alone group received the allocated intervention for at least 48 h and thus were included in the ITT analysis. At week 6, 13 (68%) of 19 patients in the CDED plus partial enteral nutrition group and 12 (57%) of 21 patients in the CDED group had achieved clinical remission (p=0·4618). Among the 25 patients in remission at week 6, 20 (80%) were in sustained remission at week 24 (12 patients in the CDED plus partial enteral nutrition group and eight in the CDED alone group). 14 (35%) of 40 patients were in endoscopic remission at week 24 (eight patients in the CDED plus partial enteral nutrition group and six in the CDED alone group). No serious adverse events or treatment-related adverse events were reported in either group.

Interpretation CDED with or without partial enteral nutrition was effective for induction and maintenance of remission in adults with mild-to-moderate biologic naive Crohn's disease and might lead to endoscopic remission. These data suggest that CDED could be used for mild-to-moderate active Crohn's disease and should be assessed in a powered randomised controlled trial.

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*Joint first authors

†Joint senior authors

Division of Gastroenterology, Rabin Medical Center, Petah Tikva, Israel (H Yanai MD, H B Eran MD, I Goren MD, H Leibovitzh MD, B Raykhel BSc, T P Gik MSc, Prof I Dotan MD); **Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel** (H Yanai, Prof A Levine MD, A Hirsch MD, R S Boneh BSc, Prof U Kopylov MD, H B Eran, N A Cohen MD, Y Ron MD, I Goren, H Leibovitzh, J Wardi MD, T Ziv-Baran PhD, N Fliss-Isakov PhD, T P Gik, Prof I Dotan, Prof N Maharshak MD); **Paediatric Gastroenterology Unit** (Prof A Levine), **Israel PIBD Research Center** (R S Boneh, L Abramas BSc) **and Gastroenterology Institute** (J Wardi), **Wolfson Medical Center, Holon, Israel; Department of Gastroenterology and Hepatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel** (A Hirsch, N A Cohen, Y Ron, N Fliss-Isakov, Prof N Maharshak); **Department of Gastroenterology, Sheba Medical Center, Ramat-Gan, Israel** (Prof U Kopylov); **The Abraham and Sonia Rochlin IBD Unit, Department of Gastroenterology, Emek Medical Center, Afula, Israel** (E Zittan MD); **Rappaport Faculty of Medicine Technion-Israel Institute of Technology, Haifa, Israel**

Introduction

The presumed pathogenesis of Crohn's disease involves a combination of environmental and genetic factors that lead to gastrointestinal inflammation and complications.[1] The current goal of medical therapy is to reduce inflammation and induce mucosal healing, which can be achieved by modifying immune pathways; however, many of the drugs used to manage Crohn's disease involve immune suppression and have additional side-effects.[2] An unmet need exists for safer therapies, particularly in patients with milder disease activity at lower risk for complicated disease, or those who have a condition precluding immune suppression.[3–5] Dietary factors are among the strongest candidates for environmental factors that might drive inflammation.[6–8] The effect of dietary exposure as an environmental factor is reflected in the high remission rate observed with exclusive enteral nutrition in children with Crohn's disease.[9] For adults

Correspondence to:
Dr Henit Yanai, Division of Gastroenterology, Rabin Medical Center, Petah Tikva 49100, Israel
henityanai@gmail.com

Research in context

Evidence before this study

The current goals of medical therapy for Crohn's disease include induction and maintenance of remission, a decrease in inflammation, and mucosal healing. At present, an effective therapy for mild disease that meets these goals while avoiding immune suppression is not available. To the best of our knowledge, the only dietary therapy that has been found to induce remission with a decrease in inflammation and mucosal healing was exclusive enteral nutrition for 6–8 weeks, used primarily in paediatric Crohn's disease at disease onset. This effect (remission and a decrease in inflammation) is not sustained once food is reintroduced into the diet, and no maintenance option is available. Few trials have been done investigating sustainable whole food diets for the treatment of Crohn's disease that have evaluated inflammation and mucosal healing. A randomised controlled trial comparing the Mediterranean diet with the specific carbohydrate diet indicated that both were effective for clinical remission but ineffective in reducing C-reactive protein and calprotectin concentrations, although mucosal healing was not assessed. One study randomly assigned patients with Crohn's disease in remission to a high red meat or low red meat intervention and found no effect on time to relapse of the disease.

The Crohn's disease exclusion diet (CDED), a whole food diet specifically designed for patients with Crohn's disease, coupled with partial enteral nutrition was found to induce remission in 80% of children in a randomised controlled trial, which was not significantly different from the 75% remission rate observed in children receiving exclusive enteral nutrition for 6 weeks. More children given CDED maintained remission and decline in inflammation at week 12 compared with those given exclusive enteral nutrition followed by partial enteral nutrition with reintroduction of food, and the group given exclusive enteral nutrition had a rebound with elevation of calprotectin and recurrence of symptoms on partial enteral nutrition. However, there is no evidence from any prospective trials that dietary monotherapy can be effective for induction and maintenance of remission or mucosal healing documented by colonoscopy. At present, it also remains unclear whether partial enteral nutrition is required for successful outcomes with CDED.

Added value of this study

To the best of our knowledge, this is the first prospective study to investigate dietary monotherapy for induction and maintenance of remission in patients with mild-to-moderate active Crohn's disease for a 6-month period, and the only dietary monotherapy study to assess mucosal remission by colonoscopy using the simplified endoscopic activity score for Crohn's disease (SES-CD) at 24 weeks. At week 6, 25 (63%) of 40 patients had achieved clinical remission, and 20 (50%) were in sustained remission at week 24. A significant decline in C-reactive protein and calprotectin concentrations was observed at week 12. 14 (35%) patients in the intention-to-treat population were in endoscopic remission by colonoscopy at week 24, and a significant reduction in median SES-CD score was observed for patients with baseline and week 24 colonoscopies. The addition of partial enteral nutrition to CDED did not improve outcomes during the first 12 weeks, although the number of patients in the CDED plus partial enteral nutrition group who achieved sustained remission and gained weight at week 24 was numerically higher than that for patients in the CDED alone group, although the difference was not significant.

Implications of all the available evidence

Dietary monotherapy with the CDED, with and without partial enteral nutrition, can be used to induce and maintain remission in adults with primarily mild-to-moderate Crohn's disease. This pilot trial demonstrated the feasibility of using the CDED as an intervention for adults with Crohn's disease. Dietary therapy reduces inflammation and induces mucosal healing in this group of patients and might allow patients with mild disease to achieve therapeutic goals without requiring immune suppression. Additional powered studies are required to assess the effect of CDED on patients with more severe disease, to compare dietary therapy with medical therapy, and to further identify patients who might benefit from this dietary strategy.

with Crohn's disease, use of exclusive enteral nutrition or any dietary intervention for induction of remission or at relapse is uncommon and is not included in current guidelines,[10,11] and no evidence is available to suggest that any dietary monotherapy can maintain remission and mucosal healing beyond a short 6–8 week induction phase.

