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Effect of Fat Composition in Enteral Nutrition for Crohn's Disease in Adults: A Systematic Review

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Abstract

Background & Aims: The role of enteral nutrition (EN) fat composition in regulating inflammation in Crohn's disease (CD) is not clear. There is, moreover, insufficient evidence to guide the choice of EN in CD with any confidence. We have reanalysed the findings of previous studies in a systematic review focusing on the relationship between EN fat content and remission rates (RR).

Methods: A systematic search with no language restriction was undertaken in Medline and Embase databases supplemented by a manual search in the reference lists of identified studies. The selection criteria were: clinical trial, exclusive EN, adults and CD. Data on the type of EN, its fat composition, achieved RR, and study design were extracted. An established assessment tool was used to assess the quality of the studies.

Results: A total of 29 clinical trials are included in this review. The quality of the studies was highly variable. No fewer than 27 formulations of enteral feed were identified including 4 elemental and 23 non-elemental preparations.

There was a positive correlation between the total n-6 fatty acid content and response rates, which was significant when expressed as the ratio between n-6 and n-3 fatty acids ($r = 0.378$, $p = 0.018$). A non-significant positive trend was founded ($r = 0.072$; $p = 0.643$) between medium chain triglycerides (MCT) delivery as a percentage of the total energy provision and RR. While a non-significant negative trend was reported for the delivery of monounsaturated fatty acids (MUFA) ($r = -0.23$, $p = 0.13$). A qualitative advantage to regimens based on safflower oil suggest that optimised therapeutic approaches are within reach.

Keywords: Crohn's disease, Enteral nutrition, Lipid, Fatty acid, Dietary fat, and Inflammatory bowel disease

Abbreviations

EN: Enteral nutrition

CD: Crohn's disease

RR: Remission rate

TGF-β: Transforming growth factor-β

MCT: Medium chain triglycerides

LCT: Long chain triglycerides

MUFA: Monounsaturated fatty acid

PUFA: Polyunsaturated fatty acid

Introduction

Crohn's disease (CD) remains an incompletely understood, inflammatory condition of the intestine. Although there are important genetic components to its origins, there are also undoubted environmental elements, amongst which dietary factors are clearly identifiable. As well as having a probable role in pathogenesis, nutrition has been identified as a key mediator in established disease, such that, in paediatrics at least, defined enteral nutrition (EN) is the treatment of first choice for many patients. However, as is often the case in clinical nutrition, the evidence base is not as strong as might be wished. Several meta-analyses have been conducted, but it remains difficult to judge the true effectiveness of EN in patients with CD. The collected evidence supports a superior effect of corticosteroids over EN in adults with CD, but many adult clinicians and most paediatricians believe that EN is an appropriate and evidence-based primary therapy in CD. This belief rests on the positive results from studies of paediatric and malnourished CD patients, which confirm beneficial effects of EN in improving growth and nutritional status, but which also indicate mucosal healing, and of course a favourable risk profile compared to pharmacological options.

Enteral nutrition comprises, however, a broad range of options, and the limited comparative evidence prevents confidence that the best choice(s) can currently be made. Polymeric, protein-based feeds with high fat content have been compared with low fat, glucose and amino acid-based feeds, and with oligomeric peptide-based feeds [1-4], but without compelling evidence that one is better than another [4]. At present a single EN formula is licenced and marketed specifically for inflammatory bowel disease in adults. This is a casein-based polymeric feed rich in transforming growth factor-β (TGF-β), but there is little evidence to support any particular efficacy [5, 6].

Meta-analysis shows a weak and non-significant positive association between the protein content of feeds and their associated clinical response rates (RR). One meta-analysis

found a negative correlation between long chain triglyceride (LCT) content and RR [7], and a second found comparable but non-significant trends favouring low LCT and low overall fat content [4]. Given the potential aetiopathogenic relevance of lipids to Crohn's disease (more disease in populations on high fat Western diets) and the curious phenomenon of fat wrapping (almost pathognomonic of Crohn's), further investigation in this area appears readily justifiable despite and partly because of the inability of the other meta-analyses to provide a verdict on this issue.

The aim of this systematic review has been to reanalyse the findings of the older studies and to combine these with the findings of those more recently published, specifically to evaluate the relationship between nutrient fat content and response rates in the treatment of patients with CD. Conscious that currently reported evidence is inconclusive and aware that many authorities consider the case for EN so weak as to argue robustly against it in the treatment of CD, we have approached this in a different and we hope more exploratory fashion than previous reviews. We focus on specific fatty acids, not just on lipid class, and on the ratios of individual fatty acids to each other, as well as to other macronutrients and to their relative contributions to energy provision.

Materials and methods

The PRISMA checklist and guidelines were used for this systematic review (see supplementary data in **Appendix A**). The study is registered with the PROSPERO database of systematic reviews, registration number: CRD42016033857.

Search strategy

A computer-based systematic search was undertaken using the Medline database (1946 to present) and the Embase database via OVID. The search strategy was customized for each database and applied to titles and abstracts of papers. For text terms related to enteral nutrition we used: “enteral”, “elemental”, “polymeric”, “whole protein”, “amino acid

based", "peptide based", "low fat", or "high fat"; these terms were all combined with "nutrition", "feeding", "diet", or "feed". For disease-related text terms we used "Crohn's disease", or "inflammatory bowel disease". Also, we searched "enteral nutrition" and "Crohn disease" as index terms (MeSH) and exploded them as appropriate. The searches were limited to studies that involved humans, adults (18-plus years), clinical trials, controlled clinical trials, randomized controlled trials, meta-analyses, and systematic reviews. The searches were not restricted to the English language. In addition, a manual search of the reference lists of previously published papers was carried out, looking specifically for clinical trials investigating the effect of EN in adult patients with active CD.

Selection criteria

The selection of studies was determined by two reviewers following set criteria. The studies included were required to be prospective clinical trials in adults with CD (including controlled and uncontrolled trials). The EN intervention was to have been given exclusively for a defined period of time without any food intake (only water and sugar/milk-free beverages were allowed). The response rate must have been measured as a primary or secondary outcome, according to clearly stated criteria. The enteral feed used had to be clearly defined (i.e. name and type of feed, oil source, and fatty acid composition). Studies were removed from consideration if EN was given together with oral food intake, the study was retrospective, or performed in a paediatric population. Trials that did not provide a defined RR for CD, and trials that investigated the effect of EN in combination with other medical therapies (e.g. with non-absorbable antibiotics or with erythropoietin) were also excluded. Studies where the full identity of the lipid content was not published were excluded only after application to researcher and/or manufacturer had failed to provide this information. When studies were published initially as interim reports our analysis used data only from the later full article.

