Review

Enteral nutrition in adult Crohn's disease: Present status and perspectives

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Enteral nutrition has long been a therapeutic alternative often used in adult Crohn's disease patients to obtain remission or clinical response, especially in those not responding to conventional therapy such as corticosteroids. However, the increasing use of immunosuppressors (6-mercaptopurine and azathioprine, methotrexate, *etc*.), and the advent of biotherapies (especially anti-tumor necrosis factor-alpha (TNF-α) antibodies), decreased its use in adult Crohn's disease. Nevertheless, enteral nutrition remains of interest in patients presenting concomitant malnutrition (in particular in nonobstructed patients needing surgery), or in those intolerant or who failed to other therapeutics. In addition, recent studies provide data indicating its potential interest in maintenance therapy in selected patients groups. Finally, future research (in particular in the field of immuno- or pharmaconutrition) could lead to enteral formula's improvement, with better tolerance and acceptability, as well as increased efficacy.

Keywords: Crohn's disease / Enteral nutrition / Malnutrition / Pharmaconutrition / Treatment

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1 Introduction

Crohn's disease (CD) is a chronic granulomatous transmural inflammatory process of the digestive tract. Together with ulcerative colitis, it belongs to the inflammatory bowel disease (IBD) family. Usually, CD clinical picture alternates remission phases (where the disease is quiescent) and active disease phases (relapse), characterized by general and intestinal disabling symptoms (*e.g*., fatigue, weight loss, abdominal pain, diarrhea, recurrent subocclusive episodes, complete obstruction requiring surgery, *etc*.), and subsequent alteration of quality of life and/or repeated hospitalization [1]. In the high incidence countries (North America and Europe), IBD affects approximately 2 million people, and it is noteworthy that in the last few decades, CD incidence continues to increase in these countries, and progresses in regions where it has been less commonly described until now [2]. CD pathogenesis is only partly understood. Whereas normally, intestinal mucosal inflammatory and immune response is tightly regulated, keeping a balance between immune effectors and regulators which results in the maintenance of gut homeostasis, in CD, the intestinal inflammatory and immune response appears deregulated [3, 4], as a result of a complex interaction between genetic predisposition [5] and environmental factors (in particular enteric bacteria, either from the nonpathogenic bacterial gut flora, or by (a) pathogenic bacterial microorganism(s)) [6].

Nutritional deficiency occurs frequently in CD, affecting both patients in remission (where usually macronutrient needs are covered by food intake, but where micronutrient deficiencies are frequent) [7], and patients with active disease [8–10] (Table 1). In contrast to the results published in the 1970s and the 1980s, today, severe global malnutrition is rare: in a prospective French series including 600 CD

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Abbreviations: CD, Crohn's disease; **EN,** enteral nutrition; **IBD,** inflammatory bowel disease; **IL,** interleukin; **LCT,** long-chain triacylglycerol; **MCT,** medium-chain triacylglycerol; **PUFA,** polyunsaturated fatty acid; **TGF-β**, transforming growth factor-beta 2; **TNF**-α, tumor necrosis factor-alpha

Table 1. Usual nutritional deficiencies reported in CD patients (adapted from Han *et al.* [9])[a)]

	Hospitalized[a)] (%)	Outpatients[a)] (%)	Recent results by Filippi *et al.* [7][b)] (%)
Weight loss	65–75	54	ND
Hypoalbuminaemia	25–80	0	ND
Anaemia	60–80	54	ND
Iron deficiency	25–50	37–53	36
Folic acid deficiency	56–62	10	25
Vitamin B12 deficiency	48	3–4	36
Calcium deficiency	13	ND[c)]	6
Magnesium deficiency	14–33	ND	2
Vitamin A deficiency	11–50	ND	0
Vitamin D deficiency	23–75	NR[d)]	8
Vitamin E deficiency	NR	ND	12
Vitamin K deficiency	NR	ND	ND
Zinc deficiency	40	1	64
Copper deficiency	ND	1–3	83
Selenium deficiency	NR	NR	ND

a) Adapted from Han *et al.* [9] which reported these data from studies published in the 1980s and early 1990s, and recent results by Filippi *et al.* [7].
b) Adult Crohn's disease patients in remission.
c) Not determined.
d) Described but frequency not reported.

