

## *A randomized controlled study comparing elemental diet and steroid treatment in Crohn's disease*

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### SUMMARY

*Background:* Elemental diet is considered an effective primary treatment for active Crohn's disease, but it is usually given by a feeding tube.

*Methods:* Twenty-two patients (12 males, median age 30 years, range 18–60) with moderately active Crohn's disease were enrolled in a randomized study in which the efficacy of an elemental diet administered orally was compared to high-dose corticosteroids in achieving clinical and laboratory remission. Ten patients were treated by oral elemental diet (Peptamen, Clintec, USA) and 10 received corticosteroids. Both treatment regimens lasted 2 weeks. The two groups did not differ with respect to age, sex, body weight, location of disease, treatment or disease activity prior to the study. In all patients studied, simple Crohn's disease activity index, nutritional status (expressed as body mass index), percentage of ideal body weight, fat mass, fat free mass,

erythrocyte sedimentation rate, interleukin-6, intestinal permeability (expressed as permeability index), prealbumin, retinol binding protein and multiskin test were evaluated before and after treatment.

*Results:* After 2 weeks of treatment, there were significant improvements in simple Crohn's disease activity index, erythrocyte sedimentation rate, permeability index, body mass index, prealbumin, retinol binding protein and multiskin test in the elemental diet group. There were significant improvements in simple Crohn's disease activity index and fat free mass in the corticosteroid group.

*Conclusions:* These data suggest that, in the short term, an oral elemental diet is at least as effective as steroids in inducing remission of mild-moderately active Crohn's disease, but it may be more effective in improving the nutritional status of these patients, probably through a more rapid restoration of normal intestinal permeability.

### INTRODUCTION

Of the many nutritional disturbances seen in patients with active inflammatory bowel disease, weight loss and emaciation are among the most commonly described.<sup>1</sup> Furthermore, undernutrition is most often evident when the disease is active. Defined formula diets were initially used for Crohn's disease in the early 1970s as nutritional support before intestinal surgery.<sup>2–4</sup> The treatment not only improved the nutritional status of

patients, but also induced remission from disease activity.<sup>5–7</sup> Subsequently, elemental diets were shown to be as successful as corticosteroids<sup>8,9</sup> and total parenteral nutrition<sup>10</sup> in promoting remission of clinical activity of the disease. Although the mechanism is unknown, it has been shown that treatment with an elemental diet reduces intestinal inflammation<sup>11</sup> and protein loss<sup>12</sup> and restores the intestinal mucosal barrier function.<sup>13</sup> However, despite its efficacy and lack of serious side-effects, elemental diet is not widely used for treatment of active Crohn's disease, partly because of its poor palatability, which in most cases requires enteral administration, and partly because of the considerable

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effort required of patients, dieticians and physicians.<sup>14, 15</sup> For these reasons, patients usually need to stay in hospital for at least a few days to start the treatment, and it is not unusual that, once back home, they stop the treatment.

In this prospective randomized study, we evaluated the effect on nutritional status, disease activity and intestinal permeability of an elemental diet eaten at home, with added flavours, in 10 patients who attended the clinic compared with 10 patients treated with steroids.

## PATIENTS AND METHODS

### Patients

Twenty-two consecutive patients (12 males, median age 30 years, range 18–60) attending the clinic because of active Crohn's disease were initially included in the study. The diagnosis of Crohn's disease was made by colonoscopy with biopsy or characteristic radiological appearances on barium studies. The subjects were randomized into two treatment groups: group A, receiving oral elemental diet; and group B, treated with oral corticosteroids. Patients in group A received a peptide-based elemental diet orally (Peptamen, Clintec, USA) (see Table 1 for composition). Patients in group B received 0.5 mg/kg/day prednisolone,

Table 1. Composition of peptide-based elemental diet (100 mL)

Energy	kcal	100
	kJ	418
Proteins	g	4
Fat	g	3.9
Carbohydrate	g	12.6
Minerals	g	0.65
H <sub>2</sub> O	g	84.75
Na	mg (mmol)	50 (2.2)
K	mg (mmol)	125 (3.2)
Cl	mg	100
Ca	mg	60
P	mg	50
Mg	mg	30
Fe	mg	0.9
I	mg	8
Cu	mg	0.13
Zn	mg	1
Mn	mg	0.2

