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Research

Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial

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Abstract

Objective To determine whether oral protein energy supplements, used long term in children with cystic fibrosis who are moderately malnourished, improve nutritional and other outcomes.
Design Multicentre randomised controlled trial.
Setting Seven specialist paediatric cystic fibrosis centres and their associated shared care clinics and seven smaller paediatric cystic fibrosis clinics.
Participants 102 children with cystic fibrosis, aged between 2 and 15 years, who were moderately malnourished.
Interventions Oral protein energy supplements in addition to usual dietary advice compared with dietary advice alone, for 12 months.
Main outcome measure Change in body mass index centile over one year.
Results Use of supplements was not associated with a change in body mass index centile (mean difference 2.99 centile points, 95% confidence interval −2.70 to 8.68) or other nutritional and spirometric outcomes in this group of children.
Conclusions Long term use of oral protein energy supplements did not result in an improvement in nutritional status or other clinical outcomes in children with cystic fibrosis who were moderately malnourished. Oral protein energy supplements should not be regarded as an essential part of the management of this group of children.
Trial registration ISRCTN: 95744468.

Introduction

Poor nutrition is common in people with cystic fibrosis—a large study in the United States reported that 50% were under the 10th centile for height, weight, or both.[1] Prevalence of poor nutritional status increases with age and is an important predictor of decline in lung function.[2–5] In recent years several guidelines have recommended that dietary intake should provide at least 120% of the recommended daily allowance for energy in people with cystic fibrosis.[6–8] Achieving this energy intake from food can be difficult and is usually not successful, particularly in young children.[9 10]

Oral protein energy supplements are widely prescribed for people with cystic fibrosis to improve energy intake and nutritional status.[8] They are used in the medium to long term when weight gain is not satisfactory or in the short term to enable weight that has been lost acutely to be regained. They are considered an acceptable, non-invasive means of improving nutritional status and overall prognosis in children who have increased energy requirements.[11] However, many people find them unpalatable, particularly when prescribed for long term use.

These supplements are expensive and have never been evaluated in a large randomised controlled trial in children.[12] A systematic review of oral protein energy supplements for people with cystic fibrosis identified two eligible trials, which together involved 29 participants.[13] Because of a lack of evidence, the review was unable to reach a conclusion on the efficacy of these supplements (fig 1). The aim of the CALICO (calories in cystic fibrosis—oral) trial was to investigate whether oral protein energy supplements, taken as drinks, in addition to dietary advice and monitoring, improve or prevent deterioration in the body mass index centile of children with cystic fibrosis compared with dietary management alone. The trial also evaluated the effect of supplements on other measures of nutritional status, macronutrient intake, spirometric lung function, activity levels, and gastrointestinal symptoms.

Methods

Study design

The trial was a multicentre randomised controlled trial of oral protein energy supplements for children with cystic fibrosis. We first did a feasibility study to refine the methods, determine which outcome measures to use, and allow consumers and collaborators to be involved in the development of the CALICO trial.[14]

Participants

We recruited children with cystic fibrosis aged between 2 and 15 years if they met one of the following criteria: body mass index of less than the 25th centile and more than the 0.4th centile, no increase in weight over the previous three months, a 5% decrease in weight from baseline over a period of less than six months. We excluded children who had cystic fibrosis related diabetes or liver disease or had a forced expiratory volume in one second of less than 30% of predicted for height and age or if, during the previous three months, they had been diagnosed as having cystic fibrosis or had received enteral nutrition. Children who were excluded were considered eligible later if these criteria no longer applied. Children were recruited by dietitians at seven specialist cystic fibrosis centres in the United Kingdom, and associated shared care clinics, and at seven smaller clinics. The parents of all

P+ *Members of Trial Steering Committee and the Collaborative Group are on bmj.com*

Table 1 Oral protein energy supplements prescribed to children in the supplement group

Supplement	Manufacturer	No prescribed this product
Calshake	Fresenius Kabi, Runcorn	6
Clinutren	Nestle UK, Croydon	7
Complan	Heinz, Hayes	2
Enlive	Fresenius Kabi, Runcorn	7
Fortifresh	Nutricia Clinical Nutrition, Croydon	1
Fortijuice	Nutricia Clinical Nutrition, Croydon	7
Fortini	Nutricia Clinical Nutrition, Croydon	1
Fortisip	Nutricia Clinical Nutrition, Croydon	4
Fresubin	Fresenius Kabi, Runcorn	5
Resource	Novartis Consumer Health, Horsham	5
Scandishake	SHS International, Liverpool	5

participating children gave informed written consent, in addition to the children's own signed assent where appropriate.

