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Oral protein–energy supplements for children with chronic disease: systematic review*

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Growth failure and poor nutritional status are features of children with chronic disease. Oral protein–energy supplements are one of a number of interventions provided with the aim of improving nutritional status in these children. The present paper describes a Cochrane systematic review assessing the efficacy of these products in children with chronic disease. The objective was to examine the evidence that in children with chronic disease oral protein–energy supplements alter nutrient intake, nutritional indices, survival and quality of life. All randomised controlled trials of the use of oral protein–energy supplements in children with chronic disease were identified through searching electronic databases and hand searching the abstract books of nutrition conferences. Studies identified were independently assessed for eligibility and methodological quality, and data on outcomes of interest were combined in a meta-analysis where possible. Two trials were eligible for inclusion in the review, both of which were undertaken with children with cystic fibrosis. No statistical differences could be found between treatment and control groups when data from both studies were combined. Oral protein–energy supplements are widely used to improve the nutritional status of children with chronic disease. No conclusions can be drawn on the efficacy of these products based on the limited data available. Further randomised controlled trials are required to investigate the use of these products in children with chronic disease. Until further data are available, these products should be used with caution.

Protein–energy supplements: Children: Chronic disease

Growth failure and poor nutritional status are common features in children with chronic diseases. These features have been demonstrated in respiratory disease, chronic renal failure, neuromuscular disease and juvenile chronic arthritis (Johansson *et al*. 1986; Hanning *et al*. 1993). Studies also show a prevalence of both acute and chronic malnutrition of children in hospital of between 15 and 25 % in the UK (Moy *et al*. 1990; Hendrickse *et al*. 1997) and 26 % in the USA (Hendricks *et al*. 1995). Growth failure and poor nutritional status in chronic disease are multi-factorial in origin. Contributing factors include reduced dietary intake as a result of poor appetite, malabsorption and increased nutritional requirements associated with some diseases. Poor nutritional status and suboptimal growth can have a detrimental effect on both short- and long-term disease outcome (Corey *et al*. 1988; Canadian Paediatric Society Nutrition Committee, 1994).

Prevention or correction of malnutrition is increasingly recognised as an important component of the management of chronic childhood disease. Several interventions are available to increase nutritional intake, thereby improving nutritional status. These interventions include dietetic advice to increase the nutritional content of the child's diet; provision of oral protein–energy supplements and providing additional nutrition in the form of tube feeding. Oral protein–energy supplements in the form of either whole-protein milk or juice drinks are used to increase the total daily protein and energy intake in order to improve weight gain and nutritional status. These supplements also contain a range of micronutrients that may be of benefit to the malnourished child. Supplements that provide only energy with no additional nutrients are available; however, these supplements are infrequently recommended for children with malnutrition, as these children require supplementation of protein and other nutrients in addition to

*The original version of the present review is available in the Cochrane Library (Poustie *et al*. 2003).
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energy, rather than energy alone. Provided protein–energy supplements are taken in addition to normal dietary intake from food, then overall nutritional intake should be improved. However, it is possible that these products may replace some of the protein and energy taken as food and their potential effect on overall nutritional intake either reduced or eliminated. A further possible adverse consequence of replacing protein and energy intake from normal food by protein and energy from these supplements may be to have a detrimental effect on eating behaviour, which is particularly critical in toddlers and young children who are learning to develop normal eating behaviour. These products may also cause a number of other unpleasant symptoms, e.g. diarrhoea, vomiting, glucose intolerance and bloating.