Vitamins (A, D, E, K<sub>1</sub>, C, B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, B<sub>12</sub>, PP, folic acid, pantothenic acid, biotin, choline, inositol) were present to meet the recommended dietary requirements

Table 2. Clinical data of patients in both treatment groups before the beginning of the study

Patients	Diet group	Drug group
n (M/F)	10 (6/4)	10 (6/4)
Age	33.5 ± 15.9	26.7 ± 9.1
% IBW	82.8 ± 12.8	89.8 ± 10.0
CDAS	5.6 ± 0.8	4.5 ± 0.7

IBW, ideal body weight; CDAS, clinical Crohn's disease activity score.

and a normal diet. Two patients were intolerant of the group A regimen, one because of the taste of the elemental diet, and one who developed diarrhoea which remitted when the treatment was discontinued. These patients were withdrawn from the study within 72 h, and restricted randomization completed, so that group A and group B each comprised 10 patients (Table 2).

Eight patients in group A had ileocolonic localization, and one ileal; in group B seven patients had ileocolonic localization, and three ileal (Table 3).

Ethical approval for the study was obtained from the local Ethics Committee.

## METHODS

All parameters considered were evaluated on admission to the study and after 14 days of treatment.

### Crohn's disease activity assessment

The clinical Crohn's disease activity score (CDAS) was calculated with the modified Crohn's disease activity index of Harvey & Bradshaw.<sup>16</sup> Erythrocyte sedimentation rate (ESR), measured by standard techniques, was also evaluated as an activity indicator.

### Nutritional assessment

Nutritional status in all subjects was assessed by anthropometric measurements: height, weight, mid-arm circumference, four skin-folds (biceps, triceps, subscapular and suprailiac) together with bioelectric impedance measurements (BEI), using the equations of Segal<sup>17</sup> and Kushner.<sup>18</sup>

BEI measurements were made using a tetrapolar impedance method (Human-Im Scan Dietosystemm, Milan, Italy) in the fasting supine state. An excitation

Table 3. Clinical disease score by group

Disease location	CDAS		ESR		PI	
	before	after	before	after	before	after
<i>Diet group</i>						
Small bowel + colon	5	4	33	27	3.63	2.76
	5	0	21	20	0.47	0.17
	6	4	20	19	0.98	0.9
	5	1	21	23	1.3	0.59
	5	2	17	15	4.2	0.1
	5	2	18	19	1.7	0.9
	7	2	16	5	6.61	2.76
	6	2	14	9	6.87	6.61
Small bowel only	7	3	27	19	18.5	3.1
	5	0	27	11	4.34	2.95
<i>Drug group</i>						
Small bowel + colon	4	3	21	18	4.54	2.42
	6	3	23	16	3.33	1.3
	4	4	21	20	2.76	3.9
	5	4	31	18	0.21	6.52
	5	4	24	20	0.85	0.21
	4	3	18	12	0	0
	4	1	20	12	0.09	0.02
Small bowel only	5	5	17	19	1.07	1.05
	4	5	21	29	0.36	0.37
	4	3	19	18	0	0

CDAS, clinical Crohn's disease activity score; ESR, erythrocyte sedimentation rate; PI, permeability index.

current of 800  $\mu$ A at 50 kHz was introduced into the subject at the distal electrodes of the hand and foot, and the voltage drop detected by the proximal electrodes enabled measurement of resistance. These measurements were then used for calculations in the specific DIETOSYSTEM software, and the results were expressed as body mass index (BMI), fat free mass (FFM) (kg, %), fat mass (FM) (kg, %) and total body water (L, %). Weight was expressed as percentage ideal body weight (% IBW).<sup>19</sup>

Prealbumin (PA) and retinol binding protein (RBP) were measured before and after treatment by standard techniques.