Interventions

We provided the children with a selection of supplements to try before randomisation. We randomised those who found the supplements palatable to receive either oral protein energy supplements plus routine dietetic advice (supplement group) or routine dietetic advice excluding prescription of such supplements (standard care group) for one year. We did not randomise children who did not find the supplements palatable. The children selected the supplements that they liked, and we recommended a daily amount sufficient to increase usual energy intake by 20% (table 1). We excluded supplements that provided only energy or protein alone. We asked the child's general practitioner to prescribe the supplements. A research assistant (JER) made five home visits to each child, one to explain the trial and sample the supplements and four to assess all outcomes at baseline and at three, six, and 12 months.

Outcomes

The primary outcome was change in body mass index centile over 12 months. We measured weight by using portable scales (Seca, Birmingham, UK) and height by using the Leicester Height Measure, a freestanding stadiometer (Seca). We assessed tricep skinfold thickness with Holtain skinfold callipers (Holtain, Crymych, UK) and mid-upper arm circumference, which we used to calculate mid-arm muscle circumference.[15] We calculated energy and macronutrient intake from four day, unweighed diet diaries by using the Microdiet software (Downlee Systems, Chapel-en-le Frith, UK) and expressed these as a percentage of the recommended daily intake for age and sex.[16] We measured spirometric lung function parameters (forced expiratory volume in one second and forced vital capacity) with a portable spirometer (Vitalograph, Buckingham, UK) and expressed them as a percentage of that predicted for age, sex, and height. We used the habitual activity estimation scale to assess activity levels expressed as a percentage of 24 hours spent being active.[17] We monitored gastrointestinal symptoms with a questionnaire adapted from a validated tool.[18] The research assistant was trained in anthropometric assessment and spirometry and used regularly calibrated equipment.

Randomisation

We used random number tables to generate the randomisation code. Sequentially numbered, opaque envelopes, administered by the pharmacy of the lead centre, were used for treatment group allocation. Randomisation was stratified within each centre. The research assistant was not masked to allocation group, but a masked investigator (VJP) used a computerised growth package for conversion of weight and height to body mass index centile.[19] The children in the trial were not masked, as we had no satisfactory placebo. On two occasions twins were randomised, both siblings at the same time. In each instance, both twins were randomised to the same group. A further pair of siblings were entered into the trial at different times and were randomised separately. We took no formal account of this in the modelling.

Statistical analysis

We set the study size to detect a difference of a change of 10 body mass index centiles between the two groups after one year. This estimation was based on data from two cystic fibrosis centres. With a 5% significance level and 90% power, using a conservatively estimated standard deviation for one year change in body mass index centile of 15 points, we needed 47 children in each arm or 94 in total. Statistical analysis was by intention to treat, which we did according to a pre-established analysis plan with the analyst masked to treatment allocation. We calculated differences in mean change in body mass index centile and all other outcomes over 12 months between the supplement and standard care groups, with 95% confidence intervals for the difference. We used Student's *t* test to calculate P values. We made