Compliance with supplement drinks has been found to be poor in adults (Bolton *et al*. 1992; Murphy *et al*. 1992). Palatability of these products has been suggested as a reason for non-compliance, and this aspect has been well investigated in adults (Fuller, 1985; Bolton *et al*. 1990; Oversen 1991), although rarely studied in children (Poustie *et al*. 1999). In addition, these products are expensive and the prescription, and subsequent economic implication, of energy supplementation is steadily increasing (McCombie, 1999). Evidence from two systematic reviews of the use of nutritional supplements in adults suggests that these products are efficacious; however, few studies of this intervention have been conducted in children (Potter *et al*. 1998; Stratton & Elia, 2000). This systematic review was therefore carried out to assess the efficacy of oral protein–energy supplements for children with chronic disease. In particular, the interest was in whether these products alter daily nutritional intake, nutritional indices, survival and quality of life, and whether in children with chronic disease they are associated with adverse effects that are either important to the patient or have long-term sequelae.

Methods

Types of studies

Studies suitable for inclusion were randomised controlled trials, published or unpublished. Trials in which pseudo-randomisation methods such as alternation were used would have been included if there were sufficient evidence that the treatment and comparison groups were comparable in terms of clinical and nutritional status.

Types of participants

Eligible participants were children aged between 1 and 16 years with any defined chronic disease, i.e. a disease that requires medical intervention for a period of ≥ 6 months, or for the remainder of the individual's lifetime. Trials of this intervention in children with malnutrition resulting from insufficient dietary intake without any causative disease, e.g. during famine, were excluded.

Types of interventions

Trials of oral protein–energy supplements compared with existing conventional therapy or placebo for a period of ≥ 1 month were considered. Existing conventional therapy could include advice on how to improve nutritional intake from food, or no specific intervention. Oral protein–energy supplements provided as either whole-protein milk or juice drinks were considered. Those supplements that provide energy alone, or protein alone, were not included. A period of ≥ 1 month was selected, as the interest was in the longer-term use of these products to improve nutritional status and growth. These products are sometimes provided in the short term to boost nutritional intake during a period when dietary intake is compromised, e.g. during an acute infection. Studies with an intervention period of < 1 month were therefore excluded.

Types of outcome measures

The primary outcomes of interest were measures of nutritional status and growth, including change in weight and/or height and/or BMI (including centile or Z score) and other anthropometric measures of body composition. The interest was also in energy and nutritional intake from food and supplements, measures of eating behaviour, severity scores for individual chronic diseases, measures of quality of life, measures of compliance with dietary treatment and adverse effects including diarrhoea, vomiting, reduced appetite and abdominal bloating.

Identification of studies

A broad search strategy combining the terms 'nutrition' and 'child' or 'children' alongside the standard terms for identifying randomised controlled trials was developed (Clarke & Oxman, 2000). This search strategy was applied to the following electronic databases: Cochrane Library (Issue 3, 2002), Medline (1966–2002), Embase (1974–1995). Hand searching of the conference proceedings of the British Association for Parenteral and Enteral Nutrition (1995 and 1997–8), the European Society for Parenteral and Enteral Nutrition (1983–8, 1993 and 1995–6) and the American Society for Parenteral and Enteral Nutrition (1983 and 1985–1998) was undertaken by V.J.P. Five manufacturers of oral protein–energy supplements were contacted in an attempt to identify unpublished trials (Abbott, Maidenhead, Berks., UK; Fresenius Kabi Ltd, Runcorn, Ches., UK; Nutricia Clinical Care, Trowbridge, Wilts., UK; Novatis Consumer Health UK Ltd, Horsham, West Sussex, UK; SHS International Ltd, Liverpool, Merseyside, UK).

Assessment of study quality

Assessment of methodological quality was undertaken independently by all three reviewers. The method used to assess the quality of the studies focused on three areas: allocation concealment, generation of randomisation sequence, intention-to-treat analysis (Schulz *et al*. 1995). Whether the allocation of subjects to treatment groups was concealed to the investigators was graded as being adequate, unclear or inadequate. The same three categories were also used to assess the adequacy of the method used to generate the randomisation sequence. The third area by which the

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quality of the studies was assessed was whether an intention-to-treat analysis was employed. This factor was assessed using the following categories: adequate, unclear, exclusions (i.e. subjects were excluded from the final analysis). Whether the study was blinded was also considered.