The Crohn's disease exclusion diet (CDED) is a novel dietary therapy specifically designed for patients with Crohn's disease that uses whole food with partial enteral nutrition to achieve remission and reduce inflammation. The diet can be loosely defined as a progressive high protein, low animal fat, low haem, low gluten, and low additive diet with exposure to fibre. The CDED contains mandatory sources of pectin and resistant starch from fruits and vegetables. Each phase of the diet allows access to a wider range of specified foods. Several studies in children using CDED with partial enteral nutrition have indicated that this approach might be as effective as exclusive enteral nutrition, but with better compliance, and that it might also reduce C-reactive protein and calprotectin concentrations, or lead to endoscopic remission.[7,12] At present, no prospective data are available for adults.

We aimed to assess the feasibility and effect of CDED on induction and maintenance of remission, compliance, and endoscopic remission in adults with Crohn's disease to investigate whether larger powered trials of this diet are warranted. We also aimed to assess whether use of partial enteral nutrition with CDED

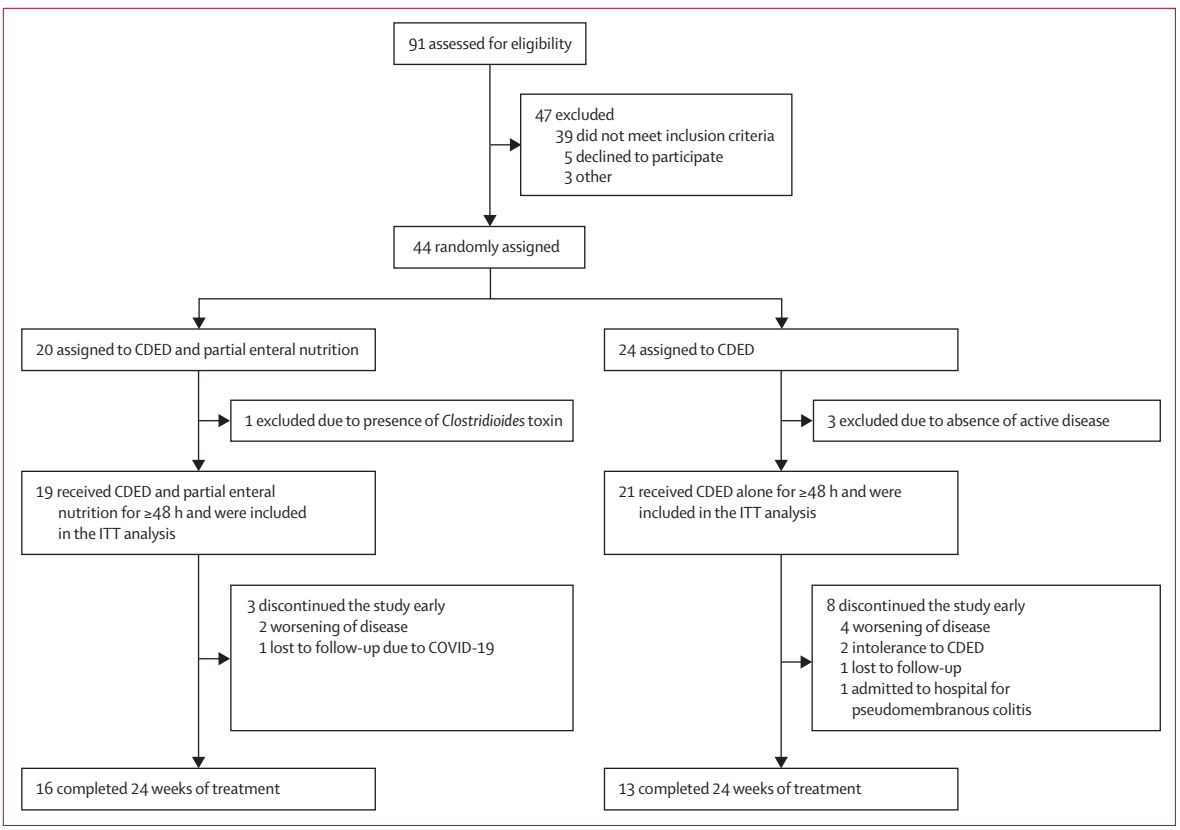

Figure 1: **Trial profile**
CDED=Crohn's disease exclusion diet. ITT=intention-to-treat.

improved outcomes in adults compared with CDED alone.

Methods

Study design and participants

We did an open-label, pilot randomised trial at three medical centres in Israel (Tel Aviv Medical Center, Tel Aviv; Rabin Medical Center, Petah Tikva; and Wolfson Medical Center, Holon). Eligible patients were aged 18–55 years with established ileal or limited ileocolonic Crohn's disease, maximal disease duration of 5 years, and active non-complicated mild-to-moderate disease (defined by a Harvey–Bradshaw Index score of 5–14 points). Active disease was defined by ileocolonoscopy or as an inflammatory finding on a dedicated small bowel imaging done within 8 weeks before enrolment and elevated inflammatory markers (either positive small bowel video capsule test, or CT enterography or magnetic resonance enterography with thickened enhancing bowel wall with either C-reactive protein >5 mg/L, or faecal calprotectin >200 µg/g).

Patients were excluded if they had stricturing or penetrating phenotype (B2/B3) active extra-intestinal or perianal disease, deep ulcers involving the distal colon, previous intestinal resection, use of an immunomodulator or dose change in the previous 8 weeks, current or past use of biologics, use of systemic steroids or more than 3 mg budesonide, positive stool cultures, stool tests for parasites or *Clostridioides difficile*, were pregnant or lactating, or if they were unwilling to consume protein from animal sources. Patients with upper gastrointestinal disease (L4) could be included if there was ileal involvement.

The study was done in accordance with International Council for Harmonisation guidelines and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent, and the study protocol was approved by an institutional review board at each study site.

Randomisation and masking

Patients were randomly assigned (1:1) to either CDED plus partial enteral nutrition (Modulen IBD; Nestle, Vevey, Switzerland) or CDED alone via block randomisation (block size six). Randomisation was done by the project manager using sealed, numbered, and opaque envelopes. Envelopes were allocated to each site and had to be used consecutively by the site study coordinator. Envelopes were opened only after informed consent was obtained and patients agreed to the entire process. Randomisation codes and allocation were not available to any of the enrolling physicians or

	CDED and partial enteral nutrition (n=19)	CDED alone (n=21)
Age, years	26 (23–38)	34 (25–39)
Sex		
Women	9 (47%)	13 (62%)
Men	10 (53%)	8 (38%)
Disease duration, months	3 (2–15)	3 (1–9)
Body-mass index, kg/m²	24 (21–31)	23 (21–27)
Weight, kg	74 (60–85)	70 (62–82)
Smoking	5 (26%)	4 (19%)
Montreal classification*		
L1	16 (84%)	19 (90%)
L3	3 (16%)	2 (10%)
L4	0	2 (10%)
Harvey–Bradshaw Index score	8 (6–8)	6 (6–8)
C-reactive protein, mg/L	9 (6–36)	9 (5–27)
Elevated C-reactive protein	16 (84%)	14 (67%)
Faecal calprotectin, µg/g†	585 (266–1027)‡	325 (224–630)‡
SES-CD	6 (5–10)§	5 (5–10)¶
Albumin, g/dL	4·2 (0·3)	4·2 (0·4)

Data are median (IQR), n (%), or mean (SD). CDED=Crohn's disease exclusion diet. SES-CD=simplified endoscopic activity score for Crohn's disease. *Some percentages for Montreal classification exceed 100, as patients could have more than one area of involvement. †Faecal calprotectin results at screening, data obtained from different laboratories. ‡Data missing for one patient. §Data missing for four patients. ¶Data missing for seven patients.