We also measured *in vivo* cell-mediated immunity by Multitest IMC (Pasteur Merieux, Lyon, France). This is a plastic multi-injection device which inoculates seven standardized antigens simultaneously into the derma (tetanus, diphtheria, streptococcus, tuberculin, proteus, trichophyton, candida) and one control solution (glycerine); 48 h after the inoculation the diameter of the skin reactions was measured and a score calculated: normal values are >5 in women and >10 in men.

#### *Intestinal permeability*

After an overnight fast, the patient emptied his or her bladder and provided a specimen of urine (to be checked for possible endogenous mannitol production), before drinking a solution containing 2.5 g mannitol, 5 g levulose and water to 100 mL. The subjects went without food during the test, but were allowed to drink water after the first 2 h. The urine passed in the 5 h after they had drunk the test fluid was collected. The urine volume was measured and aliquots were stored frozen at  $-20^{\circ}\text{C}$ . To calculate the levulose/mannitol ratio, permeability index (PI), samples were analysed for levulose and mannitol by gas chromatography as previously described<sup>20</sup> (normal values: 0.00–0.9).

#### *Interleukin-6 assay*

Fasting serum interleukin-6 was measured in duplicate in venous blood samples taken from each subject on the day of study. A commercially available enzyme-linked immunoabsorbent assay (T Cell Sciences, Cambridge, MA)

was used and results were expressed in pg/mL, the lower level of detection being 10 pg/mL.

#### Statistical analysis

Results are expressed as means  $\pm$  standard error of the mean. Differences in variables between groups of subjects were analysed using analysis of variance or Student's *t*-test where appropriate.

### RESULTS

After 2 weeks of treatment, there was a significant improvement of CDAS ( $5.6 \pm 0.8$  vs.  $2 \pm 1.4$ ,  $P < 0.01$ ), ESR ( $21.4 \pm 6$  vs.  $16.7 \pm 6.7$ ,  $P < 0.05$ ) and PI ( $4.9 \pm 5.3$  vs.  $2.1 \pm 2$ ,  $P < 0.01$ ) (Table 3), BMI ( $18.5 \pm 3$  vs.  $19.2 \pm 3.1$ ,  $P < 0.02$ ), PA ( $22.2 \pm 8$  vs.  $23.5 \pm 7.8$ ,  $P < 0.01$ ), RBP ( $3.7 \pm 0.7$  vs.  $4 \pm 0.8$ ,  $P < 0.02$ ), IMC test ( $4.2 \pm 2.1$  vs.  $5.9 \pm 2.3$ ,  $P < 0.01$ ) in the diet group; no significant differences were found for the other parameters studied.

In the corticosteroid group there was a significant improvement of simple Crohn's disease activity index (SCDAI) ( $4.5 \pm 0.7$  vs.  $3.5 \pm 1.2$ ,  $P < 0.04$ ) (Table 3) and of FFM (kg) ( $45.9 \pm 10.5$  vs.  $47.2 \pm 10.7$ ,  $P < 0.05$ ).

We did not find any correlation between activity and nutritional parameters and disease location in either group; disease location itself did not appear to influence therapeutic results.

Among the 12 patients enrolled in the diet group, two were withdrawn from the study because of intolerance, eight (67%) went into remission after 2 weeks of treatment: two of these relapsed within 8 months and six (75%) had no relapse in the 12 months following the study.

Among the 10 patients enrolled in the drug group, five (50%) went into remission after 2 weeks of treatment, one relapsed within 3 months, four (80%) had no relapse in the 12 months following the study.

The intention-to-treat analysis, as far as remission and relapse rate are concerned, showed that there was no difference between the two treatments both in inducing remission of the disease after 2 weeks of treatment and in maintaining remission over 12 months of follow-up.

### DISCUSSION

Several studies have shown the efficacy of elemental feeding in the treatment of Crohn's disease.<sup>6–15</sup>

However, the effect and the efficacy of defined formula diets as the sole therapy in this disease are still controversial, and their practical use has been limited by the need for enteral feeding. Furthermore, although few hypotheses have been proposed, the mechanism by which this treatment acts is unknown.