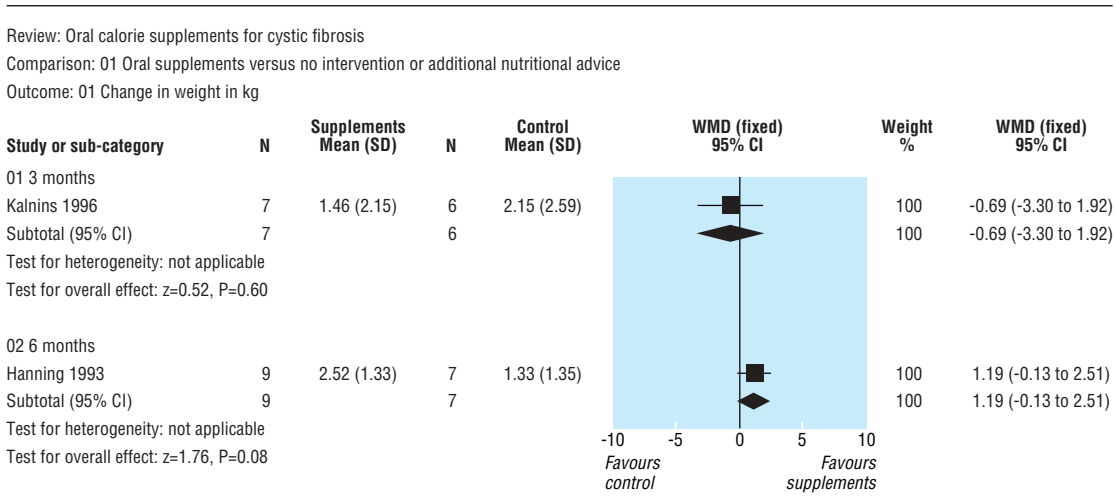

Fig 1 Forrest plot showing effect of oral protein energy supplements, compared with no intervention or additional nutritional advice, on change in weight (taken from Cochrane systematic review of oral calorie supplements for cystic fibrosis[13])

Table 2 Baseline characteristics of participants. Values are means (SDs)

Characteristic	Supplement group (n=50, 27 boys)	Standard care group (n=52, 27 boys)
Age (years)	8.75 (3.72)	8.79 (3.67)
BMI centile	34.27 (23.96)	31.52 (25.36)
Weight centile	25.07 (20.37)	24.69 (22.79)
Height centile	26.69 (24.83)	28.15 (26.93)
Energy intake (% EAR)	118.43 (28.71)	116.24 (29.59)
FEV_1 (% predicted)	81.34 (16.16)	73.67 (18.58)

BMI=body mass index; EAR=estimated average requirement for age and sex; FEV_1=forced expiratory volume in 1 second.

every effort to obtain full outcome data on all participants, but we replaced any missing data with routinely collected data where appropriate. This was necessary on only two occasions for diet diary data. Children aged 5 and above did spirometry. As oral protein energy supplements are an established treatment with few adverse effects, the trial did not have a data monitoring committee. The trial steering committee received regular independent audits to check progress of the trial and completeness of documentation.

Results

Twenty seven dietitians from 21 hospitals recruited 132 of 160 eligible children to the trial. We randomised 102 children recruited from 17 hospitals, 50 to the supplement group and 52 to the standard care group. Figure 2 shows the trial profile. Baseline characteristics of the two groups of children were balanced (table 2). The children recruited but not randomised (20 boys, 10 girls) were similar in age (mean age 9.43 (SD 3.75) years) and nutritional status (mean body mass index centile 26.01 (SD 19.85)) to those randomised.

All children were followed up to 12 months, although we were unable to collect interim data on two children from the supplement group (owing to parental choice or illness) and one child from the standard care group (illness). We found no difference in mean change in body mass index centile from baseline to 12 months between the supplement group and the standard care group (mean difference 2.99 (95% confidence interval −2.70 to 8.68) centile points) (table 3, fig 3). The confidence interval excludes the 10 point difference that the trial was powered to detect. No significant differences at these time points existed between the groups for weight and height centiles or for any other anthropometric outcomes.

Table 3 Change in outcomes over 12 months. Values are means (SDs) unless stated otherwise

Outcome measure	Supplement group	Standard care group	Mean difference (95% CI)	P value
BMI centile	0.67 (18.20)	−2.32 (9.63)	2.99 (−2.70 to 8.68)	0.30
Weight centile	0.83 (10.96)	−1.00 (7.14)	1.83 (−1.79 to 5.45)	0.32
Height centile	−0.53 (6.94)	1.18 (5.62)	−0.65 (−3.12 to 1.83)	0.61
Mid-arm muscle circumference	0.76 (1.37)	0.62 (1.00)	0.14 (−0.34 to 0.61)	0.08
FEV_1 (% predicted)	−3.41 (13.50)	−1.50 (14.89)	−1.91 (−8.73 to 4.93)	0.58
FVC (% predicted)	0.06 (17.82)	−5.21 (20.02)	5.28 (−3.93 to 14.48)	0.26
Activity (% of day active)	−4.97 (9.77)	−4.89 (10.70)	−0.07 (−4.1 to 3.96)	0.97
Energy intake (% EAR)	24.48 (22.87)	6.63 (25.21)	17.85 (5.11 to 30.58)	0.01
Gastrointestinal symptom score	−0.42 (2.05)	−0.62 (2.03)	0.20 (−0.61 to 1.00)	0.63