Table 1: **Baseline characteristics**

investigators. Patients and investigators were aware of which group patients were assigned to due to the nature of the different interventions.

Procedures

All patients were to receive the CDED for 24 weeks. The CDED is divided into three phases; composition for phase 1 and phase 2 of the diet have been previously published.[7] Briefly, phase 1 is a 6-week phase in which participants are only allowed chicken breast, eggs, and partial enteral nutrition as sources of animal protein, wheat and food additives are excluded, and certain fruits are mandatory with some allowed fruits and vegetables. Phase 2 from week 7–12 involves the gradual introduction of almost all fruits and vegetables, restricted amounts of beef and legumes, and one slice of wholegrain bread daily. The maintenance phase from week 13 does not have any mandatory foods and was divided into weekdays and weekends. During weekdays (ie, Monday to Friday) patients could consume any food from phase 2, all fruits and vegetables, one plain yoghurt daily, any fresh fish or seafood once weekly, lean beef such as sirloin steak 200 g once a week and chicken (all parts with the exception of the wings) any day, eggs any day, and specified amounts of legumes. On weekends, patients were allowed two home cooked main meals (no takeaway or restaurant food allowed) with any food (including fish, any meat or dairy, and wheat) and a glass of wine or beer and home cooked breakfasts.

Patients who were assigned to CDED plus partial enteral nutrition received a combination of CDED with 1000 kcal of partial enteral nutrition (1 kcal per mL) daily for the first 6 weeks (induction phase 1), and calcium supplements plus 600 kcal of partial enteral nutrition from week 7–12 (phase 2). At week 13 (maintenance phase or phase 3), partial enteral nutrition was no longer required but patients could continue drinking partial enteral nutrition (600 kcal per day) or elect to continue with the CDED plus calcium supplement alone until week 24. Patients in the CDED plus partial enteral nutrition group who stopped partial enteral nutrition were permitted to remain in the trial if they continued CDED alone, since they could still be assessed for overall response to the CDED diet in the primary endpoint. Patients who were allocated to CDED alone received only the calcium supplement with CDED from enrolment until week 24. Patients in both groups received 2000 IU of vitamin D per day.

Disease activity was assessed using the Harvey–Bradshaw Index, complete blood count, C-reactive protein, albumin, and weight at baseline and weeks 6, 12, and 24. Stool samples for faecal calprotectin were obtained at baseline and at weeks 6 and 12. Endoscopic disease activity was assessed using the simplified endoscopic activity score for Crohn's disease (SES-CD)[13] both at inclusion for patients with documented colonoscopies and at colonoscopy at week 24.

Baseline faecal calprotectin concentrations were measured at the enrolling centres and samples from baseline and week 6 and 12 were analysed at a centralised laboratory (Rabin Medical Center) using the LIAISON calprotectin assay (DiaSorin, Saluggia, Italy); concentrations of less than 50 µg/g were considered normal.

Dietary compliance was assessed separately for the CDED and partial enteral nutrition at each clinic visit by the modified Medication Adherence Report Scale (MARS) questionnaire[7] in addition to a physician assessment for compliance. Compliance was assessed by dietitians, assessed using a 3-day food journal completed by patients at three timepoints (weeks 3, 9, and 18), complemented with telephone calls at weeks 1, 7, and 13. A dietary helpline was available three times a week. 24-h dietary recall was performed at baseline and weeks 6 and 12. Poor compliance was defined as having at least one of: intolerance (cessation of dietary therapy because of patient's refusal to continue diet); poor adherence defined by the modified MARS questionnaire; or poor compliance as per physician's and dietitian's assessment for compliance in the case report form. The modified MARS adherence rating scale asks participants to answer

nine separate closed questions (yes or no answers) to evaluate the veracity of adherence and then rates adherence to the intervention (never adhered, rarely, sometimes, often, very often, and always adhered). The rating scale was used once for CDED and a second questionnaire with the same questions was used to assess adherence to partial enteral nutrition. High compliance was defined by a rating of very often or always. For the physician's and dietitian's assessment for compliance based on direct questioning, any answer other than "adheres to diet very often/always" was considered poor compliance. Dietitians also reviewed patient 24-h recall and food diaries for disallowed foods. Patients were scored as highly compliant if all three measures assessed demonstrated high compliance, whereas patients who withdrew for any reason were deemed to be non-compliant.

Outcomes

The primary endpoint was clinical remission (defined as a Harvey–Bradshaw Index score of <5) at week 6. Secondary endpoints were the proportion of patients in corticosteroid-free remission at weeks 6, 12, and 24; change from baseline in median C-reactive protein and faecal calprotectin at weeks 6, 12, and 24; endoscopic remission (ie, mucosal healing) at weeks 24–26 (a SES-CD score of 3 or less was considered to indicate endoscopic remission[14]), difference in remission between CDED plus partial enteral nutrition and CDED alone at weeks 6, 12, and 24 (added in an amendment to the protocol); and compliance (added in an amendment to the protocol).

Patients who had worsening disease, or who did not achieve remission or good response (defined as a decrease in Harvey–Bradshaw Index of 3 points or more[15]) by week 6, discontinued the study and did not progress to the next phase; treatment was deemed to have failed for these patients for the purposes of the intention-to-treat (ITT) analysis. Patients who did not achieve remission at week 12 or did not achieve a good response did not progress to the maintenance phase of the diet. Use of any other additional therapy was considered treatment failure from that timepoint.

Statistical analysis

Since the effect of the CDED diet in adults is unknown, and the effect of supplemental formula on remission is also unknown, we could not perform a formal sample size calculation. Therefore, we used a pilot study design to assess the general impact of dietary therapy on adults with mild-to-moderate Crohn's disease and to assess differences between CDED plus partial enteral nutrition and CDED alone.

We used an uncorrected χ^2 statistic or Fisher's exact test, as appropriate, to analyse categorical variables and Mann-Whitney *U* tests and paired *t*-tests or Wilcoxon's signed rank tests to analyse continuous variables, as appropriate. The Bonferroni method was used to adjust for multiple comparisons. For patients with paired measures before and after intervention, we calculated the percentage change for each patient relative to baseline.