patients with moderately active disease, only 6.6% of patients had a body mass index (BMI) <17, and enteral nutrition (EN) was necessary for isolated nutritional purpose in only two patients [11]. Actually, nutritional deficiencies affect principally micronutrients including vitamins (*e.g.*, vitamin D, vitamin B12, and folic acid) and mineral or trace elements (*e.g.*, iron, calcium, selenium, and zinc). Many factors contribute to malnutrition in CD including (i) poor dietary intake due to anorexia, nausea and vomiting, fasting for tests, (ii) increased nutrient losses by diarrhea, protein-loosing enteropathy, fistulae, (iii) increased nutrient requirements by inflammation, (iv) nutrient malabsorption secondary to inflammation, surgery, short bowel syndrome, transient lactose intolerance or malabsorption, bacterial overgrowth, and (v) medical therapy (*e.g.*, corticosteroids [12, 13], methotrexate, sulfasalazine) (Table 2).

Malnutrition worsens the course of the disease, as the multiple (macronutrient and micronutrient) deficiencies participate in impaired inflammatory and immune intestinal response [14], and contribute to decreased quality of life [15].

This review will summarize the available data reporting efficacy and tolerance of EN, research perspectives, and discuss its current role in the management of adult CD.

2 Enteral nutrition mode of action

Soon after the introduction of EN as a treatment in CD, it appears that, despite nutritional status is usually a component of CD activity scores, the clinical improvement reported in CD patients receiving EN could not only result from its effects on nutritional status. Actually, it is well-known that dietary [16] or microbial constituents of intestinal lumen alter the expression of molecules in intestinal epithelial cells, thereby interfering with the intestinal inflammatory and immune response. In fact, several studies have shown that EN formulas (including standard formulas) may decrease systemic inflammatory markers [17–19], and directly affect intestinal inflammation by regulating gene expression in the gut epithelium [14, 20], as well as modulating intestinal inflammatory and immune mediators production [14, 20–24]. Concerning dietary factors, most recent research has focused on the role of lipids. Dietary lipids can modulate inflammation by influencing production of cytokines and eicosanoids. As an example, ω-6 polyunsaturated fatty acids (*n*-6 PUFAs) are precursors of arachidonic acid (AA), an important substrate for proinflammatory eicosanoids production, in contrast to *n*-3 PUFAs, which inhibit AA production and protein kinase C activity needed for tumor necrosis factor-alpha (TNF-α) release from macrophages, suggesting that a relative increase in *n*-3 PUFAs might negatively regulate intestinal inflammatory and immune response. Recently, Whiting *et al.* [25] examined this hypothesis in a mouse model of CD. Mice with severe combined immune deficiency (SCID) were fed orally either by a standard diet or by a diet enriched in *n*-3 PUFAs both before and following induction of colitis by injection of $CD4^+$ $CD45RB^{high}$ T cells. Animals fed with a *n*-3-enriched diet had similar immune cell infiltration than those fed with the standard diet, but they had significantly reduced disease scores, reduced neutrophil infiltration, and lower mucosal concentrations of proinflammatory cytokines: TNF-α, interleukin (IL)-1β and IL-12. Expression of

Table 2. Causes of malnutrition in Crohn's disease patients

Decrease in dietary intake
Disease- and/or drug-induced anorexia, abdominal pain, diarrhoea, nausea and/or vomiting, poor appetite, deliberate alimentary restriction
Malabsorption
Extensive small bowel involvement and/or small bowel resections (short bowel syndrome), bacterial overgrowth, bile salts malabsorption, drug-related malabsorption (see below)
Increased nutrient loss
Diarrhoea, vomiting, entero-cutaneous or entero-colonic fistulas, protein-loosing enteropathy
Altered energy (and protein) metabolism
Chronic inflammation, fistulas, corticosteroids
Medications
Corticosteroids (inhibit intestinal calcium absorption, increase renal magnesium excretion), methotrexate (inhibits folic acid metabolism), salazopyrine (inhibits folate intestinal transport), cholestyramine (inhibits liposoluble vitamins absorption)