BMI=body mass index; EAR=estimated average requirement for age and sex; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

Nine children failed to return the baseline diet diary, and 39 failed to return the 12 month diet diary. Dietary intake data are therefore based on the 58 children who completed both baseline and 12 month diaries. We found no differences between mean change from baseline to 12 months for dietary intake outcomes, apart from energy intake expressed as a percentage of that recommended for age and sex (mean difference 17.85 (5.11 to 30.58) percentage points), as shown in table 3. Spirometry data were available for 70 of the 72 participants aged 5 and above. We found no significant differences between the groups for any lung

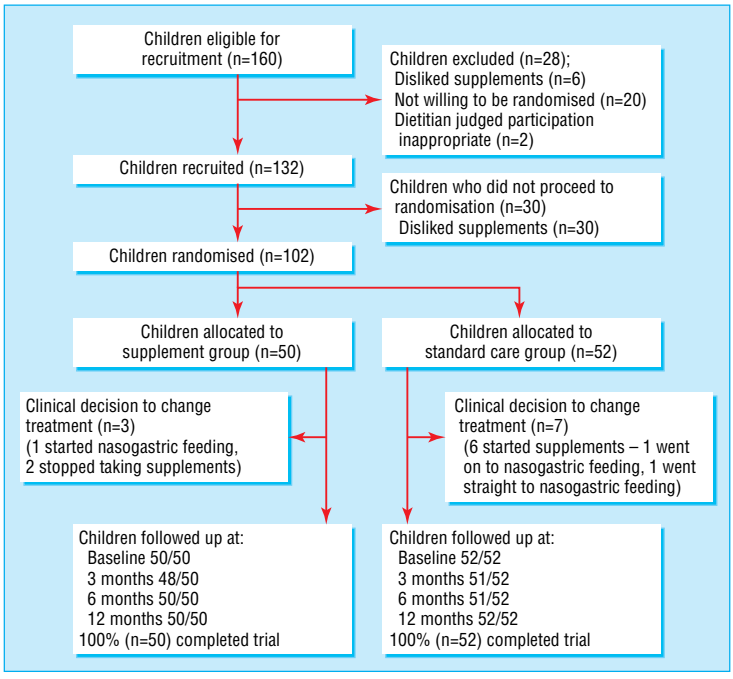

Fig 2 Trial profile

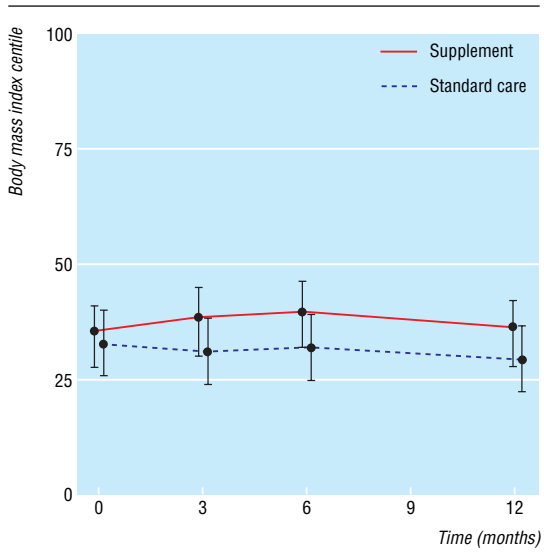

Fig 3 Body mass index centile over one year, by treatment group (lines show means, error bars show 95% confidence intervals)

function outcomes. All children completed the activity diaries and gastrointestinal symptom questionnaires, and we found no differences between the groups for these outcomes (table 3).

Discussion

These data suggest that oral protein energy supplements prescribed over one year, compared with dietary advice alone, did not result in a clinically important change in body mass index centile or other nutritional outcomes in children with cystic fibrosis. This pragmatic trial was informed by a systematic review and a pilot study. Addition of our trial data to the systematic review of oral protein energy supplements for people with cystic fibrosis clearly shows the limited efficacy of these products (fig 4).