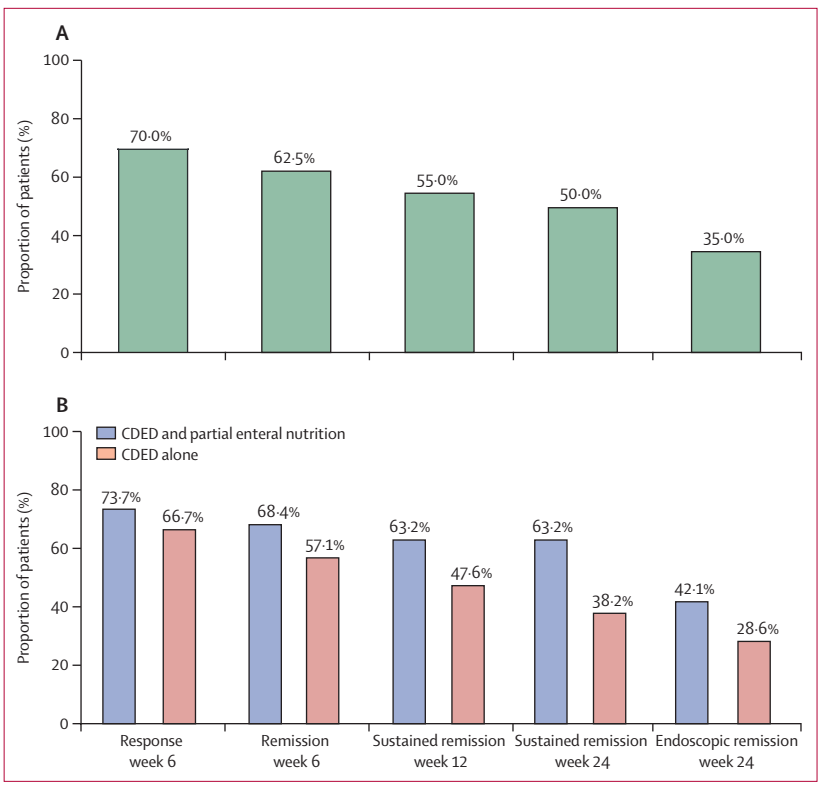

Figure 2: **Response and remission rates in the intention-to-treat population (n=40)**
(A) The proportion of patients who achieved remission in the entire cohort over time. (B) The proportion of patients who achieved remission by treatment group. Clinical remission was defined as a Harvey–Bradshaw Index score of <5 points. Clinical response was defined as a decrease in Harvey–Bradshaw Index score of ≥3 points. Endoscopic remission was defined as a SES-CD score of ≤3. CDED=Crohn's disease exclusion diet. SES-CD=simple endoscopic score for Crohn's disease.

All analyses were done in the ITT population, which included all patients who used the dietary therapy for at least 48 h, analysed according to their randomly assigned treatment group. All patients in the CDED plus partial enteral nutrition group who refused to consume the partial enteral nutrition supplement but were willing to adhere to CDED alone could remain in the study, and were analysed in the ITT analysis as being in the CDED plus parenteral nutrition group, and in the as-treated analysis as being in the CDED alone group.

We also did an as-treated analysis to assess the outcomes of patients who received CDED alone without partial enteral nutrition even if they were allocated to the CDED plus partial enteral nutrition group. For this analysis, we included patients who were allocated to the CDED group and patients who were primarily allocated to CDED plus partial enteral nutrition group who stopped partial enteral nutrition due to intolerance during the first 6 days of the study. Patients who ceased partial enteral nutrition after week 1 or who were not compliant were included in the as-treated analysis (not according to their assigned

	CDED and partial enteral nutrition	CDED alone	Difference (95% CI)	p value
C-reactive protein concentrations for patients with elevated levels at enrolment (n=30)				
Baseline				
Patients with available data, n	16	14	..	..
C-reactive protein concentration, mg/L	15·8 (6·9 to 36·1)	12·1 (8·7 to 43·7)	3·7 (–26·8 to 20·6)	0·5520
Week 6				
Patients with available data, n	16	14	..	..
C-reactive protein concentration, mg/L	8·8 (5·3 to 17·7)	8·2 (5·5 to 43·7)	0·5 (–20·3 to 8·5)	0·7901
Week 12				
Patients with available data, n	16	14	..	..
C-reactive protein concentration, mg/L	7·4 (5·7 to 19·5)	6·1 (4·3 to 33·6)	1·3 (–18·8 to 10·3)	0·4726
Week 24				
Patients with available data, n	16	14	..	
C-reactive protein concentration, mg/L	8·0 (5·3 to 18·9)	7·7 (5·0 to 35·0)	0·2 (–21·5 to 10·3)	0·7901
Faecal calprotectin concentration from central lab (n=38)				
Baseline				
Patients with available data, n	18	20	..	..
Faecal calprotectin concentration, µg/g	229·0 (97·6 to 1050·0)	294·5 (53·5 to 1620·0)	–65·5 (–633·0 to 573·0)	0·9424
Week 6				
Patients with available data, n	17	15	..	..
Faecal calprotectin concentration, µg/g	268·0 (127·0 to 859·0)	216·0 (50·3 to 761·0)	52·0 (–199·0 to 525·0)	0·3125
Week 12				
Patients with available data, n	16	15	..	..
Faecal calprotectin concentration, µg/g	104·1 (65·4 to 370·3)	97·3 (49·2 to 212·0)	6·7 (–81·0 to 182·0)	0·5985

Data are median (IQR). CDED=Crohn's disease exclusion diet.

Table 2: **Inflammatory markers over time**

treatment group), since some of these patients might have already achieved remission by week 3.

Patients who withdrew from the study or required additional therapy were considered treatment failures and were imputed for non-response. Similarly, patients who withdrew for any reason were imputed as non-responders in the ITT analysis. For patients with a change in medical therapy due to treatment failure (ie, addition of drugs for remission due to withdrawal from diet or non-response), continuous variable data were carried forward from the observation before the change in therapy (last observation carried forward).

Statistical analyses were performed using SPSS (version 27.0) and R (version 4.0.5). This study is registered with ClinicalTrials.gov, NCT02231814.

Role of the funding source

The study funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 12, 2017, and May 11, 2020, 91 patients were screened, of whom 44 were randomly assigned to the CDED plus partial enteral nutrition group (n=20) or CDED alone group (n=24). 19 patients in the CDED plus partial enteral nutrition group and 21 patients in the CDED alone group received the allocated intervention for at least 48 h and were thus included in the ITT analysis (figure 1). Four patients in the CDED plus partial enteral nutrition group refused partial enteral nutrition (one patient after 24 h, one patient from day 4, and two patients from day 6), and continued CDED only to week 24. 29 (73%) of 40 patients completed the study: two patients were lost to follow-up, six patients discontinued treatment due to worsening of disease, two stopped because of intolerance to CDED, and one patient was admitted to hospital for another condition.