Data analysis

Data were independently extracted by two reviewers (R.L.S. and V.J.P.). Where studies addressed sufficiently-similar participants, interventions and outcomes, available data were combined using a fixed-effects meta-analysis (Clarke & Oxman, 2000). Heterogeneity between studies was tested for by the use of a standard Chi-squared test. Where heterogeneity did exist between the studies a random-effects meta-analysis was performed (Clarke & Oxman, 2000).

Results

The search identified 2101 references to studies and a further four studies were identified from hand searching the nutrition conference proceedings. All these titles were checked by one reviewer (V.J.P.), and those that appeared to meet the criteria for inclusion in the review, or those in which it was not clear whether they were relevant for inclusion, were selected for perusal of the abstract; 130 abstracts were obtained. Two reviewers (V.J.P. and R.M.W.) independently reviewed the abstracts and selected those for which the full paper should be obtained. If there was any doubt whether a study was relevant, then the full paper was obtained. Following this process, a total of thirty-nine full papers were obtained and independently assessed for eligibility by all three reviewers. These thirty-nine references described twenty-seven different studies. The reference lists of these studies were checked for further possible trials; however, none was found. Fig. 1 shows a

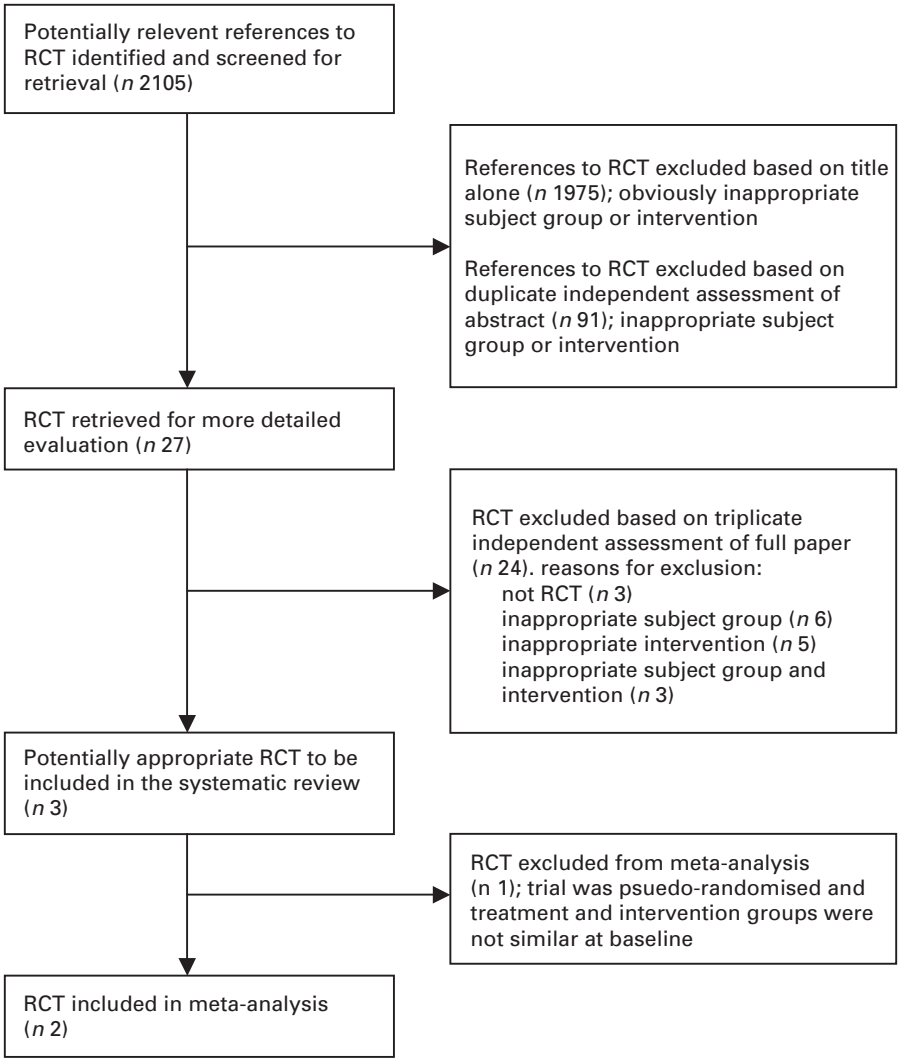

Fig. 1. Summary of the systematic review process used to select studies on oral protein–energy supplements for children with chronic disease for inclusion (for details, see p. 802). RCT, randomised controlled trial.

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Table 1. Characteristics of the studies on oral protein–energy supplements for children with chronic disease included in the review*

Study	Methods	Participants	Interventions	Outcomes	Allocation concealment
Hanning *et al*. (1993)	Randomised controlled trial of parallel design. Intention-to-treat analysis not performed	Twenty children (7–15 years) with cystic fibrosis and mild-to-moderate lung disease. Data presented on sixteen children	Dietary supplements (drinks, powders, milk shakes, puddings) to increase energy intake by 25 % in addition to normal intake for 6 months. No intervention in control group	Skeletal and respiratory muscle strength, pulmonary function, anthropometric measures, nutritional intake, biochemical markers of nutrition	Adequate