Data extraction

For each eligible study, a detailed review was undertaken using a report form, looking for the type and quantity of fatty acids in the enteral feeds, the RR achieved by EN, which was calculated on the basis of a "per protocol" analysis, and selected characteristics related to study design (e.g. duration of intervention, criteria for remission, geographical location, number of patients). The gender and age of patients, and the anatomical location and duration of their disease were recorded. Any apparent discrepancies in the data extracted were discussed and resolved between the two reviewers.

Most papers did not provide sufficient detail of the fat composition in the enteral feeds for our purposes. These deficits have been addressed as follows. Where the formula was described by a proprietary name the manufacturer's data sheet has been interrogated. Where no proprietary name was provided a query was sent to the primary investigator of the study concerned. In each case our analysis was based on the fatty acid content of the feed used. In the great majority of cases this information was not provided either by authors or by manufacturers. However, the nature and proportion of the oils in the feeds was generally available or possible to estimate from the information given. The fatty acid profile of each oil was then drawn from a thorough published analysis [8]. One additional and unexpected problem arose from the fact that the composition of some feeds has been modified within the last fifteen years. Care was therefore taken to ensure that the analysis of the lipid content referred to that of the feed available at the time of the study.

Quality assessment

The quality of the included studies was judged according to the Downs and Black quality checklist on reporting, external validity, internal validity (study bias), and confounding (selection bias) [9], with Livingston's amendment for assessment of power [10].

This is considered a reliable assessment tool for both randomized and non-randomized clinical trials: the higher the score the better the quality of the methods.

Data synthesis and statistical analysis

The primary aim of this review has been to review and interpret the available evidence in order to test the potential correlation between the fat composition of enteral feeds and the resultant RR. Scatter plots were used to identify trends. The significance of possible relationships was tested by the Pearson correlation test (SPSS Statistics for Windows, Version 22.0, released 2013. IBM Corp., Armonk, NY, USA). Subgroup analysis was also conducted which stratified RR by the different levels of fats in EEN feeds (e.g. low vs. moderate vs. high MCT) and by the different levels of response rate (i.e. low RR <70% vs. high RR >70% response rate).

Results

Literature search

The electronic searches yielded 63 articles and the manual search from previous meta-analyses and reviews identified an additional 14 articles. Initial screening of the 77 articles comprised examination of title and abstract in the context of our selection criteria. Forty articles were judged relevant and were further assessed for eligibility. In each case the full paper was read (professionally translated if necessary) and checked against our selection criteria. Joint decisions on selection were made by the two reviewers, following discussion if any initial discrepancy arose. Ultimately our systematic review was based on 29 pertinent papers (Fig. 1).

Study characteristics

From the total of 29 studies, 24 were controlled trials and 5 were uncontrolled. Among the controlled trials: 10 compared the efficacy of EN against drug therapy; 2

compared EN with PN; and 8 investigated the effect of the type of EN by comparing elemental feeds with non-elemental feeds (which include polymeric and semi-elemental, oligomeric feeds). Only 4 trials specifically addressed the effect of fat composition; these trials compared similar types of feeds but with different fat composition. The study design, patient characteristics, and criteria used to measure RR in the papers considered by this review are provided in Appendix B.

Quality of studies

The quality of the included studies was highly variable. The study with the highest quality [11] scored 26 (out of 28) by the assessment tool [9, 10], while the lowest quality study scored only 10 [12]. Poor (or unknown) representativeness of study subjects and the lack of power calculations were the commonest defects overall, and in the controlled trials, there were high risks of performance and detection bias due to the lack of blinding, and high risk of selection bias due to the lack of allocation concealment during randomization (Appendix B).

Characteristics of identified enteral feeds

No fewer than 29 distinct enteral feeds have been used in the published studies. We have excluded one study [13], and therefore data on two formulae, because patients who were randomized to receive polymeric feeding were prescribed one or other of the two formulae depending on availability, but the RR was provided only as a combined rate for the two formulae. Therefore, the final number of reviewed formulae is 27: 4 elemental formulae and 23 non-elemental preparations. The fatty acid composition of these formulae with reference to RR is demonstrated in Table 1. More detailed fat composition data are provided in Appendix B.

Correlation between fat composition and remission rate

Total amount of fat

Eight studies have compared a pair of feeds with different nutrient composition (e.g. polymeric versus elemental or semi-elemental versus elemental). It is difficult to determine the effect of fat content from these comparisons, as their composition for other nutrients was not standardised. Only two studies have specifically examined the effect of the amount of total fat. High and low fat feeds (fat mainly in the form of LCT) were compared. The earlier study showed that the feed with a low percentage of fats (15.6% of total calories) achieved a higher RR (92%), than the high fat feed (35.6% of total calories), which achieved a RR of 55% [7]. The later study indicated that a very low fat feed (1.15% of total calories) achieved a significantly higher RR (80%) than a modest fat feed (11.27% of total calories), which achieved a RR of (25%) [14]. It will be noted that the amount of fat in this higher fat feed was barely distinguishable from that of the low fat feed of the earlier study and yet the clinical effects were hugely different. Overall we find no significant correlation or trend between total fat content and RR ($r= 0.176$, $p= 0.252$) (Fig. 2A).

Medium chain triglycerides (MCT)

Varying MCT content does not have a consistent strong effect. A single study which compared a feed with added MCT against a feed with no MCT, generated significantly different RRs of 77% and 67% respectively [15]. However, the high MCT feed was semi-elemental and the low MCT feed was elemental, which precludes any firm conclusions about the contribution of the lipid to the observed differences. Our quantitative analysis, which is based on results from all studies, finds a weak non-significant positive trend between MCT delivery as a percentage of the total energy provision and RR ($r = 0.072$; $p = 0.643$) where the range was from 0 to 30% of total energy supply (Fig. 2B). The apparent outlier to the upper left of the plot comes from Leiper's study [16] in which there was a particularly high concentration of MCT (>86% of all fat) with a high proportion of MUFA (29%) and a low n-6:n-3 ratio (see below) amongst the fats that were LCTs.