The median age of patients was 30 years (IQR 24–39) and the median Harvey–Bradshaw Index score was 7 (6–8). One patient aged 60 years was also enrolled in error and was included in the final analysis. Baseline age, sex, location, disease activity, C-reactive protein concentrations, and albumin were similar between treatment groups. One patient from each group was enrolled after treatment failure with budesonide, which was stopped at entry for both patients. Four patients were on stable mesalamine at entry (two patients in both treatment groups), of whom two stopped (both in the CDED and partial enteral nutrition group), and two continued mesalamine during the first 12 weeks (both in the CDED alone group). A baseline SES-CD was performed for 29 patients (15 patients in the CDED and partial enteral nutrition group and 14 patients in the CDED alone group). Although baseline SES-CD scores were similar between groups, median faecal calprotectin concentration at enrolment was higher in the CDED plus partial enteral nutrition group than in the CDED alone group; however, this difference was not statistically significant (p=0·2666). Baseline characteristics are summarised in table 1. At enrolment, five patients had active disease at endoscopy (SES-CD score ≥5) and faecal calprotectin concentrations of less than 200 µg/g, of whom four had elevated C-reactive protein concentrations.

At week 6, 25 (63%) of 40 patients had achieved clinical remission with no significant differences observed between the treatment groups (13 [68%] of 19 patients in the CDED plus partial enteral nutrition group *vs* 12 [57%] of 21 patients in the CDED group; p=0·4618; figure 2). At week 6, 28 (70%) of 40 patients had achieved a response (14 patients in the CDED and partial enteral nutrition group and 14 patients in the CDED alone group). At week 12, 22 patients (55% of the overall ITT population, 88% of those in remission at week 6) were in sustained remission: no significant differences were observed in the proportion of patients in remission at this timepoint (12 [63%] of 19 patients in the CDED plus partial enteral nutrition group *vs* ten [48%] of 21 patients

in the CDED alone group; p=0·3238). At week 24, 20 patients (50% of the overall ITT population, 80% of those in remission at week 6) were in sustained remission; the number of patients who had sustained remission in the CDED plus partial enteral nutrition group was numerically higher than that in the CDED alone group, but this difference was not statistically significant (12 [63%] of 19 patients *vs* eight [38%] of 21 patients; p=0·1133; figure 2B). C-reactive protein and faecal calprotectin concentrations at weeks 6 and 12 were similar between the treatment groups (table 2).

The as-treated analyses of remission at weeks 6, 12, and 24 are shown in the appendix (p 5). In the as-treated analysis, at week 12, eight (53%) of 15 patients in the CDED plus partial enteral nutrition group were in sustained corticosteroid-free remission, as were 14 (56%) of 25 patients in the CDED alone group. At week 24, the number of patients who had achieved corticosteroid-free remission was numerically higher in the CDED plus partial enteral nutrition group than the CDED alone group (nine [60%] of 15 patients *vs* 12 [48%] of 25 patients), but the difference was not statistically significant. No significant difference was noted in the proportion of patients who achieved endoscopic remission between groups (eight [53%] of 15 patients in the CDED plus partial enteral nutrition group *vs* six [46%] of 13 patients in the CDED alone group; p=0·7047).

Overall, median Harvey–Bradshaw Index score decreased significantly between baseline and week 6, week 12, and week 24 (figure 3A). Median Harvey–Bradshaw Index scores were not significantly different between groups at any timepoint. In the ITT population, at week 6, median change in Harvey–Bradshaw Index score from baseline was numerically higher for the CDED and partial enteral nutrition group than the CDED alone group (p=0·0988; figure 3B).

Among the 30 patients with elevated C-reactive protein at baseline, a decrease in median C-reactive protein was observed, from 14·5 mg/L (IQR 7·7 to 37·1) to 8·4 mg/L (5·4 to 18·5) at week 6 (p=0·0378), which was sustained at week 24 (8·0 mg/L [5·2 to 19·9]; p=0·0098). At week 24, the median difference in C-reactive protein concentration from baseline to week 24 was –4·1 mg/L (–11·7 to 0·0). No differences were identified between groups in change in C-reactive protein concentrations at weeks 6, 12, or 24 among individuals with elevated C-reactive protein at baseline (table 2).

Median faecal calprotectin concentrations decreased significantly between baseline and week 12 (262 µg/g [IQR 73–1092] *vs* 97 µg/g [54–212]; p=0·0123). 16 (40%) of 40 patients had a faecal calprotectin concentration of less than 100 µg/g at week 12. The overall change in faecal calprotectin concentrations in the entire cohort and by group is presented in the appendix (p 6). No differences were identified between groups in change in faecal calprotectin concentrations at weeks 6 or 12 (table 2).

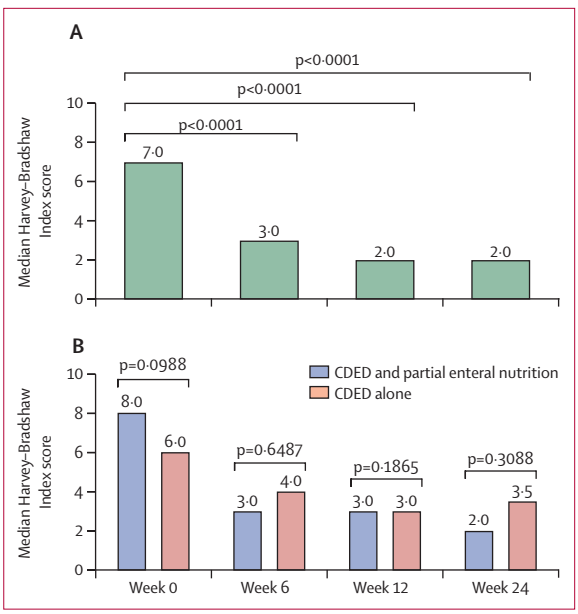

Figure 3: **Change in median Harvey–Bradshaw Index score over time in the entire cohort (A) and by treatment group (B)**
No statistical differences were identified between treatment groups. CDED=Crohn's disease exclusion diet.

See **Online** for appendix

No significant differences in patient characteristics were identified when analysed by remission status at week 6 (table 3).

Among 22 patients with paired colonoscopies at baseline and week 24, median SES-CD score decreased by 5·0 points (IQR –6·2 to –1·0); 72·8% decrease from baseline; p=0·0025; appendix p 7).

At enrolment, four patients (two patients per treatment group) were underweight (body-mass index [BMI] <18·5) and nine patients (six patients in the CDED plus partial enteral nutrition group and three patients in the CDED alone group) were overweight (BMI >30). Among the 17 patients for whom data on weight was available in the CDED plus partial enteral nutrition group, median weight increased between baseline and week 6 (73·7 kg [IQR 60·1–85·4] *vs* 76·4 kg [60·9–85·7]). Among the 15 patients for whom data on weight was available in the CDED alone group, median weight remained stable between baseline and week 6 (70·0 kg [62·0–82·5] *vs* 70·3 kg [60·2–82·6]). Both groups gained weight on their respective diets by week 12. At week 12, median weight for the CDED plus partial enteral nutrition group was 77·5 kg (67·0–83·2), corresponding to a median increase of 3·8 kg, and in the CDED alone group, median weight at week 12 was 72·0 kg (60·4–79·4), corresponding to a median increase of 2·0 kg. The changes in weight between treatment groups at weeks 6 and 12 were not significantly different (p=0·4110 for week 6, p=0·5050 for week 12).