Kalnins *et al*. (1996)	Pseudo-randomised controlled trial of parallel design. Intention-to-treat analysis not performed	Five adults and eight children (10–14 years) with cystic fibrosis and depleted nutritional status (< 90 % weight-for-height). Data on all children were presented and included in analysis for this review	High-energy supplements provided to increase energy intake by 20 % in addition to normal diet for 3 months. Control group received dietary counselling to increase energy intake from normal foods	Anthropometric measures, pulmonary function, nutritional intake, faecal fat content	Inadequate

*For details of the review procedure, see p. 802 and Fig. 1.

summary of the systematic review process, with details of numbers of studies identified and included or excluded at each stage of the review.

Two randomised controlled trials were considered eligible for inclusion in the review; both investigated the use of oral protein–energy supplements for patients with cystic fibrosis (Hanning *et al*. 1993; Kalnins *et al*. 1996). A third study was also identified (Koletzko *et al*. 1992). This study was a randomised controlled trial investigating the use of oral protein–energy supplements as a means of increasing the essential fatty acid content of the diet of children with cystic fibrosis. It was initially published in abstract form, and subsequently published in full (Steinkamp *et al*. 2000). Based on assessment of the abstract alone the study appeared to meet the criteria for inclusion in the review. However, it was clear from the full paper that a pseudo-randomisation method was employed, and the treatment and comparison groups were not comparable at the start of the trial. Thus, this study was not included in the meta-analysis.

Table 1 shows the characteristics of the studies that were included. The results of the independent assessment of study methodological quality are presented in Table 2.

Table 2. Methodological quality of studies on oral protein–energy supplements for children with chronic disease included in the review

Study	Allocation concealment	Sequence generation	Intention to treat	Blinding
Hanning *et al*. (1993)	Adequate	Adequate	No	Yes
Kalnins *et al*. (1996)	Inadequate	Inadequate	No	No

*For details of the review procedure, see p. 802 and Fig. 1.

Data on growth, nutritional status, dietary intake and forced expiratory volume in 1 min (expressed as a percentage of that predicted for age, gender and height of the child) from one study involving only eight children were available for inclusion in the review (Kalnins *et al*. 1996). There were no significant differences between the treatment and control groups for any of these outcomes except a mean change in total fat intake (g/d) at 3 months (weighted mean difference 69·20 (95 % CI 11·05, 127·35)), which favoured the treatment group (see Fig. 2).