Long chain triglycerides

The effect of undifferentiated LCTs has been addressed by comparing feeds with similar amounts of total fat but with different percentages of LCT. One study (already mentioned above) compared four feeds: elemental, elemental with added LCT, elemental with added MCT, and semi-elemental [7]. The feed with high LCT was associated with the lowest RR (55%), while the elemental feed with added MCT performed best, with a RR of 92%. However, a second study found no significant difference in RRs between use of feed with 5% LCT and an isocaloric feed with 30% LCT [16]. Our quantitative analysis of all the reported studies of all feedings reveals a non-significant negative trend between LCT provision and RR ($r = -0.254$; $p = 0.096$) where the range was from 4 to 35% of total energy supply and where in most cases the predominant lipids were of the n-6 class (where not, the relative excess came from n-9 lipid which we also consider disadvantageous (Fig. 2C and see below).

Saturated fats

No single study has directly compared feeds with different levels of saturated fatty acids. We found no significant correlation or trend between the amount of saturated fat and the RRs ($r = -0.007$, $p = 0.964$) where the range was from trace amounts to over 30% of total energy supply (Fig. 2D).

Olive oil/MUFA

Only a single study has compared two feeds with the same amount of total fat but with different amounts of oleic acid (balanced by linoleic acid) [11]. The feed with higher oleic acid content (79% of total fat) was significantly less effective (RR = 27%) than the feed with lower oleic acid (28%) and higher linoleic acid (45%), which achieved a RR of 63%. Although there are no other specific studies addressing MUFAs, our overall quantitative analysis is concordant, showing disadvantage from monounsaturated fatty acids (MUFA)

with no statistical significance (r = -0.23, p = 0.13) with a range from trace amounts to about 25% of total energy supply (Fig. 2E).

n-6 and n-3 PUFAs

Only the study by Gassull et al. has directly investigated the effect of an n-6-rich feed (specifically linoleic acid), in which a significantly higher RR was achieved than with a lower n-6 content [11]. No study of non-elemental formulae readily allows assessment of the individual effects of an n-3-rich approach.

In our quantitative analysis a very weak non-significant negative correlation was found between the amount and proportion of PUFA (of all types) and the response rates from all feeds (r = -0.157, p = 0.308) (Fig. 2F) as was also the case for n-3 fatty acids (r = -0.166, p = 0.313) (Fig. 2H).

However, there was a weak positive correlation between the total n-6 fatty acid content and response rates (r = 0.253, NS) (Fig. 2G), statistical significance (r= 0.378, p = 0.018) which remained significant after correction for multiple tests (Fig.2I). In the subgroup analysis (TABLE 2), when RR was stratified by the level of n-6:n-3, significant difference (p = 0.011) was reported in the pooled RR between EEN feeds with moderate n-6:n-3 (58.94% RR) (95% CI 48.99, 68.9) versus feeds with high n-6:n-3 (79.91% RR) (95% CI 72.31, 87.51).

When patients exposed to only a single oil are considered (informal subgroup analysis) then the use of safflower oil is favoured, with a mean (median) response rate of 83.6% (84%) compared to the overall average response of 68.1% and mean (median) values for isolated exposure to soybean or arachis oil of 63.7% (68.5%) and 68.6% (75%) respectively.

Discussion

The wide range of patient characteristics, the low number of participants in each study, and varying study designs obstruct the route to confident and generalizable conclusions. We deliberately used results taken from observations on patients who followed treatment protocols (rather than intention to treat), but although biologically justifiable this will be of limited clinical value if a future "optimal" formula is not tolerated and thus the treatment plan is not completed. Fortunately the compliance/acceptance of the many different formulae did not appear systematically different according to the particular lipid profiles. This may have been obscured however by the range of duration of the intended therapies. The duration of intervention in most of the trials examined was between 3 and 8 weeks, 12 weeks in one trial [17], and only 2 weeks in 3 studies [18-20].

No fewer than eight different sets of criteria have been utilised to define response. Some were strict and binary (e.g. complete steroid withdrawal) and associated with relatively low response rates [21, 22], while others were more qualitative (subjective). It should not have had a major effect on our interpretations since a full analysis performed on this basis provides the same qualitative results (data not shown).

Our methods may not have been sufficient to overcome bias introduced by the differing anatomical location of the CD (small bowel, large bowel, or both). The trials with the highest proportions of patients with small bowel CD (50% and 52%) also had amongst the highest RRs (86% and 75% respectively)[21, 23], a linkage already well recognized in the literature, and perhaps a confounder despite apparently well-matched controls.

It has been thought that EN is more effective in those with early, purely inflammatory disease. Although not all evaluated studies provided the duration of the disease, the shortest and longest mean disease durations (1.3 and 18 years) were associated with similar and very

respectable RRs of 90% and 80% respectively, suggesting that this effect is not profound [18, 24].

Considerable differences were observed in respect of sex ratio (0-89% male [15], [25]), but although prognosis of CD may differ between the sexes [25] a systematic bias could not be detected within our analysis [26].

The divergence between the different types of unsaturated LCTs (n-3, n-6 and n-9) and outcome appear at first surprising, but are fully consistent with the negative results from supplementary fish oil in CD [27]. In terms of specific oil content, interpretation is clouded by the number of feeds which contain multiple oils. However the numerical advantage to safflower oil is very much in line with the overall conclusion that high n-6:n-3 ratio is advantageous and low proportion of MUFA could be relatively effective as well, given the relative paucity of MUFA in safflower oil (13.9% compared to 23.9% in soy and 56% in arachis oil) and its n-6:n-3 ratio, which, at over 90, is the highest of all the dietary oils. It has been more difficult still to link interpretation to individual fatty acids, but linoleic acid is favoured, and oleic acid as the only n-9 fatty acid in artificial feeds is targeted for avoidance.

There is a little supportive evidence also for our hypothesised complementary combination of safflower oil and MCT. One of the highest response rates in the literature (92% [7]) was in patients on this combination, and only the study of Lindor *et al* appears to point in the opposite direction, this being a small study in which the comparator was steroid therapy [28].

Conclusions

The fat content of EN formulae and its influence on controlling the inflammation of CD has generated interest, but its true role has remained unclear. Given its potential importance it is surprising that most authors have not thought it worthwhile or necessary to disclose the lipid analysis of the formulae used in their study. This systematic review has

dissected the previously very broad classification of lipids in order to try to assess the effects of individual dietary oils and their fatty acids. It is recognised that definitive analysis is not possible given, on the one hand, the incomplete comparative information available, and, on the other, the inevitable complexity introduced by the replacement of one lipid with another and/or by different total fat content in different feeds. We manifestly lack sufficiently robust clinical trials in this area [29].