29 patients attended week 24 visits: 16 in the CDED plus partial enteral nutrition group and 13 in the CDED alone group. Mean BMI increased from 24·7 (SD 6·2) at baseline to 26·0 (6·1) at week 24 in the CDED plus partial

	Remission at week 6 (n=25)	Not in remission at week 6 (n=15)	Difference (95% CI)	p value
Age, years	27 (23 to 40)	31 (25 to 38)	3·4 (–9·4 to 10·3)	0·9779
Sex	..	..	..	0·1396
Women	16 (64%)	6 (40%)	24·0% (–49·6 to 7·1)	..
Men	9 (36%)	9 (60%)	..	..
Disease duration, months	2·9 (1·6 to 7·1)	2·6 (1·4 to 20·6)	–0·4 (–1·7 to 11·0)	0·9121
Body-mass index, kg/m^2	24·5 (21·2–29·5)	22·9 (21·3–26·5)	–1·6 (–5·4 to 1·9)	0·5250
Montreal classification (L1 or L3)				
L1	21 (84%)	14 (93%)	9·0% (–15·7 to 28·8)	0·6329
L3	4 (16%)	1 (7%)	..	..
Montreal classification (L4)				
L4	1 (4%)	1 (7%)	3·0% (–13·8 to 26·0)	0·9999
Baseline				
Harvey–Bradshaw Index score	7·0 (6·0 to 8·0)	7·0 (6·0 to 9·0)	0·0 (–1·0 to 2·0)	0·2795
C-reactive protein, mg/L)	8·2 (5·3 to 21·0)	9·4 (2·9–41·6)	1·2 (–6·5 to 30·4)	0·5997
Elevated C-reactive protein	19 (76%)	11 (73%)	2·7% (–22·4 to 30·9)	0·8504
Faecal calprotectin, µg/g*	342·5 (82·9 to 1160·0)	195·5 (60·1–1092·5)	–147·0 (–735·2 to 557·0)	0·7087
SES-CD†	6·0 (5·0 to 11·0)	5·0 (5·0 to 7·0)	–1·0 (–5·0 to 1·0)	0·2038
Albumin, g/dL	4·2 (0·3)	4·2 (0·5)	0·1 (–0·3 to 0·3)	0·5717
Weight, kg	72·0 (59·3 to 84·5)	69·6 (62·5 to 78·5)	–2·4 (–16·1 to 7·5)	0·8038
Smoker	5 (20%)	4 (27%)	7·0% (–18·1 to 34·3)	0·7053
Week 6				
Harvey–Bradshaw Index score‡	2·0 (0·5 to 3·0)	6·0 (5·0 to 7·5)	4·0 (3·0 to 6·0)	<0·0001
C-reactive protein, mg/L§	5·8 (5·0 to 11·4)	8·2 (1·8 to 46·5)	2·0 (–4·9 to 34·6)	0·9829
Faecal calprotectin, µg/g¶	268·0 (69·4 to 761·0)	223·0 (103·2 to 1542·5)	–45·0 (–280·6 to 2138·0)	0·7419
High compliance‖	22 (88%)	9 (60%)	28·0% (–56·5 to 2·4)	0·0572
Weight, kg**	74·0 (60·2 to 82·6)	73·3 (59·7 to 110·5)	–0·7 (–18·3 to 38·9)	0·7110

Data are median (IQR), n (%), or mean (SD). SES-CD=simple endoscopic score for Crohn's disease. *Data not available for one patient in the remission group and one patient in the group that did not achieve remission. †Data not available for seven patients in the remission group and four patients in the group that did not achieve remission. ‡Data were available for 25 patients in the remission group and nine patients in the group that did not achieve remission. §Data were available for 22 patients in the remission group and nine patients in the group that did not achieve remission. ¶Data were available for 23 patients in the remission group and nine patients in the group that did not achieve remission. ‖Data were available for 24 patients in the remission group and nine patients in the group that did not achieve remission.**Data were available for 23 patients in the remission group and nine patients in the group that did not achieve remission.

Table 3: **Comparison of patients who had achieved remission at week 6 versus patients not in remission at week 6**

enteral nutrition group. Mean BMI in the CDED alone group increased slightly from 25·9 (5·9) at baseline to 26·7 (5·9) at week 24.

Data regarding macronutrients are presented in the appendix (p 1). By week 12, patients who received partial enteral nutrition had received numerically more daily calories (mean 1994 kcal [SD 845] *vs* 1524 kcal [382] for the CDED group, p=0·080), and by week 24 this difference was statistically significant (2221 kcal [913] for the CDED plus partial enteral nutrition group *vs* 1582 kcal [273] for the CDED group, p=0·018). Nutritional data for the CDED alone group might have been skewed by two patients in the CDED alone group who were on intentional weight loss diets. Despite numerically lower mean protein consumption with CDED alone versus CDED plus partial enteral nutrition, mean protein intake in the CDED alone group remained high at 148% of the recommended dietary allowance.

Compliance data are summarised in the appendix (p 2). Overall, compliance with dietary therapy at week 6 was high in 12 (63%) of 19 patients in the CDED plus partial enteral nutrition group and 18 (86%) of 21 patients in the CDED alone group. The most common adverse event was disease exacerbation, which was reported in three patients in the CDED plus partial enteral nutrition group and two patients in the CDED alone group. No serious adverse events or treatment related adverse events were observed (appendix p 3).

Discussion

The mainstay of therapy for Crohn's disease in adults is suppression of the immune system. However, even newer selective drugs cause immune suppression and side-effects, and are associated with high costs.[16–18] Among patients with progressive disease at risk for complications,[10,19–22] these therapies represent a beneficial approach,[23,24] although these drugs might be unnecessary for milder or uncomplicated disease if effective alternatives are available. Dietary therapy might be ideal for patients with milder disease or as a bridge to medical therapy if there is a delay in instituting medical therapy, and might address the involvement of diet as a trigger of inflammation.