Studies of intestinal permeability in Crohn's disease<sup>21–23</sup> demonstrate a disturbed intestinal permeability in various parts of the intestine showing a general leakiness of the intestinal mucosa, not only in inflamed parts but also in parts not subject to inflammation. The fact that this leakiness is not dependent on the presence of inflammation agrees with the possibility that increased intestinal permeability may be a primary expression of Crohn's disease and a possible pathogenetic factor. To support this hypothesis it has also been demonstrated that increases in intestinal permeability precede clinical relapses in Crohn's disease, so much so that they can be considered an indicator of subclinical disease.<sup>23</sup>

Malnutrition is a common presenting feature in patients with active Crohn's disease. Significant weight loss has been reported in 20–75% of such patients,<sup>24, 25</sup> and approximately two-thirds to three-quarters of patients hospitalized with Crohn's disease are malnourished.<sup>26, 27</sup> The major factor contributing to weight loss is suppression of food intake secondary to anorexia and pain associated with eating,<sup>29</sup> although in young growing patients with Crohn's disease an increased energy expenditure has also been described.<sup>29</sup>

The first controlled trial performed to evaluate the efficacy of an elemental diet was by O'Morain *et al.*<sup>7</sup> and the conclusions drawn were that elemental diet was as effective as steroids in inducing remission. Another study demonstrated the efficacy of elemental diet but was associated with antibiotics, making the analysis of the trial not completely clear.<sup>30</sup> After these initial controlled studies, several more were performed demonstrating the beneficial effect of elemental diet on inflammation and on nutritional status in patients with Crohn's disease,<sup>31–34</sup> also showing its efficacy on steroid-refractory patients.<sup>35</sup> Elemental diets have also been demonstrated to be effective in improving intestinal permeability.<sup>11, 13</sup> In a recent study, Teahon *et al.* tried to determine the importance of nutritional factors in inducing remission from the disease: they concluded that the fact that changes in disease activity appear to precede any detectable changes in nutritional state suggest that the beneficial action of elemental diet in

patients with active Crohn's disease is not due to an improvement in nutritional status.<sup>36</sup>

We performed this controlled study with the aim of better defining a relatively simple route of administration, i.e. oral, and, at the same time, of evaluating the effects of an elemental diet (Peptamen, Clintec) on the activity of the disease, intestinal permeability and nutritional status, compared to classic steroid treatment. Clinical activity of the disease significantly improved in both treatment groups, although there was a higher number of remissions in the diet group; furthermore, there was no difference between the two groups as far as relapse rates were concerned at 12 months follow-up. Although intestinal permeability improved in both groups, this improvement was significant only in the diet group. However, we cannot say that elemental feeding was really more effective than prednisolone in promoting restoration of mucosal integrity, because the baseline values of the permeability index were randomly significantly lower in the drug group compared to the diet group. Nutritional status prior to the study was impaired in both study groups: it improved in both groups, but the improvement was more evident in the diet group.

It is important to underline that, in this study, compliance and tolerability in patients treated with oral elemental diet was very good. The efficacy of this treatment and its simple administration (oral) make this kind of therapy extremely easy to perform, so much so that it could well be considered an effective alternative to steroid treatment. This consideration appears particularly relevant when considering the well-known adverse effects of steroids, such as sodium retention, osteoporosis, gastroduodenal intolerance, hyperglycaemia, growth retardation in children and adolescents etc. In Crohn's disease patients, where the relapse problem cannot be ignored, treatment needs to be frequent and sometimes over long periods of time. Oral elemental diet may also be preferred in steroid-resistant subjects and when malnutrition is a relevant aspect.

In conclusion, our study confirms the efficacy of elemental diet in promoting and maintaining remission of Crohn's disease activity, in restoring intestinal permeability and in improving nutritional status. Furthermore, oral elemental diet appears to be generally well tolerated, with a high degree of compliance. It appears to be even more effective than steroid treatment, at least in the short term, in restoring intestinal

permeability and is certainly better than steroids in improving nutritional status.

Although a prospective study is obviously necessary to determine the mechanism of action of this treatment, it could be suggested that elemental diet acts mainly on intestinal permeability. Improvement of intestinal permeability may be responsible for remission of the disease by reducing contacts with various antigens that could damage the mucosal barrier and for improvement of nutritional status.<sup>37-40</sup>

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