However, our results expose significant results from individual studies, and, as well as several suggestive trends, support significant advantage from a high n-6 to n-3 ratio and perhaps from avoidance of MUFA. The various trends are, moreover, not mutually exclusive despite the considerable variation in study design and response rates. Aiming for a relatively low total LCT content and proportionately high MCT content, with a relative low MUFA and high n-6:n-3 fatty acid ratio can now be argued to offer an optimised approach. This might most easily and effectively be achieved by development of feeds based on a combination of safflower oil and MCT.

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The authors' responsibilities were as follows - both of the authors have contributed to the protocol design, data collection/analysis, and writing of this systematic review. AF has recently undertaken speaker engagements for B Braun and Fresenius-Kabi, but there are no

other potential conflicts of interest to be declared. He is the study's guarantor.

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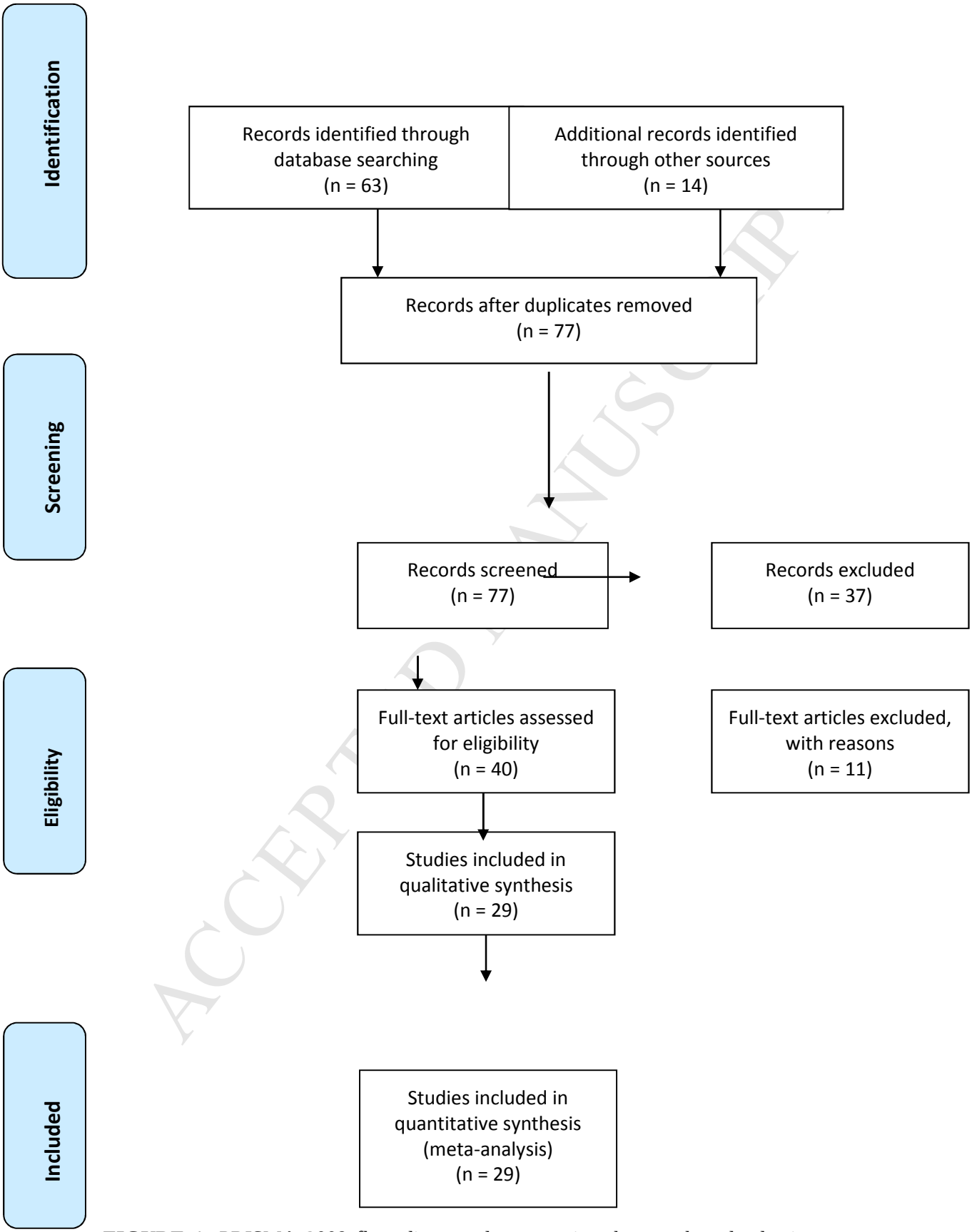
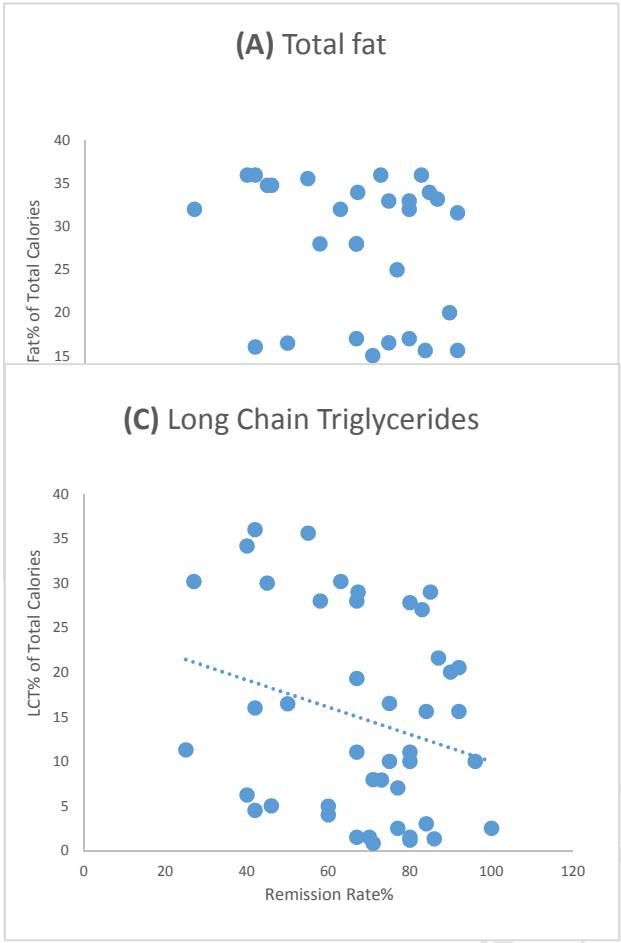
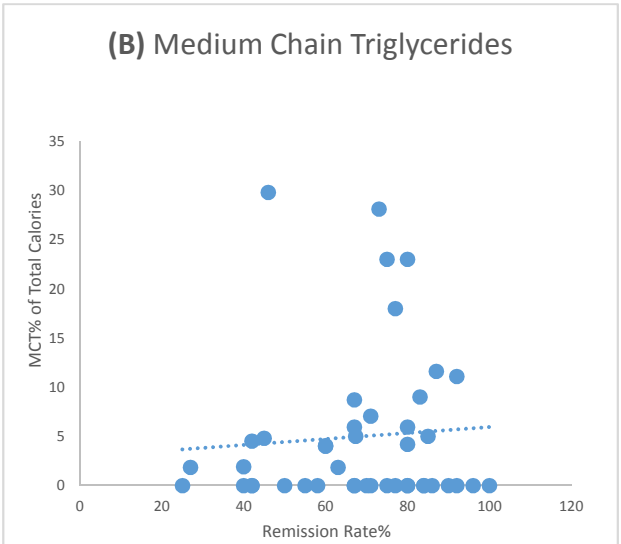
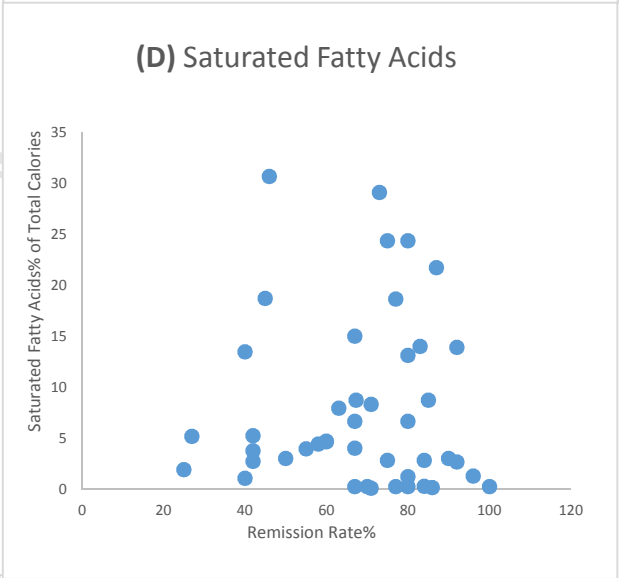