In this pilot study, we demonstrated that dietary therapy (CDED with or without partial enteral nutrition) seemed to be effective for induction and maintenance of remission in a cohort of adults with mild-to-moderate inflammatory uncomplicated ileal Crohn's disease, although the study was not powered to detect differences between groups for this endpoint. Around 60% of patients achieved clinical remission by week 6 without additional drugs. Another clinically relevant finding was that 80% of patients in remission at week 6 maintained clinical remission at week 24 on dietary monotherapy, allowing more than 50% of patients in the ITT population to achieve sustained remission at 6 months. Dietary therapy was accompanied by a significant and progressive reduction in C-reactive protein and faecal calprotectin. Mucosal healing is an important goal in Crohn's disease, and to our knowledge this is the first study to demonstrate the ability of any dietary intervention to achieve endoscopic remission over an extended period of dietary therapy (35% of the ITT population had achieved endoscopic remission at 24 weeks). Previous studies of exclusive enteral nutrition (a non-sustainable diet in children[25]) have included immunomodulators, thus this

is also the first study to demonstrate that dietary therapy can achieve these goals in a prospective trial in adults without concurrent immunomodulators or steroids. However, we cannot extrapolate these results to patients who have been treated with biologics since this patient group was not included in this pilot trial.

CDED with partial enteral nutrition was developed for the paediatric population to provide balanced nutrition over time while reducing exposure to certain dietary substrates. Partial enteral nutrition provides nutritional security and ensures nutritional needs are met in patients who might be malnourished. However, it can also be a barrier to dietary therapy in adults. We used a randomised study design to address the need for partial enteral nutrition in adults. Previous case series with small numbers of patients have suggested that patients who stop partial enteral nutrition or refuse partial enteral nutrition might also respond.[12] Although our findings in the ITT population suggested numerical advantages for the CDED plus partial enteral nutrition group, this was not the case when analysing outcomes in the as-treated population. In the as-treated analysis, no significant differences in remission were identified between groups, with more than 50% of participants achieving sustained remission at week 12 in both groups. These data suggest that CDED without partial enteral nutrition can be used as an alternative if partial enteral nutrition is not tolerated. CDED is a high protein diet and both groups had high protein intake at baseline and throughout the study. Our data were insufficient to analyse the types of oils consumed accurately. CDED alone is deficient in calcium during the first 12 weeks and therefore, we provided calcium supplements for the CDED alone group. Patients who are malnourished are more likely to correct these deficiencies with added partial enteral nutrition. Furthermore, patients with obesity might benefit from CDED alone since patients in the CDED alone group gained less weight and ingested fewer calories than did patients in the CDED plus partial enteral nutrition group. Emerging data suggest that overweight and obesity in inflammatory bowel disease might be associated with poorer outcomes such as decreased response to biologic therapies.[26,27]

Use of partial enteral nutrition in the CDED plus partial enteral nutrition group might have had a beneficial effect on sustained remission since the number of patients in this group who achieved sustained remission at week 24 was numerically higher than that among patients in the CDED alone group, although this difference was not statistically significant.

Dietary therapy has been postulated to reduce inflammation by altering the microbiome and reducing intestinal permeability.[9,28] The mechanism by which exclusive enteral nutrition works remains unclear.[29] Exposure to habitual diet in addition to formula seems to negate or reduce the effects of exclusive enteral nutrition therapy.[6,28] Moreover, once habitual diet is re-introduced after a course of exclusive enteral nutrition, many patients have a rebound increase in inflammatory indices or experience flare within weeks of re-exposure to food.[7,8] The clinical efficacy of CDED was previously shown in several studies in the paediatric population[7,12,30] and it is also mechanistically supported by the sustained effects on the composition of the microbiome after using CDED and partial enteral nutrition in children.

Compliance and adherence are an obstacle to dietary therapies. Data for adults using exclusive enteral nutrition are conflicting, with poor compliance postulated to drive an inadequate response is some studies.[13] A 2020 study reported that about a third of adults with inflammatory bowel disease who were prescribed self-injectable biologic therapy were non-adherent.[31] In this study, compliance was fairly high. After 12 weeks, 14 (35%) of 40 patients had either stopped the diet or were found to be poorly compliant. Clinical trials might overestimate compliance since more motivated patients inclined to try dietary therapies might agree to participate in such trials, and they might receive more support needed to maintain dietary therapy over time.

Our study had several limitations. Our pilot study included a selected patient population considered most likely to receive a trial of dietary therapy in future clinical practice. We excluded older patients (aged >60 years) and patients on steroids, those who had received treatment with biologics, and those who had previously had surgery. Although these exclusion criteria assured a well-defined homogenous population and reduced confounders, they also prevented extrapolation to populations such as those who had received treatment with anti-TNF drugs or those with more severe disease. Since this was a pilot study, we did not include a control group, as it would be unethical to treat patients with active disease with a placebo intervention for 6 months. This cohort included only patients with evidence of active inflammation at enrolment who required an intervention to control active Crohn's disease. Most of the patients had a baseline colonoscopy and we documented improvement in inflammation and mucosal healing using paired SES-CD scores. Given the pilot nature of the study, it was underpowered for all endpoints and to detect differences between the CDED alone or CDED plus partial enteral nutrition groups, or to define who could benefit from partial enteral nutrition. Furthermore, some patients who were allocated to partial enteral nutrition refused the formula, although this is likely to reflect real world experience. Additionally, although all patients who had not withdrawn or received additional medication for poor response (n=28) had a colonoscopy at week 24, we did not perform colonoscopies in patients who withdrew from the study and as such we imputed no endoscopic remission for all patients without a colonoscopy in the ITT analysis.

In summary, this study is the first prospective investigation of dietary monotherapy in adults with active Crohn's disease, designed and performed using rigorous

criteria and an evaluation of mucosal healing, with the aim of meeting the current goals of therapy in Crohn's disease. Although this was only a pilot trial, our findings suggest that this diet could be used in adults with uncomplicated mild-to-moderate Crohn's disease at diagnosis and possibly serve as a therapeutic alternative for patients who cannot receive medical therapy due to underlying health conditions. Our findings suggest that the CDED alone or CDED with partial enteral nutrition should be explored further in powered randomised controlled trials. Personalisation of therapeutic diets in the future should take in to account the need to deliver energy requirements tailored to the nutritional and therapeutic goals of the patient.

Contributors

HY was a member of the steering committee and was involved in study design, patient recruitment, data collection, data analysis, and writing of the report. AL was a member of the steering committee, was involved in study design, patient recruitment, data collection, and writing of the report, and also acquired grant funding. ID was a member of the steering committee, and was involved in the study design, patient recruitment, data collection, and writing of the report. NM was a member of the steering committee, and was involved in patients recruitment, data collection, data analysis, and writing of the report. RSB was a member of the steering committee and was involved in data analysis, dietary monitoring, and produced the tables and figures. LA was the project manage and trial monitor. AH, UK, HBE, NAC, YR, IG, HL, JW, and EZ were involved in patients recruitment and data collection. TZB was involved in data analysis. NFI, BR, and TPG were involved in dietary therapy and data collection. HY, AL, RSB, LA, and NM had full access to the data. AL, RSB, and LA verified the underlying data. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

