ORIGINAL ARTICLE

# Does polymeric formula improve adherence to liquid diet therapy in children with active Crohn's disease?

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**Background:** Active Crohn's disease can be treated using liquid diet therapy (LDT), but non-adherence may limit success, necessitating corticosteroid therapy. Whole-protein polymeric formula (PF) seems to be much more palatable than amino acid-based elemental formula (EF) and thus may significantly improve adherence to LDT.

**Aim:** To compare adherence to LDT using PF versus EF.

**Methods:** Success in completing a 6-week course of LDT, need for nasogastric tube administration of formula and use of LDT for relapses were compared between children presenting with active disease and treated with EF (n = 53) and children given PF (n = 45).

**Results:** Remission rates were similar (EF 64%, 95% CI 51 to 77 vs PF 51%, 95% CI 37 to 66; p>0.15). 72% (95% CI 60 to 84) given EF completed the initial course of LDT compared with 58% (95% CI 44 to 72) given PF (p = 0.15). Of those failing to complete the initial course, 13% on EF and 16% on PF gave up by choice (non-adherence), the remainder stopping due to treatment failure. Nasogastric administration was more frequent with EF (55%, 95% CI 42 to 68) compared to PF (31%, 95% CI 17 to 45) (p = 0.02). Among those treated successfully at first presentation, LDT was used for 28% of relapses in the EF group (95% CI 12 to 44) and 39% in the PF group (95% CI 19 to 59) (p>0.2) over the next year.

**Conclusion:** PF did not effect adherence to LDT but was associated with significantly reduced need for nasogastric tube administration of formula.

Exclusive liquid diet therapy (LDT) is a well-established treatment for active Crohn's disease.[1 2] Typically, patients with moderate to severe disease activity are treated for a period of about 6 weeks by discontinuing normal foods and providing all of their nutritional requirements as liquid formula. Several meta-analyses have suggested that this treatment is somewhat less effective than corticosteroid therapy in adults.[3–6] However, a meta-analysis of paediatric clinical trials reported that LDT and corticosteroids were of comparable effectiveness in children.[7] In any event, the use of LDT could potentially reduce the need for corticosteroids in Crohn's disease and hence lower the risk of corticosteroid toxicity.

An important element in success with any paediatric treatment is its acceptability to both child and family. LDT requires the consumption of a large volume of formula each day and children must temporarily give up eating. This is a major challenge. Young children, especially those who are particularly unwell, may be unable to consume an adequate volume of the formula. This then necessitates enteral tube administration, which may also be difficult for both child and family to accept. Such difficulties often result in treatment failure. Even if the treatment at the time of first presentation proves successful, refusal of LDT for subsequent disease relapses may be encountered. If LDT is not used for disease relapse, its value as a corticosteroid sparing strategy must be questioned.

For many years after its introduction in the 1970s, LDT usually entailed the use of an amino acid-based elemental formula (EF). However, subsequently studies suggested that this was not necessary and a whole protein polymeric formula (PF) was reported to be equally effective.[8–11] PF is generally considered to have a significant advantage in that it is thought to more palatable. Its use has been widely hailed as an important advance improving adherence to LDT.

In this department the EFs Elemental 028 and Elemental 028 Extra (SHS International, Liverpool, UK) were used for LDT until 2001. A review of our experience with LDT prior to 2001 showed that while the initial course of therapy given at the time of first presentation was often successful, a high proportion of children were subsequently treated with corticosteroids for relapses.[12] The reasons for corticosteroid usage varied, but included considerations of patient and parent preference. From 2001 onwards the department's policy changed, and children were treated using a PF. The products used were Clinutren (Nestlé Clinical Nutrition, Deerfield, IL, USA), Fortisip (Nutricia, Trowbridge, UK) and Ensure plus (Abbott Laboratories, Chicago, IL, USA). The aim of this study was to determine whether this change in policy was associated with improved adherence to LDT and a reduction in corticosteroid usage in patients with active Crohn's disease.