Table 3. Randomized studies comparing EN to corticosteroids as induction treatment in adult Crohn's disease patients

Authors	References	Patient populations and study treatments	Study duration (weeks)	Clinical remission or response at the end of the trial[a)]		
Malchow *et al.* (1990)	[35]	Semi-elemental EN, $n = 51$	6	21/51	41%	$p < 0.05$
		6-Methylprednisolone 48 mg/day progressively decreasing, $n = 44$		32/44	73%	
Lochs *et al.* (1991)	[33]	Semi-elemental EN, $n = 55$	4	29/55	53%	$p < 0.01$
		6-Methylprednisolone 48 mg/day progressively decreasing, $n = 52$		44/2	85	
Lindor *et al.* (1992)	[36]	Semi-elemental EN, $n = 9$	4	3/9	33%	p = NS
		Prednisone 0.75 mg/kg/day, $n = 10$		7/10	70%	
		Semi-elemental + prednisone		6/8	75%	
Gonzalez-Huix *et al.* (1993)	[37]	Polymeric EN, $n = 15$	4	12/15	80%	p = NS
		Prednisone 1 mg/kg/day, $n = 17$		15/17	88%	
Gorard *et al.* (1993)	[27]	Elemental EN, $n = 22$	4	10/22	45%	$p < 0.01$
		Prednisolone 0.75 mg/kg/day, $n = 20$		17/20	85%	

a) Treatment criteria (disease activity scores, definition of clinical remission and clinical response) differ from one study to another.

epithelial tight junction protein ZO-1 (a marker of intestinal permeability) was also better preserved, suggesting improved epithelial barrier function.

It has also been suggested that EN might have effects on the gut microbial flora. A recent small study [26] among children with CD showed that the enteric microflora is modified during and after a course of exclusive EN. However, it is not clear, whether the observed changes in the intestinal flora occur as a direct response to EN, or as a consequence of decreased inflammation induced by EN.

3 Enteral nutrition to induce clinical remission

The first studies evaluating the effectiveness of EN as a primary therapy in active adult CD have been published in the early 1970s. Since that time, numerous authors have reported their results with remission rates varying considerably, between 20 and 84.2%, roughly 60% on average (*i.e.*, about two times higher than that obtained by placebo in most of the clinical trials in CD), despite no study compared EN to placebo. This range in efficacy has to be considered in the light of differences in study populations (*e.g.*, disease activity at inclusion, concomitant therapy or not with 5-aminosalicylates or antibiotics), type of diet (elemental, semi-elemental, polymeric) and route of administration (nasogastric feeding tube, oral route), outcome assessments, and methodology (*e.g.*, sample size, many studies being performed in small-sized populations, blinding, randomization). In addition, tolerance and drop out due to poor acceptance (in some studies up to 41% of patients randomized to receive EN [27]) have not been assessed and taken into account for data interpretation.

General conclusions can be drawn from randomized controlled trials (RCT), summarized in five meta-analysis [28 – 32]: (i) EN as primary therapy is an effective therapeutic tool in moderately active CD, inducing remission in 50 – 70% of patients (after 3 – 6 wk of treatment), (ii) in adult CD patients, EN is as effective as parenteral nutrition, but