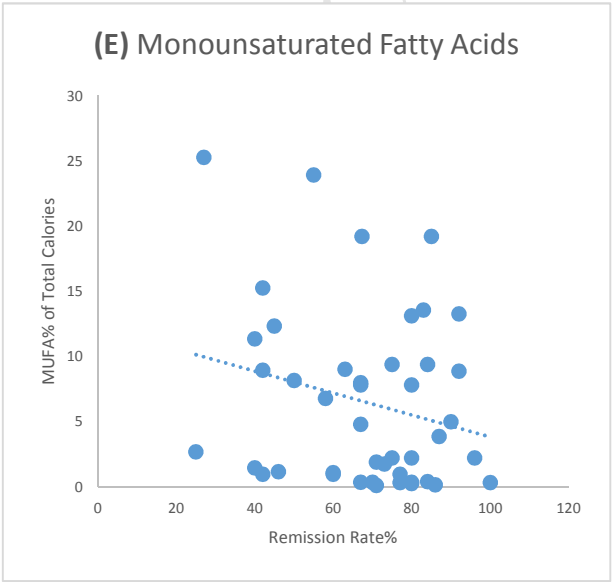
FIGURE 1: PRISMA 2009 flow diagram demonstrating the search and selection strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

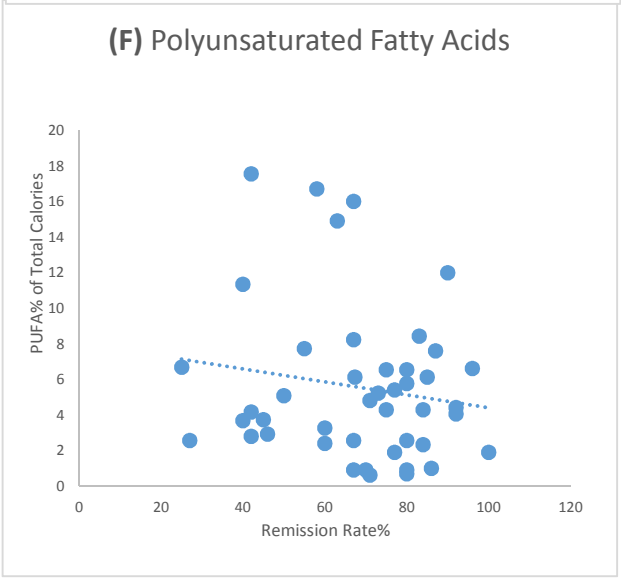

(A) Total fat
Fat% of Total Calories
40
35
30
25
20
15

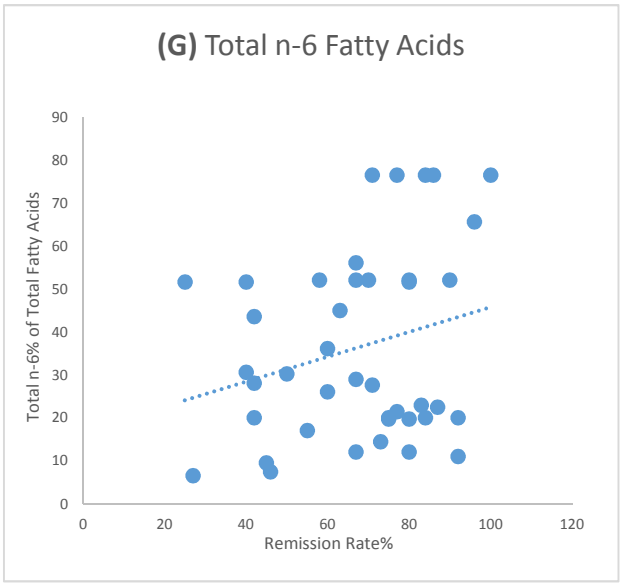

(B) Medium Chain Triglycerides
MCT% of Total Calories
35
30
25
20
15
10
5
0
0
20
40
60
80
100
120
Remission Rate%