## METHODS

The medical records of children presenting with active Crohn's disease between 1992 and 2004 were reviewed. The diagnosis of Crohn's disease in these children was based on conventional clinical, radiological, endoscopic and histological criteria.[13] In children presenting with mild symptoms neither LDT nor corticosteroid therapy was indicated. Those who were very seriously ill at the time of presentation usually received intravenous corticosteroid therapy. Children with moderate to severe disease at presentation were usually offered a choice of LDT or corticosteroids, although LDT was strongly advocated as the preferred treatment. In total, 98 children received LDT at the time of first presentation. These included 53 who received EF (1992–2001) and 45 subsequent patients who received PF (2001–2004).

To compare adherence to LDT with EF and PF, we studied the proportions of children completing the initial 6-week course of

**Abbreviations:** EF, elemental formula; LDT, liquid diet therapy; PF, polymeric formula

**Table 1** Characteristics of patients presenting with Crohn's disease and receiving treatment with LDT

| | Elemental formula (1994–2001) | Polymeric formula (2001–2004) | p Value |
|---|---|---|---|
| LDT for active disease at first presentation | n = 53 | n = 45 | |
| Age, median (years) (range) | 11.8 (3.7–16.9) | 12.2 (2.6–16.1) | 0.2 |
| Sex (male) | 52% | 48% | 0.85 |
| Weight for height z score, mean | −1.22 | −1.12 | 0.52 |
| Height for age z score, mean | −0.57 | −0.56 | 0.95 |
| Disease location (% subjects) | | | |
| Small bowel only | 25% | 11% | 0.09 |
| Colon only | 17% | 29% | 0.16 |
| Small bowel and colon | 58% | 60% | 0.9 |

treatment at first presentation, the proportions requiring nasogastric tube administration of the liquid feed, and the proportions receiving LDT and avoiding corticosteroid therapy for disease relapses during the first year following presentation. Nasogastric tube administration was reserved for those who were found to be unable to consume an adequate volume of the LDT orally. The tests used for comparison of proportions were the $\chi^2$ test or Fisher's exact test as appropriate. Comparisons of group medians of continuous variables were by Mann Whitney tests.

## RESULTS

The characteristics of the patients in both the EF and PF groups at the time of presentation are shown in table 1. The groups were comparable in terms of age and sex distribution. The weight-for-height and height-for-age z scores were not significantly different, both groups being underweight and below average height. The sites of involvement in terms of small bowel and/or colonic disease were also similar in the two groups.

In all cases the volume and caloric density of the formula were determined on the basis of recommended energy allowance for age. The amount of feed was then gradually adjusted individually with the aims of preventing hunger and promoting appropriate weight gain in each case.

The initial outcome in the two groups is summarised in table 2. There was no significant difference in the clinical remission rates with EF compared to PF. The duration of remission was very similar in the two groups.

Table 3 summarises the relapse outcome in those successfully treated with LDT over a 1-year follow-up period. Overall, 65% of those treated with EF and 61% of those treated with PF experienced at least one relapse. The EF and PF groups experienced mean relapse rates of 0.9 and 1.0 relapses, respectively, in the first year.

**Table 2** Initial clinical outcome in patients treated with LDT for active Crohn's disease at first presentation

| | Elemental formula | Polymeric formula | p value |
|---|---|---|---|
| Commenced on liquid diet therapy for active disease at first presentation | n = 53 | n = 45 | |
| Remission induced, % (95% CI) | 64% (51 to 77) | 51% (37 to 66) | 0.19 |
| Remission duration, weeks (95% CI) | 28 (22 to 34) | 24 (17 to 31) | 0.38 |

**Table 3** Outcome during 1 year of follow-up in patients successfully treated with LDT at first presentation

| | Elemental formula, n = 34 | Polymeric formula, n = 23 | p Value |
|---|---|---|---|
| One or more relapse(s), % (95% CI) | 65% (47 to 79) | 61% (41 to 81) | 0.88 |
| Mean number of relapses (95% CI) | 0.9 (0.6 to 1.2) | 1.0 (0.5 to 1.5) | 0.96 |

Table 4 summarises the outcomes in relation to LDT and adherence. In total, 72% (95% CI 60 to 84) given EF finished the initial course of LDT compared with 58% (95% CI 44 to 72) given PF. In most cases this was because it was clear that LDT failed to alleviate symptoms and bring about disease remission. Liquid feed was discontinued at the request of the patient in just 13% of the EF group and 16% of the PF group. Of the PF group, only 31% (95% CI 17 to 45) received the LDT by nasogastric tube infusion compared with 55% (95% CI 42 to 68) of the EF group ($p = 0.02$).