Table 4. Randomized studies comparing different EN formulas

Authors	References	Patient populations and study treatments	Study duration (weeks)	Clinical remission or response at the end of the trial[a]	
Giaffer *et al.* (1990)	[42]	Elemental EN[b], $n = 19$	10 days	14/19	75%
		Polymeric EN, $n = 21$		8/21	36%
Rigaud *et al.* (1991)	[43]	Elemental EN, $n = 15$	4	10/15	67%
		Polymeric EN, $n = 15$		11/15	73%
Raouf *et al.* (1991)	[44]	Elemental EN, $n = 13$	3	9/13	69%
		Polymeric EN, $n = 11$		8/11	73%
Park *et al.* (1991)	[45]	Elemental EN, $n = 7$	4	2/7	29%
		Polymeric EN, $n = 7$		5/7	71%
Royall *et al.* (1994)	[46]	Elemental EN, $n = 19$	3	16/19	84%
		Semi-elemental EN, $n = 21$		15/21	71%
Middleton *et al.* (1995)	[47]	Elemental EN, $n = 17$	3	12/13[e]	92%
		Elemental EN-enriched with LCTs[c], $n = 22$		11/20	55%[f]
		Semi-elemental EN, $n = 18$		13/15	87%
		Elemental EN enriched with MCTs[d], $n = 19$		13/14	92%
Mansfield *et al.* (1995)	[41]	Elemental EN, $n = 22$	3	8/22	36%
		Semi-elemental EN, $n = 22$		8/22	36%
Verma *et al.* (2000)	[39, 68]	Elemental EN, $n = 10$	4	8/10	80%
		Polymeric EN, $n = 11$		6/11	55%
Sakurai T *et al.* (2002)	[48]	Elemental EN, $n = 18$	6	12/18	67%
		Semi-elemental EN-enriched with MCTs, $n = 18$		13/18	72%

a) Treatment criteria (disease activity scores, definition of clinical remission, and clinical response) differ from one study to another.
b) Enteral nutrition.
c) Long-chain triacylglycerols.
d) Medium-chain triacylglycerols.
e) Presented results only include those of patients achieving the daily energy target (at least 75% of basal energy requirement)
f) Remission rate was negatively correlated to the energy amount provided by LCTs ($r = -0.97$, $p = 0.016$)

less effective than systemic corticosteroids [27, 33–38] (Table 3), (iii) nonelemental diets are as effective as elemental formulas, or medium-chain triacylglycerol (MCT)-enriched formulas [39–48] (Table 4). As with all therapies, response rates may vary according patient's characteristics: in the case of EN, response rates seem to be higher in the setting of CD patients presenting recent-onset disease [29, 49], and it has been suggested that patients with CD affecting the small intestine respond better than those with isolated colonic location of the disease [50]; this has been particularly suggested in pediatric series and remains to be definitively proven in adult CD patients.

EN has also been suggested to be a therapeutic alternative in corticosteroid-dependent CD patients. However, few studies, all retrospective, evaluated EN in this patients setting; they report clinical response in 71–90% of patients [51–55].

Despite EN is largely free from significant side effects, one of its most important drawbacks in clinical trials but also in clinical practice, is represented by its acceptance. Intolerance has been reported in clinical studies providing EN by oral route in 18–41% of CD patients [17, 27, 36], the pooled odds ratio related to acceptance of EN compared to corticosteroid therapy, reported in Griffith's meta-analysis, being 0.57 (95% CI: 0.35–0.94) [28]. This results, at least in part, from the poor palatability of the used formulas, mainly elemental diets. However, in recent years, this point benefited from ongoing research, leading to improvement of the palatability of some products, and as a consequence, to a better acceptance of EN [56].

4 Enteral nutrition as maintenance therapy in Crohn's disease

Beside induction of remission, CD treatment has a second objective, sometimes difficult to obtain: *i.e.*, remission maintenance, ideally without any corticosteroids and as long as possible. Remission maintenance ameliorates not only patient's physical status, but also health-related quality of life [57]. After remission has been obtained by induction treatment, many patients continue to have frequent relapses or continuous periods of active disease in the absence of any maintenance treatment. For example, during the first year following diagnosis, up to a third of patients have active disease [58, 59], and after surgical resection, approximately 75% of patients have new endoscopic lesions at 1 year [60] with a reoperation risk varying between 20 and 70% depending mainly on the follow-up time [61]. Therefore, a number of treatments have been proposed and are used in clinical practice to maintain remission, most of them being immunosuppressors (*e.g.*, purine analogues and