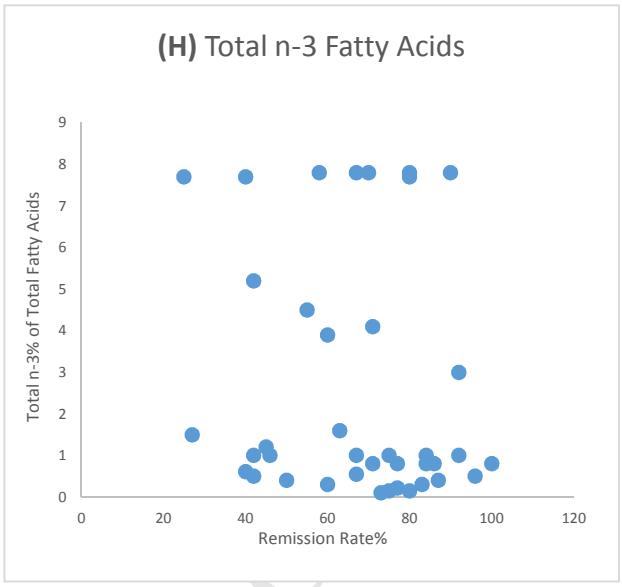
(C) Long Chain Triglycerides
LCT% of Total Calories
40
35
30
25
20
15
10
5
0
0
20
40
60
80
100
120
Remission Rate%


(D) Saturated Fatty Acids
Saturated Fatty Acids% of Total Calories
35
30
25
20
15
10
5
0
0
20
40
60
80
100
120
Remission Rate%


(E) Monounsaturated Fatty Acids
MUFA% of Total Calories
30
25
20
15
10
5
0
0
20
40
60
80
100
120
Remission Rate%


(F) Polyunsaturated Fatty Acids
PUFA% of Total Calories
20
18
16
14
12
10
8
6
4
2
0
0
20
40
60
80
100
120
Remission Rate%





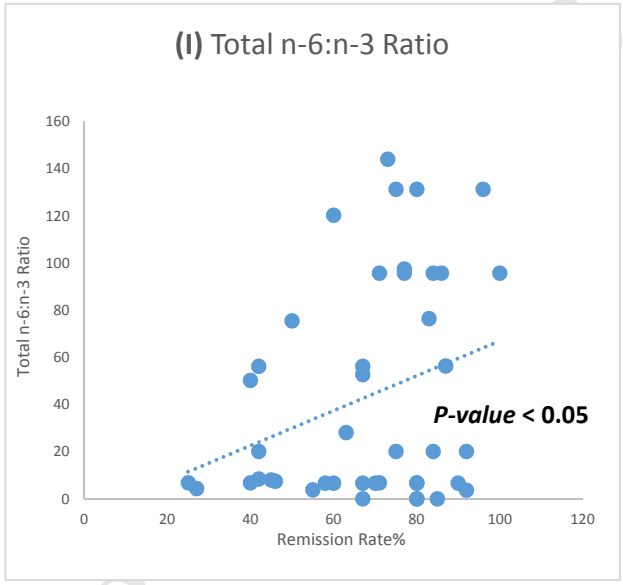


FIGURE 2: The association between fat composition of enteral nutritional feeds and remission rates (calculated based on per protocol analysis) in patients with Crohn's disease. Pearson correlation test was used to measure the strength of the correlation. **(A)** Total fat percentage (r= -0.176, P-value= 0.252). **(B)** Medium chain triglycerides (MCT) percentage (r= 0.072, P-value= 0.643). **(C)** Long chain triglycerides (LCT) percentage (r= -0.254, P-value= 0.096). **(D)** Saturated fatty acids (SFA) percentage (r= -0.007, P-value= 0.964). **(E)** Monounsaturated fatty acids (MUFA) percentage (r= -0.23, P-value= 0.13). **(F)** Polyunsaturated fatty acids (PUFA) percentage (r= -0.157, P-value= 0.308). **(G)** Total linoleic acid (n-6) percentage (r= 0.253, P-value= 0.110). **(H)** Total linolenic acid (n-3) percentage (r= -0.166, P-value= 0.313). **(I)** Total n-6:n-3 ratio (r= 0.378, P-value= 0.018*).