Among those who were treated successfully with LDT at the time of first presentation, tolerating the full course of treatment and achieving a disease remission, the use of LDT for subsequent relapses was relatively infrequent. In the PF group 39% (95% CI 19 to 59) of relapses were treated with LDT compared with 28% (95% CI 12 to 44) in the EF group. Only 32% of the EF group and 24% of the PF group avoided corticosteroid therapy completely in the first year following presentation.

## DISCUSSION

Currently there are two first-line treatments for moderate to severe active Crohn's disease. Corticosteroid therapy has been used in treatment since the 1940s. A course of corticosteroids typically consists of oral prednisolone tablets taken daily over a period of 10–12 weeks, with a step-wise weekly dose reduction. LDT provides an alternative and radically different strategy. There is no dispute that both corticosteroid therapy and LDT can control active Crohn's disease. However, there is much disagreement as to which is best.

Corticosteroids are usually highly effective and symptoms are often relieved within days.[14–16] Unfortunately children often develop features of Cushing syndrome, and the associated cosmetic effects (moon facies, central obesity, acne and cutaneous striae) may cause distress, especially in young people. There are many other possible adverse effects, but the greatest concerns relate to chronic steroid usage. There is serious concern that corticosteroids may be associated with growth impairment and osteoporosis in children with Crohn's disease. Unfortunately, both growth impairment and osteoporosis are serious and common complications of Crohn's disease itself.

The accidental discovery in the 1970s that LDT could induce remission was seen at once as a possible way of avoiding corticosteroid toxicity. Many children with Crohn's disease suffer from nutritional deficiencies and even malnutrition,[17] and so the use of nutrition as primary therapy is appealing. Many are convinced that LDT is the treatment of choice. Various meta-analyses[3–5] and a Cochrane review[6] have concluded that steroid therapy has a significantly higher remission rate than LDT. In our study the remission rates with both EF (64%; 95% CI 51 to 77) and PF (51%; 95% CI 37 to 66) were also lower than those generally reported with corticosteroid therapy

**Table 4** Success with and adherence to LDT at presentation and during 1-year follow-up period

| | Elemental formula | Polymeric formula | p Value |
|---|---|---|---|
| Total number treated | n = 53 | n = 45 | |
| Completed initial course, % (95% CI) | 72% (60 to 84) | 58% (44 to 72) | 0.15 |
| Non-completion due to treatment failure* | 13/15 (87%) | 16/19 (84%) | 0.84 |
| Non-completion due to non-adherence* | 2/15 (13%) | 3/19 (16%) | 0.84 |
| Nasogastric tube required, % (95% CI) | 55% (42 to 68) | 31% (17 to 45) | 0.02 |
| Relapses treated with LDT, % (95% CI) | 28% (12 to 44) | 39% (19 to 59) | 0.22 |
| Patients avoiding corticosteroid therapy for relapses, % (95% CI) | 32% (20 to 45) | 24% (12 to 37) | 0.4 |

*Four children from the EF group and three from the PF group completed the LDT course but failed to enter remission.

but consistent with previously published reports on LDT.[8 9] However, a modest disadvantage with LDT in terms of a slightly lower remission rate could be counterbalanced by major advantages in terms of steroid avoidance, growth promotion and a reduced risk of osteoporosis.

In comparing treatment efficacy, adherence is a crucially important consideration. This is especially pertinent if one of the treatments is inherently more difficult than the other. Compared with corticosteroids, LDT can be an arduous undertaking for patient and family. In a randomised controlled trial of 95 adults comparing LDT with an EF to corticosteroid treatment, the latter was more effective in large part because the patients were often unwilling to accept LDT.[18] Overall, 57% withdrew from LDT, often because they found it difficult to tolerate, whereas only 9% withdrew from corticosteroid therapy.[18] In contrast, a meta-analysis of paediatric trials comparing LDT and corticosteroids reported that the two treatments had comparable efficacy.[7] The experience in this department indicates that while LDT may often be initially successful, bringing about a remission in children presenting with moderate or severe Crohn's disease, its long-term success in avoiding corticosteroid usage is less certain.