Table 5. Recent studies evaluating EN as maintenance treatment in adult Crohn's disease patients

Authors and type of study	References	Patient populations and study treatments	Study duration (months)	Clinical recurrence		
After remission has been obtained by medical treatment						
Verma *et al.* (2000) Prospective, not randomized	[39, 68]	Supplement oral elemental diet, $n = 51$	12	11/21	52%	$p < 0.0003$
		No supplemental EN[a], $n = 18$		14/18	78%	
Takagi *et al.* (2006) Prospective, randomized	[71]	Supplemental oral or NGF[b] half elemental diet + mesalazine (MSZ, 2.25–3 g/day), $n = 26$	24	9/26	35%	Significant[c]
		No supplemental EN + MSZ, $n = 25$		16/25	64%	
Yamamoto *et al.* (2007) Prospective, not randomized[d]	[24, 72]	Supplement elemental diet (NGF) + MSZ (3 g/day), $n = 20$	12	5/20	25%	$p < 0.03$
		No supplemental EN + MSZ, $n = 20$		13/20	65%	
After remission has been obtained by surgery						
Esaki *et al.* (2005) Prospective, not randomized[e]	[70]	EN > 1200 kcal/day[f], $n = 24$	6–83	11/24	46%	$p = 0.017$
		EN < 1200 kcal/day[e], $n = 16$		12/16	75%	
Yamamoto *et al.* (2005) Prospective, not randomized[d]	[74]	Supplement elemental diet (NGF) + MSZ (3 g/day), $n = 20$	12	1/20	5%	$p = 0.048$
		No supplemental EN + MSZ, $n = 20$		7/20	35%	

a) "Enteral" nutrition (feeding using EN diets).
b) Nocturnal administration by self-inserted naso-gastric tube feeding.
c) Hazard ratio: 0.40 (95% CI: 0.16–0.98).
d) Patients assigned to the EN group were those showing a good compliance to EN before study started.
e) Groups have been defined regarding each patients' ability to achieved or not a supplemental EN > 1200 kcal/day.
f) Most patients were on polymeric diet, some on elemental diet.

methotrexate) or biologicals (*i.e.*, anti-TNF-α antibodies) [62]. However, they have their limitations: in particular, potentially serious adverse events may occur with these medications [62]. Therefore, "the notion that EN may be effective for maintenance of remission is an attractive proposition" [63], as additionally, quality of life in the long-term depends also on nutritional status [64].

Few studies have explored the efficacy of EN as maintenance treatment in CD (Table 5). They are heterogeneous, in particular as the type of diets used vary from one study to another. One common feature of all studies is that EN was used in addition to normal food intake (representing at least 50% of total calorie intake), either as a nightly tube feeding, or as an oral supplement [24, 65–72]. Recent controlled studies include those of Verma *et al*. [68], Takagi *et al*. [71] and Yamamoto *et al*. [24], related to maintenance after remission induction has been obtained by medical treatment, and those of Esaki *et al*. [70] and Yamamoto *et al*. [72] after surgical resection. All studies demonstrate a benefit of EN support in addition to normal diet. In the study by Verma *et al*. [39] CD patients with quiescent disease (CDAI < 150) at the time of inclusion (and a documented clinical relapse within the preceding 12 months) were given the choice to continue on normal unrestricted and unsupplemented diet ($n = 18$) in addition to their usual medication, or to receive a nutritional supplementation by an elemental diet taken orally ($n = 21$) in an amount providing 35–50% of the estimated pretrial total calorie intake, in addition to their normal diet and to their usual medication [68]. A total of 17 patients (81%) tolerated the nutritional supplementation. On an intention-to-treat (ITT) basis, 48% remain in remission at 12 months compared to 22% of those in the control group ($p < 0.0003$) [68]. Takagi *et al*. [71] randomized 51 CD patients in remission to receive either a nutritional supplementation by a half elemental diet providing 50% of their calorie requirements ($n = 26$) (in addition to normal diet and usual medication), or a normal diet and their usual medication ($n = 25$). The mean overall follow-up was 11.9 months (1–29 months). Nine patients in the half elemental diet group (34.6%) relapsed compared to 16 in the free diet group (64%) with a hazard ratio of 0.40 (95% CI: 0.16–0.98) [71]. In the third study, 40 patients were included, all in clinical remission since less than 8 wk (CDAI < 150) after medical treatment; in addition, patients have experienced EN at least one time before inclusion, in order to improve compliance during the study period [24]. As the trial was not randomized, 20 patients which had showed a good