HY reports institutional research grants from Pfizer; consulting fees from AbbVie, Ferring, Janssen, Neopharm, Pfizer, and Takeda; honoraria for lectures from AbbVie, Janssen, Pfizer, Takeda; and participation on data safety monitoring boards or advisory boards for AbbVie, Neopharm, Pfizer, and Takeda. AL reports grants from Nestle Health Science, Janssen, and AbbVie; advisory board fees, travel expenses, and speaker fees from Takeda, Nestle Health, and Megapharm; and a licensing and consulting agreement with intellectual property with Nestle Health to develop new products. RSB reports consultancy and speaker fees from Nestle Health Science and Megapharm; and travel expenses from Nestle Health. UK reports consulting fees from AbbVie, Janssen, Takeda, Merck Sharpe Dohme, Pfizer, Takeda, and Medtronic; honoraria for lectures from AbbVie, Janssen, Takeda, Merck Sharpe Dohme, Pfizer, Takeda, and Medtronic; and research grants from Takeda, Janssen, and Medtronic. IG reports research grants from Pfizer; travel expenses from ECCO and the International Organization for the Study of Inflammatory Bowel Disease. ID reports institutional research grants from Altman and Pfizer; consulting fees from Arena, Gilead, Cambridge Healthcare, Wild bio, Food Industry Association, Integra Holdings; honoraria for lectures from Janssen, AbbVie, Takeda, Pfizer, Roche, Arena, Neopharm, Celltrion, Rafa Laboratories, Ferring, Falk Pharma, Nestle, Bristol-Myers Squibb, and Abbott; and participation on data safety monitoring boards for Janssen, AbbVie, Takeda, Pfizer, Roche, Arena, Neopharm, Gilead, Galapagos, Celltrion, Sublimity, Wild bio, Athos therapeutics, Food industries Organization, Bristol-Myers Squibb, and Abbott. NM reports grants from Takeda, Abbott, Israel Scientific Foundation, AbbVie, Pfizer, and Janssen; consulting fees from BiomX; honoraria for lectures from AbbVie, Ferring, Janssen, Pfizer, and Takeda; and participation on a data safety monitoring board or advisory board from Neopharm, Pfizer, Takeda, and BiomX. All other authors declare no competing interests.

Data sharing

Based on reasonable request to the corresponding author, anonymised data underlying this article (study protocol that are not part of an ongoing or planed regulatory submission, informed consent forms, de-identified participant data, data dictionary, and statistical analysis) will be shared following approval of the institutional review board. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered.

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References

1 Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015; **12:** 720–27.
2 Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018; **155:** 337–46.
3 Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010; **105:** 289–97.
4 Reenaers C, Pirard C, Vankemseke C, Latour P, Belaiche J, Louis E. Long-term evolution and predictive factors of mild inflammatory bowel disease. *Scand J Gastroenterol* 2016; **51:** 712–19.
5 Yanai H, Goren I, Godny L, et al. Early indolent course of Crohn's disease in newly diagnosed patients is not rare and possibly predictable. *Clin Gastroenterol Hepatol* 2021; **19:** 1564–72.
6 Levine A, Sigall Boneh R, Wine E. Evolving role of diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gut* 2018; **67:** 1726–38.
7 Levine A, Wine E, Assa A, et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. *Gastroenterology* 2019; **157:** 440–50.
8 Logan M, Clark CM, Ijaz UZ, et al. The reduction of faecal calprotectin during exclusive enteral nutrition is lost rapidly after food re-introduction. *Aliment Pharmacol Ther* 2019; **50:** 664–74.
9 Cohen-Dolev N, Sladek M, Hussey S, et al. Differences in outcomes over time with exclusive enteral nutrition compared with steroids in children with mild to moderate Crohn's disease: results from the GROWTH CD Study. *J Crohn's Colitis* 2018; **12:** 306–12.
10 Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohn's Colitis* 2020; **14:** 4–22.
11 Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol* 2018; **113:** 481–517.
12 Sigall-Boneh R, Pfeffer-Gik T, Segal I, Zangen T, Boaz M, Levine A. Partial enteral nutrition with a Crohn's disease exclusion diet is effective for induction of remission in children and young adults with Crohn's disease. *Inflamm Bowel Dis* 2014; **20:** 1353–60.
13 Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; **60:** 505–12.
14 Löwenberg M, Vermeire S, Mostafavi N, et al. Vedolizumab induces endoscopic and histologic remission in patients with Crohn's disease. *Gastroenterology* 2019; **157:** 997–1006.
15 Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol* 2010; **8:** 357–63.
16 Colombel J-F, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut* 2017; **66:** 839–51.
17 Engel T, Yung DE, Ma C, et al. Effectiveness and safety of Ustekinumab for Crohn's disease; systematic review and pooled analysis of real-world evidence. *Dig Liver Dis* 2019; **51:** 1232–40.
18 Rencz F, Gulácsi L, Péntek M, et al. Cost-utility of biological treatment sequences for luminal Crohn's disease in Europe. *Expert Rev Pharmacoecon Outcomes Res* 2017; **17:** 597–606.
19 Safroneeva E, Vavricka SR, Fournier N, et al. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. *Aliment Pharmacol Ther* 2015; **42:** 977–89.

20 Peyrin-Biroulet L, Loftus EV, Colombel J-F, Sandborn WJ. Early Crohn disease: a proposed definition for use in disease-modification trials. *Gut* 2010; **59:** 141–47.

21 Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut* 2017; **66:** 2179–87.

22 D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; **371:** 660–67.

23 Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut* 2019; **68:** 423–33.

24 van den Heuvel TRA, Jeuring SFG, Zeegers MP, et al. A 20-year temporal change analysis in incidence, presenting phenotype and mortality, in the Dutch IBDSL cohort-can diagnostic factors explain the increase in IBD incidence? *J Crohn's Colitis* 2017; **11:** 1169–79.

25 Grover Z, Muir R, Lewindon P. Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in paediatric Crohn's disease. *J Gastroenterol* 2014; **49:** 638–45.

26 Guerbau L, Gerard R, Duveau N, et al. Patients with Crohn's disease with high body mass index present more frequent and rapid loss of response to infliximab. *Inflamm Bowel Dis* 2017; **23:** 1853–59.

27 Brown P, Clark T, Dowson G, et al. Relationship of body mass index to clinical outcomes after infliximab therapy in patients with Crohn's disease. *J Crohn's Colitis* 2016; **10:** 1144–50.

28 Johnson T, Macdonald S, Hill SM, Thomas A, Murphy MS. Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: a randomised controlled trial. *Gut* 2006; **55:** 356–61.

29 Logan M, Gkikas K, Svolos V, et al. Analysis of 61 exclusive enteral nutrition formulas used in the management of active Crohn's disease-new insights into dietary disease triggers. *Aliment Pharmacol Ther* 2020; **51:** 935–47.

30 Sigall Boneh R, Van Limbergen J, Wine E, et al. Dietary therapies induce rapid response and remission in pediatric patients with active Crohn's disease. *Clin Gastroenterol Hepatol* 2021; **19:** 752–59.

31 Shah NB, Haydek J, Slaughter J, et al. Risk factors for medication nonadherence to self-injectable biologic therapy in adult patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2020; **26:** 314–20.