Several randomised controlled trials of EF versus PF in Crohn's disease and a Cochrane review have concluded that these formulas are of comparable efficacy.[6 8–11] In keeping with this, there was no significant difference in remission rates in this study with EF versus PF. Power calculation shows that for the 13% difference observed to achieve statistical significance at a level of $p<0.05$ with 80% power, it would be necessary to have included 240 subjects in each group.

No previous study has reported on the outcome following the initial course of LDT. In this study outcome during a 1-year follow-up period was examined. During this time there was no significant difference in the time to first relapse, in the proportion of patients relapsing or in the number of relapses experienced.

Several authors have suggested that PF is more palatable than EF.[19–21] Whatever the taste preferences of children and young people, there are no studies that examine the influence of formula choice on adherence. The use of PF has been anecdotally reported to greatly improve acceptance of LDT. The findings in this study do not support that assertion, there being no significant difference in the proportions completing the initial course of treatment or in the disappointingly low proportions using LDT and avoiding corticosteroids for subsequent relapses. It is possible that a much larger study would have revealed small difference in adherence, but large and important differences are very unlikely. Thus, in relation to completion of the initial 6-week course of LDT, power calculation shows that for the 14% difference observed to achieve statistical significance at a level of $p<0.05$ with 80% power, it would be necessary to have 196 subjects in each group.

Discontinuation of LDT during the initial course was usually due to treatment failure rather than refusal by the patient to continue. The study was not conducted as a randomised trial and there are inherent difficulties in the comparison of patient outcomes over time. However, there were no intentional changes in management strategy during the time period studied. Throughout that time the policy of using LDT as the preferred treatment option remained and all of the patients were supported in their treatment by a dedicated gastroenterology dietician.

One possible benefit of the use of PF was that its introduction was associated with a significant reduction in the need for nasogastric tube administration of LDT. There was no change over time in the policy in relation to the use of nasogastric tube feeding. Oral administration was the preferred option, with the nasogastric route being reserved for those who were found to be unable to consume an adequate quantity of the formula. The use of nasogastric feeding has many disadvantages, both practical and psychological. Families undertaking this process require considerable support and training. Children usually find tube placement distressing. Difficulties may also arise in relation to school attendance. PF may therefore have an important advantage in this regard.

A primary reason for the use of LDT is that it may avoid or reduce the need for corticosteroid treatment. Many patients with Crohn's disease experience disease relapses at intervals,

## What is already known on this topic

- A course of exclusive liquid diet therapy is effective in inducing remission in children with active Crohn's disease.
- Elemental (amino acid-based) formulas and polymeric (whole protein-based) formulas appear to be equally effective.
- It has been suggested that polymeric formula is more palatable and would hence improve adherence to therapy.

## What this study adds

- In this study the replacement of elemental formula with polymeric formula did not improve adherence.
- The use of polymeric formula was associated with decreased need for nasogastric tube administration of the feed.
- There were significant difficulties with sustaining liquid diet therapy, particularly in patients experiencing relapses.

and consequently it is important that LDT should be used in preference to corticosteroids for such relapses. In this study there was no significant improvement in adherence to LDT following the introduction of PF. Despite its use many patients experiencing relapses continued to receive treatment with corticosteroids as had been the case in the earlier EF era. Overall, despite the fact the departmental policy favoured LDT as the first choice therapy, about 70% of children received corticosteroids at some time in the first year after presentation.

In conclusion, the use of PF was not associated with a major change in adherence to LDT. The main advantage appears to have been a significant reduction in the need for nasogastric tube administration. In this department long-term avoidance of corticosteroid therapy through the use of LDT has proved difficult. A randomised trial comparing corticosteroid therapy with LDT as long-term strategies for managing active Crohn's disease is required.


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