compliance to EN during a previous treatment regimen with EN, were assigned (with their agreement) to receive an isocaloric elemental diet (1200 – 1800 mL/day, representing about 50% of the daily calories intake) provided by an overnight (6 – 10 h) continuous infusion through a self-inserted nasogastric feeding tube, in addition to a daily low-fat diet and 3 g/day of mesalazine [24]. The second group of 20 patients (controls) characterized by their previous limited compliance to EN, received neither nutritional therapy nor food restriction, but took 3 g/day of mesalazine as in the EN group [24]. In contrast to the two other studies no patient from both groups received any other medical treatments (except in case of clinical relapse) [24]. Probably due to their patient's selection procedure, only two patients in the EN group dropped out during the 1 year study time (10%). On ITT basis, five patients in the EN group relapsed (25%) compared to 13 in the control group (65%; odds ratio: 5.6, $p < 0.03$). In addition to clinical assessment, the authors performed also endoscopic grading at study entry, and after 6 and 12 months: at 12 months, the mean (± standard error) grading (according to Wardle *et al.*, ref. [73]) was of 1.25 ± 0.25 in the EN group *versus* 2.00 ± 0.26 in the control group ($p < 0.04$), with scores at entry of 0.95 ± 0.22 and 0.85 ± 0.22 ($p = 0.75$), respectively [24]. Finally, mucosal IL-1β, IL-6 and TNF-α concentrations which do not differ at inclusion between the two groups, were significantly higher in the control group at 6 and 12 months compared to the EN group were they remain stable during the whole study period [24]. Two other studies (both performed in Japan) evaluate the effect of EN supplementation on postoperative recurrence [70, 72]. Esaki *et al*. [70] reported a decrease in postoperative recurrence in 21 patients taking more than 1200 kcal/day of EN compared to 18 patients who did not reach an intake of 1200 kcal/day of EN; EN reduced the cumulative rate of postoperative relapse ($p = 0.017$), especially in those with penetrating type of disease ($p = 0.005$), in those who did not have colitis ($p = 0.051$), and in patients who did not have active mucosal lesions at intra-operative endoscopy exploring the remaining small bowel ($p = 0.02$). Yamamoto *et al*. [70] performed a prospective nonrandomized parallel, controlled trial, where 20 patients with high compliance to EN during the immediate postoperative period continued long-term EN (nocturnal elemental diet infusion), in addition to a low fat diet in the daytime and 3 g/day of mesalazine, and 20 patients showing low compliance to EN during the immediate postoperative period, where allowed to have an unrestricted food intake in addition to 3 g/day of mesalazine. In this study, no patient dropped out in the EN group, clinical recurrence after 1 year occurred in one patient (5%) in the EN group *versus* seven patients (35%, $p = 0.048$) in the nonEN group, endoscopic recurrence after 6 months following surgery in five patients (25%) *versus* eight (40%, $p = 0.50$), respectively, and 5 (25%) *versus* 14 (70%, $p = 0.027$), respectively after 12 months [72].

These different trials clearly suggest that in selected CD patients supplemental EN could represent an interesting alternative as a maintenance treatment. In fact, there is no direct comparison of supplemental EN to the drugs usually advocated to help to maintain remission, but the reported results with supplemental EN (in combination at least to 5-aminosalicylates) compare quite favorably to current drug therapy, and in particular appears significantly more effective than 5-aminosalicylates alone. Interestingly, impact of long-term supplemental EN on mucosal healing and cytokine levels indicate that EN is active *per se* and that decreased relapse rates in EN groups are not only the consequence of symptomatic effects [24, 72]. These observations, which confirm other recent published data in adults or children [74, 75], may keep the attention of investigators, as mucosal healing appears more and more as an ideal (unfortunately difficult to achieve) goal for maintenance treatment in IBD [76].