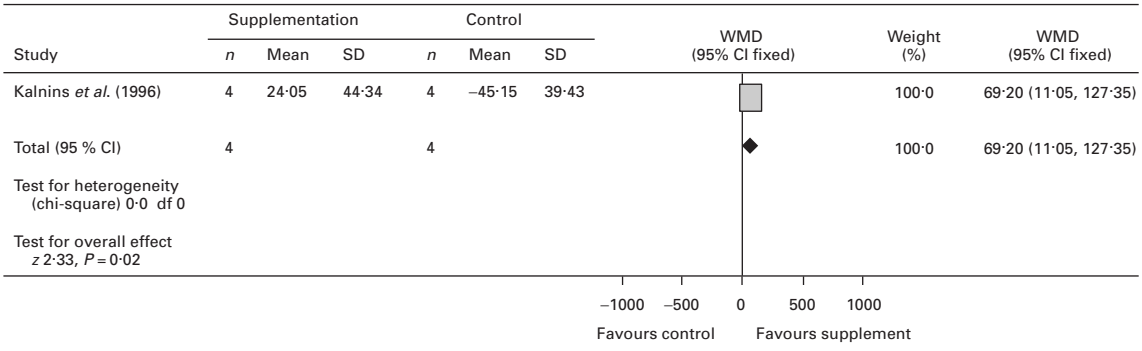

Fig. 2. Change in total fat content (g/d) after 3 months for patients with cystic fibrosis who received oral protein–energy supplements compared with those receiving no intervention, placebo or additional nutritional advice. WMD, weighted mean difference. The Forrest plot shows the point estimate of the result of the included study (■) and the overall pooled estimate for all included studies (in this case only one study was included; ◆; the horizontal tips represent the confidence interval of that estimate).

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For one outcome, change in weight at 6 months, data from both studies could be combined in a meta-analysis. The chi-square test for heterogeneity indicated that heterogeneity could be present ($P = 0{\cdot}06$). Thus, the data were analysed twice, using the fixed- and random-effects models. No significant differences were found between the treatment and control groups using either model.

Discussion

Oral protein–energy supplements are widely used in an attempt to improve nutritional status of children with a number of chronic diseases, at some considerable cost. It is very disappointing, therefore, that the effectiveness of these supplements has not been assessed by adequate clinical trials. It is interesting to note that the three trials identified were all in the field of cystic fibrosis, and that the use of these products in other chronic conditions of childhood does not appear to have been investigated. The importance of nutritional support in cystic fibrosis has long been recognised, which may explain why the use of supplements in this population has been investigated (Corey *et al*. 1988). It may be that as the importance of nutritional support becomes more recognised in other childhood conditions trials will be conducted in the future. However, as oral protein–energy supplements are now accepted as an established treatment, persuading clinicians and patients to participate in further studies may be difficult.

In contrast to our findings, the use of oral protein–energy supplements has been investigated in adults in a number of trials and several systematic reviews (Potter *et al*. 1998; Stratton & Elia, 2000). It is acknowledged that undertaking research in children can be more arduous than in adults; however, it is important not to assume that an intervention that is applied to both children and adults would have the same implications for both groups (Smyth & Weindling, 1999). The potential detrimental effects of malnutrition, and its treatment, may be greater for children than adults. In children an additional consideration is the need for normal growth, alongside the development of social skills and behaviour. For example, the provision of normal food and meals helps the child to develop normal eating behaviour patterns and any disruption to this process may lead to long-term eating problems. Furthermore, in children with lifelong chronic disease supplementation may be introduced in childhood and by the time they reach adulthood become established therapy.

Conclusions

No conclusions can be made about the use of oral protein–energy supplements in children with chronic disease from the information currently available. This position does not mean that these products may not be efficacious, and clinicians must balance potential benefits against possible adverse effects of treatment in making decisions about individual children. This systematic review has clearly identified the need for a series of well-designed adequately-powered multicentre randomised controlled trials assessing the effectiveness and possible adverse effects of oral protein–energy supplements for children with chronic disease. A number of trials would be required to assess the effectiveness of these products in children with diseases associated with poor growth and nutritional status that lead to the prescription of these products.

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