TABLE 1: Fat composition and remission rate for enteral nutritional formulas

Reference	Type of enteral nutrition	Energy Kcal/day	Fat% of total calories	Source of oil	LCT% of total calories	LCT% of total fat	MCT% of total calories	MCT% of total fat	SFA% of total calories	SFA% of total fat	MUFA% of total calories	MUFA% of total fat	PUFA% of total calories	PUFA% of total fat	Total n-6% of total fatty acids	Total n-3% of total fatty acids	n-6:n-3 Ratio	RR%
Bamba *et al.* (2003)[14]	Elemental, Low fat (6 packs of Elental + 6 packs of dextrin)	2400	1.15	Soybean oil	1.15	100	0	0	1.19	16.8	0.27	23.9	0.68	59.3	0	7.7	6.70	80
	Elemental, Medium fat (6 packs of Elental + 3 packs of dextrin+ 3 packs of C-1 dextrin)	2400	6.21	Soybean oil	6.21	100	0	0	1.04	16.8	1.48	23.9	3.68	59.3	51.6	7.7	6.70	40
	Elemental, High fat (6 packs of Elental + 6 packs of C-1 dextrin)	2400	11.27	Soybean oil	11.27	100	0	0	1.89	16.8	2.69	23.9	6.68	59.3	51.6	7.7	6.70	25
Gassull *et al.* (2002)[11]	Polymeric, high in n-9 MUFA	2307	32	Synthetic Trioleate	30.17	94.28	1.83	5.71	5.16	16.11	25.28	79	2.56	8	6.5	1.5	4.33	27
	Polymeric, high in n-6 PUFA	2266	32	Corn oil	30.17	94.28	1.83	5.71	7.94	24.8	9.02	28.2	14.91	46.6	45	1.6	28.13	63
Giaffer *et al.* (1990)[21]	Elemental (Vivonex)	2500	1.3	Safflower oil	1.3	100	0	0	0.12	9.1	0.18	13.9	1	77.3	76.5	0.8	95.63	86
	Polymeric (Fortison)	2500	36	Vegetable oil (canola & sunflower)	36	100	0	0	3.74	10.4	15.26	42.4	17.55	48.75	43.6	5.2	8.38	42
Leiper *et al.* (2001)[16]	Polymeric, 5% LCT	-	34.8	Soybean & coconut oils	5	13.8	29.8	86.2	30.69	88.2	1.18	3.4	2.92	8.4	7.4	1	7.40	46
	Polymeric, 30% LCT	-	34.8	Palm, Canola, and coconut oils	30	84.7	4.8	15.3	18.72	53.8	12.35	35.5	3.72	10.7	9.5	1.2	7.92	45
Mansfield *et al.* (1995)[22]	Elemental (E028)	2250	16	Arachis oil	16	100	0	0	2.72	17	8.96	56	4.16	26	20	1	20.00	42
	Semi-elemental (Pepti-2000 LF liquid)	2250	9	Corn (50%) & MCT oils	4.5	50	4.5	50	5.22	58	0.99	11	2.79	31	28.05	0.5	56.10	42
Middleton *et al.* (1995)[7]	Elemental (E028)	-	15.6	Arachis oil	15.6	100	0	0	2.65	17.1	8.88	56.9	4.06	26	20	1	20.00	92
	Elemental (E028), High LCT	-	35.6	Safflower & canola oils	35.6	100	0	0	3.95	11.1	23.92	67.2	7.73	21.7	17	4.5	3.78	55
	Elemental (E028), High MCT	-	31.6	Safflower, canola, and coconut oils	20.5	64.9	11.1	35.1	13.9	44	13.27	42	4.42	14	11	3	3.67	92
	Semi-elemental (Peptide 2+)	-	33.2	Corn & coconut oils	21.6	65	11.6	34.9	21.71	65.4	3.88	11.7	7.6	22.9	22.5	0.4	56.25	87
Park *et al.* (1991)[25]	Elemental (E028)	2266	16.47	Arachis oil	16.47	100	0	0	3.01	18.3	8.17	49.6	5.07	30.8	30.2	0.4	75.50	50
	Polymeric (Enteral 400)	2289	36	Arachis (75%) & MCT oils	27	75	9	25	14	38.9	13.57	37.7	8.42	23.4	22.9	0.3	76.33	83
Raouf *et al.* (1991)[30]	Elemental (EO28)	-	16.5	Arachis oil	16.5	100	0	0	2.82	17.1	9.39	56.9	4.29	26	20	1	20.00	75
	Polymeric (Triosorbon)	-	36	Sunflower (22%) & MCT oils	7.9	22	28.1	78	29.09	80.8	1.76	4.9	5.22	14.5	14.4	0.1	144.00	73
Rigaud *et al.* (1991)[13]	Elemental (Vivonex HN)	2286	0.8	Safflower oil	0.8	100	0	0	0.07	9.1	0.11	13.9	0.62	77.3	76.5	0.8	95.63	71
Royall *et al.* (1994)[23]	Elemental (Vivonex-TEN)	-	3	Safflower oil	3	100	0	0	0.27	9.1	0.42	13.9	2.32	77.3	76.5	0.8	95.63	84
	Semi-elemental (Peptamen)	-	33	Sunflower (30%) & MCT oil	10	30.3	23	69.7	24.37	73.84	2.22	6.72	6.53	19.8	19.68	0.15	131.20	75
Sakurai *et al.* (2002)[15]	Elemental, Low fat (Elental)	-	1.5	Soybean oil	1.5	100	0	0	0.24	15.7	0.36	24.2	0.9	59.8	52.1	7.8	6.68	67
	Semi-elemental, High MCT (Twinline)	-	25	Safflower & MCT oil (tricaprilin)	7	28	18	72	18.64	74.54	0.97	3.89	5.41	21.64	21.42	0.22	97.36	77
Verma *et al.* (2000)[31]	Elemental	2500	17	NS	11.05	65	5.95	35	6.63	39	7.82	46	2.55	15	12	-	-	80
	Polymeric	2500	17	NS	11.05	65	5.95	35	6.63	39	7.82	46	2.55	15	12	-	-	67
Gonzalez-Huix *et al.* (1993)[32]	Polymeric (Edanec HN)	2800	32	Olive oil (55%) & milk fat	27.8	87	4.2	13	13.12	41	13.12	41	5.76	18	-	-	-	80
Lindor *et al.* (1992)[28]	Semi-elemental (Vital HN)	-	9	Safflower (55%) & MCT (45%)	4.95	55	4.05	45	4.68	52.04	1.1	12.32	3.26	36.3	36.08	0.3	120.27	60
Lochs *et al.* (1991)[33]	Semi-elemental (Peptisorb)	-	8	Soybean oil (50%) & MCT	4	50	4	50	4.62	57.85	0.97	12.1	2.39	29.9	26.05	3.9	6.68	60
Malchow *et al.* (1990)[34]	Semi-elemental (Survimed)	-	10	Sunflower	10	100	0	0	1.28	12.8	2.24	22.4	6.6	66	65.6	0.5	131.20	96
Greenberg *et al.* (1988)[35]	Polymeric (Precision-Isotonic)	-	28	Soybean oil	28	100	0	0	4.4	15.7	6.8	24.2	16.7	59.8	52.1	7.8	6.68	58
Kobayashi *et al.* (1998)[36]	Elemental (Elental)	-	1.5	Soybean oil	1.5	100	0	0	0.24	15.7	0.36	24.2	0.9	59.8	52.1	7.8	6.68	70
	Polymeric (Clinimeal)	-	28	Corn & coconut oils	19.3	69	8.7	31.15	15	53.7	4.8	17.1	8.23	29.5	28.95	0.55	52.64	67
Mantzaris *et al.* (1996)[12]	Polymeric (Nutrison HE)	-	36	Corn, palm, & coconut oils	34.17	94.92	1.9	5.27	13.45	37.41	11.35	31.54	11.35	31.24	30.63	0.61	50.21	40
O'moráin *et al.* (1984)[37]	Elemental (Vivonex)	-	2.5	Safflower	2.5	100	0	0	0.23	9.1	0.35	13.9	1.9	77.3	76.5	0.8	95.63	100
Gorard *et al.* (1993)[38]	Elemental (Vivonex TEN)	2100	2.5	Safflower	2.5	100	0	0	0.23	9.1	0.35	13.9	1.9	77.3	76.5	0.8	95.63	77
Okada *et al.* (1990)[24]	Elemental (Elental)	-	1.5	Soybean	1.5	100	0	0	0.24	15.7	0.36	24.2	0.9	59.8	52.1	7.8	6.68	80
Bodemar *et al.* (1991)[18]	Polymeric (Semper lowfat)	-	20	Soybean	20	100	0	0	3	15.7	5	24.2	12	59.8	52.1	7.8	6.68	90
Coyle and Sladen (1989)[39]	Polymeric (Enteral 250)	2000-3000	28	Corn oil	28	100	0	0	4	14.8	8	28.1	16	57.1	56.1	1	56.10	67
Riordan *et al.* (1993)[19]	Elemental (E028)	-	15.6	Arachis oil	15.6	100	0	0	2.82	17.1	9.39	56.9	4.29	26	20	1	20.00	84
Guo *et al.* (2013)[40]	Polymeric (Nutrison Fiber)	1500-2000	34	Sunflower, canola, & MCT oils	29	84.6	5	15.4	8.7	25.6	19.2	56.4	6.12	18	-	-	-	85