Although most studies used elemental formulas, type of provided diet (elemental *versus* half elemental *versus* polymeric, no study investigating *n*-3-enriched EN formula) seems not to influence clinical response. As an example, Verma *et al*. [69] compared 19 corticosteroid-dependent CD patients randomized to receive elemental EN to 14 corticosteroid-dependent CD patients receiving polymeric diet as maintenance treatment. EN was given as a supplement in amounts between 33 and 50% of pretrial caloric intake [69]. In the elemental EN group, 42% of patients remained in remission at 1 year compared to 43% in the polymeric diet group.

5 Perspectives for enteral nutrition in Crohn's disease patients

In the recent years, a number of specific dietary agents such as particular lipids, selected amino acids (especially arginine and glutamine), *etc*., have been suggested to improve the efficacy and/or metabolic tolerance of EN leading to the concept of pharmaconutrition. The hypotheses of a benefit of specific EN formulas have also been tested in some studies in CD patients.

5.1 Lipid composition

Until now, lipids have been the most studied dietary component as potential pharmaconutrients, as they may influence a series of cellular and molecular pathways involved in the inflammatory and immune response. A detailed review of their close interplay with inflammation and immunity is available elsewhere in this issue [77]. Despite an increasing number of *in vitro* studies in animals and humans as well as *in vivo* studies in animal models of experimental colitis,

only few results are available in clinical practice. Three randomized studies tried to prove a relationship between the efficacy of EN and its lipid content and/or composition [48, 78]. The first study provided in adult CD patients compared the short-term therapeutic efficacy of an EN formula containing 3.4 g of fat per 2000 kcal-dose of MCTs to a formula with high MCTs content (55.6 g of fat *per* 2000 kcal-dose) in 36 active CD patients (CDAI > 150) [48]. This prospective, randomized, controlled trial did not show any difference in response rates at 6 wk between the two groups (67 *versus* 72%, not significant) [48]. A second study compared three therapeutic regimens in 62 CD patients with active disease: a polymeric enteral diet containing 35 g of lipids *per* 1000 kcal-dose, high in oleate (79%) and low in linoleate (6.5%), an EN formula identical in composition except for the type of fat which was high in linoleate (45%) and low in oleate (28%), or oral prednisone (1 mg/kg/day) [78]. Diets were double blindly administered. After excluding patients who were not compliant to treatment, the investigators showed that the remission rate at 4 wk was significantly lower in patients receiving the high oleate/low linoleate diet (27% compared to 63% in the low oleate/high linoleate group, and 79% in patients on prednisone; $p < 0.008$) [78]. Finally, Bamba *et al*. [79] evaluate three different EN formulas varying in their long-chain triacylglycerols (LCTs) content, for inducing remission at 4 wk in adult CD patients with active disease ($n = 10$ in each group). The three diets were identical in respect to total calorie amount and nitrogen source and amount, but vary in the proportion of energy provided from fat: 1% (3.06 g/day; low-fat group), 6% (16.56 g/day; medium-fat group), and 11% (30.06 g/day; high-fat group) of soybean oil, with the principal fatty acids being *n*-9 PUFAs (24% of oleic acid) and *n*-6 PUFAs (52% of linoleic acid) [79]. The authors showed that clinical remission (assessed by the International Organization of IBD rating, a clinical index very rarely used), but not markers of inflammation (CRP and erythrocyte sedimentation rate), was significantly higher in the low-fat group (80%), than in the medium-fat (40%), or high-fat (25%) groups ($p = 0.048$) [79]. They conclude that a high amount of LCTs as energy source in EN for active CD treatment decreased its therapeutic effect [79]. Taken together, these results suggest that the type of lipids in EN may be of importance in inducing remission in CD, and (i) that high provision of LCTs may be deleterious, and/or (ii) that an excess of synthetic oleate may preclude this effect or even be detrimental in these patients. Unfortunately, no other studies addressing specifically the question of fat content have been published, but data from seven trials of EN in CD, analyzed together by Zachos *et al*. [32] in their *Cochrane* meta-analysis, showed a non significant trend favoring very low fat (<3 g/1000 kcal) and/or very low LCTs EN formulas. Nevertheless, larger trials are required to provide more data before to conclude definitively. Moreover, the conclusions on LCTs should take into account that the predominant LCTs used were from the *n*-6 (more than 50%) and the *n*-9 series. Unfortunately, despite numerous experimental data suggesting an anti-inflammatory and immune-modulating effect of *n*-3 PUFAs, no clinical trial has been performed to explore the potential therapeutic effect of *n*-3 PUFAs-enriched EN in CD. Therefore, observations concerning the negative effects of *n*-6 and/or *n*-9 PUFAs cannot be extrapolated to *n*-3 PUFAs. Further research is urgently needed in that specific field.

5.2 Glutamine

Some amino acids with specific immunomodulatory properties have been suggested as potential therapeutic tools in intestinal inflammation and other clinical conditions (Cöeffier, M., Marion-Letellier, R., Déchelotte, P., submitted). Among these amino acids, glutamine has been the most studied. It is considered as a conditionally essential amino acid, and experimental studies have shown that it plays an important role in maintaining gut functional integrity [80]. In addition, it is used at a high rate not only by enterocytes (glutamine represents the preferred energy source of enterocytes), but also by cells of the immune system [81], therefore potentially influencing the inflammatory and immune response [82]. In CD, intestinal glutamine levels and glutaminase activity have been found to be decreased, suggesting that glutamine supplementation may be a tool in CD treatment [83]. However, until now, two studies comparing glutamine-enriched formulae to standard formulae in CD did not show any significant decrease in disease activity or improvement of biological parameters, neither in children [84], nor in adults [85].

5.3 Transforming growth factor-beta 2 (TGF β-2) enrichment

TGF-β2 is a regulatory cytokine which down-regulates the production of a panel of inflammatory cytokines such as TNF-α, IL-1β, IL-6, or IL-8. Therefore, it has been used in a TGF-β2-enriched EN formula (Modulen IBD®, Nestlé, Vevey, Switzerland), and first showed a clinical efficacy and tolerance in an open trial performed in childhood CD [22, 56]. In addition to its clinical effects [22, 56, 86, 87], Modulen IBD shows also a reduction of endoscopic and histological mucosal inflammation as well as (i) a downregulation of proinflammatory cytokines (IL-1β and interferon-γ in the ileum, IL-1β and IL-8 in the colon [22, 56], and (ii) an increase in regulatory cytokine TGF-β mRNA in the ileum of pediatric CD patients [22]. As stated above, some positive clinical results have been published [22, 56, 86, 87]; in 45 adult CD patients (the majority being resistant or intolerant to corticosteroids, immunosuppressants or infliximab), a retrospective study by Ramirez *et al*. [86] showed a 50% clinical remission rates, more often in those with severe acute attacks than in those with chronic active dis-

ease. Nevertheless, until now, the real efficacy and the place for Modulen IBD in the CD treatment strategy remain to be definitively validated and defined, in particular in adults.

6 Conclusion

Despite the increasing use of immunosuppressants in CD patients, and the efficacy of new generation biotherapies, EN still kept a role in the management of adult CD. It should be used as early as possible in malnourished CD patients (who do not exhibit clinical signs of obstruction), in particular if surgery is planed. In situations where other treatments are contra-indicated, or in the case of resistance to other therapies, EN can also be a therapeutic alternative. Finally, recent data suggest a possible role for EN as adjunctive treatment in long-term maintenance in CD, a new direction for therapeutic research in adults CD.

In the future, improvement of formula's composition could lead to a greater acceptability of EN in the short- and long-term, and, with the use of immune modulating nutrients (specific series of lipids, immunomodulatory amino acids, *etc*.), may result in better efficacy.

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