Zoli *et al.* (1997)[20]	Semi-elemental (Peptamen)	-	33	Sunflower (30%) & MCT oil	10	30.3	23	69.7	24.37	73.84	2.22	6.72	6.53	19.8	19.68	0.15	131.20	80
Hu *et al.* (2014)[17]	Semi-elemental (Peptisorb liquid)	-	15	Soy oil % MCT oil	7.95	53	7.05	47	8.3	55.3	1.9	12.8	4.8	31.7	27.6	4.1	6.73	71
Zhu *et al.* (2013)[41]	Polymeric (Nutrison Fibre)	2037	34	Sunflower, canola, & MCT oils	29	84.6	5	15.4	8.7	25.6	19.2	56.4	6.12	18	-	-	-	67

TABLE 2: Subgrouping analysis for the effect of fat composition of enteral nutritional feeds on CD remission rate stratified by the level of lipid class

Factor assessed	Subgroup	Number of comparisons (compared enteral feeds)	Pooled RR (95% CI)
Total fat level	Low fat	11	74.09 (63.63, 84.56)
	Moderate fat	21	66.9 (57.53, 76.28)
	High fat	12	64.86 (53.34, 76.38)
MCT level	No MCT	22	69.59 (60.59, 78.59)
	Moderate MCT	10	56.93 (43.8, 70.06)
	High MCT	12	74.83 (67.32, 82.35)
LCT level	Low LCT	11	74.27 (64.1, 84.45)
	Moderate LCT	22	70.55 (62, 79.09)
	High LCT	11	57.21 (45.35, 69.07)
SFA level	Low SFA	11	77.36 (66.55, 88.18)
	Moderate SFA	22	62.83 (54.36, 71.31)
	High SFA	11	69.55 (57.47, 81.62)
MUFA level	Low MUFA	11	77.45 (70.25, 84.65)
	Moderate MUFA	21	65.29 (56.53, 74.05)
	High MUFA	12	64.61 (50.74, 78.48)
PUFA level	Low PUFA	12	76.83 (70.03, 83.63)
	Moderate PUFA	20	65.17 (56.02, 74.31)
	High PUFA	12	64.42 (50.46, 78.37)
Total n-6 level	Low n-6	11	65.45 (52.23, 78.68)
	Moderate n-6	18	61.11 (51.29, 70.93)*
	High n-6	12	78.83 (70.7, 86.97)*
Total n-3 level	Low n-3	10	72.3 (60.26, 84.34)
	Moderate n-3	19	67.84 (58.07, 77.62)
	High n-3	10	60.7 (45.96, 75.44)
n-6:n-3 level	Low n-6:n-3	10	67.9 (54.06, 81.74)
	Moderate n-6:n-3	18	58.94 (48.99, 68.9)*
	High n-6:n-3	11	79.91 (72.31, 87.51)*

-Low level (lower quartile range); moderate level (interquartile range); high level (upper quartile range).
-RR (remission rate); MCT (medium chain triglycerides); LCT (long chain triglycerides); SFA (saturated fatty acids); MUFA (monounsaturated fatty acids); PUFA (polyunsaturated fatty acids).
-One-way ANOVA with multiple correction test have been used to test the significance of difference in RR between the subgroups.
*Difference between subgroups is significant (P-value<0.05).

TABLE 3: Subgrouping analysis for the correlation between the fat composition of enteral nutritional feeds and CD remission rate stratified by the level of remission rates achieved

Factor assessed	Subgroup	Number of comparisons (compared enteral feeds)	r (95% CI)	P-value
RR for total fat correlation	Low RR < 70%	20	-0.03 (-0.46, 0.42)	0.91
	High RR ≥ 70%	24	-0.00 (-0.41, 0.40)	0.99
RR for MCT correlation	Low RR < 70%	20	0.05 (-0.39, -0.48)	0.83
	High RR ≥ 70%	24	-0.28 (-0.62, 0.14)	0.18
RR for LCT correlation	Low RR < 70%	20	-0.05 (-0.49, 0.39)	0.81
	High RR ≥ 70%	24	0.27 (-0.15, 0.60)	0.21
RR for SFA correlation	Low RR < 70%	20	-0.00 (-0.44, 0.44)	>0.99
	High RR ≥ 70%	24	-0.21 (-0.57, 0.21)	0.32
RR for MUFA correlation	Low RR < 70%	20	-0.16 (-0.56, 0.31)	0.51
	High RR ≥ 70%	24	0.23 (-0.19, 0.58)	0.29
RR for PUFA correlation	Low RR < 70%	20	0.13 (-0.33, 0.54)	0.57
	High RR ≥ 70%	24	0.24 (-0.18, 0.59)	0.26
RR for n-6 correlation	Low RR < 70%	19	0.19 (-0.29, 0.59)	0.44
	High RR ≥ 70%	22	0.19 (-0.26, 0.56)	0.41
RR for n-3 correlation	Low RR < 70%	18	-0.08 (-0.53, 0.39)	0.74
	High RR ≥ 70%	21	-0.13 (-0.53, 0.32)	0.59
RR for n-6:n-3 correlation	Low RR < 70%	18	0.30 (-0.19, 0.67)	0.22
	High RR ≥ 70%	21	-0.01 (-0.44, 0.43)	0.98

-r (Pearson correlation coefficient)
-RR (remission rate); MCT (medium chain triglycerides); LCT (long chain triglycerides); SFA (saturated fatty acids); MUFA (monounsaturated fatty acids); PUFA (polyunsaturated fatty acids).