One of our outcomes related to whether the prescription of oral protein energy supplements improved energy intake, as we were concerned that drinking these products would reduce energy intake from food, thereby not increasing the total intake. A marked improvement in energy intake seemed to occur in the supplement group, compared with the control group, despite the lack of difference in nutritional outcomes. The supplement group seemed to be consuming about 18% more than the standard care group, relative to their estimated average requirement for energy intake. We made conservative assumptions that, in this group, efficiency of energy storage is 50% and energy content of new tissue is 6000 kcal/kg and calculated that, if this difference in energy intake was maintained over one year, the average weight would be 10 kg greater in the supplement group. The actual mean difference in weight between the groups was 0.17 kg (95% confidence interval −0.68 to 1.02 kg), which led us to conclude that the diet diary data are inaccurate. Energy intake data derived from diet diaries are acknowledged to show considerable inaccuracies compared with an objective measure.[20] Just under half the participants failed to return their diaries, and for those who did it was unclear whether the recording of the number of supplements consumed was accurate. It therefore seems likely that children prescribed supplements overestimated their intake of supplements, food, or both in the diet diaries.

Several studies have investigated the association between nutritional status and lung disease in cystic fibrosis,[2 3] but determining whether poor nutritional status is the cause or an effect of decline in lung function is difficult. However, longitudinal studies in children with cystic fibrosis have shown that weight,

Review: Oral calorie supplements for cystic fibrosis
Comparison: 01 Oral supplements versus no intervention or additional nutritional advice
Outcome: 01 Change in weight in kg

Study or sub-category	N	Supplements Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 3 months							
Kalnins 1996	7	1.46 (2.15)	6	2.15 (2.59)		2.56	-0.69 (-3.30 to 1.92)
CALICO	48	1.11 (1.25)	51	0.84 (0.85)		97.44	0.27 (-0.15 to 0.69)
Subtotal (95% CI)	55		57			100.00	0.25 (-0.17 to 0.66)
Test for heterogeneity: χ^2=0.50, df=1, P=0.48, I^2=0%							
Test for overall effect: z=1.15, P=0.25							
02 6 months							
Hanning 1993	9	2.52 (1.33)	7	1.33 (1.35)		16.78	1.19 (-0.13 to 2.51)
CALICO	50	2.05 (1.80)	51	1.72 (1.18)		83.22	0.33 (-0.26 to 0.92)
Subtotal (95% CI)	59		58			100.00	0.47 (-0.07 to 1.02)
Test for heterogeneity: χ^2=1.35, df=1, P=0.25, I^2=25.8%							
Test for overall effect: z=1.71, P=0.09							
03 12 months							
CALICO	50	3.13 (2.35)	52	3.03 (2.00)		100.00	0.10 (-0.75 to 0.95)
Subtotal (95% CI)	50		52			100.00	0.10 (-0.75 to 0.95)
Test for heterogeneity: not applicable							
Test for overall effect: z=0.23, P=0.82							

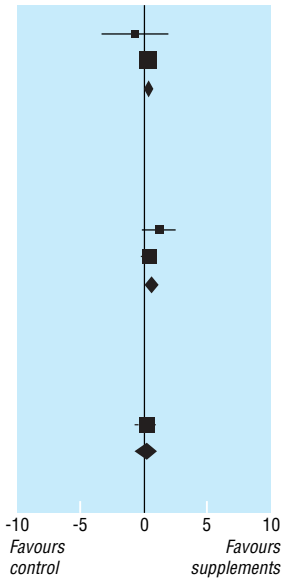

Fig 4 Forrest plot showing effect of oral protein energy supplements, compared with no intervention or additional nutritional advice, on change in weight—adjusted to include evidence from CALICO trial (adapted from Cochrane systematic review of oral calorie supplements for cystic fibrosis[13])

What is already known on this topic

Oral protein energy supplements are often prescribed to improve growth and nutritional status in children with cystic fibrosis and other chronic conditions

These supplements are expensive, and many children do not like taking them regularly

Evidence from randomised controlled trials for the effectiveness of supplements is lacking

What this study adds

Long term use of oral protein energy supplements does not improve nutritional status in children with cystic fibrosis

Dietary advice alone is a satisfactory approach to the management of children with cystic fibrosis and moderate malnutrition

adjusted for age, is an independent predictor of percentage forced expiratory volume in one second some years later.[4 5] This study provides important reassurance that children who do not receive supplements, because they either are not prescribed them or do not like them, will not have a decline in nutritional status, with potentially serious long term consequences.

Nutritional supplements are used widely by children with a range of chronic diseases,[21] for similar indications. That their use has not been evaluated in well designed trials is therefore astonishing. The lack of effectiveness of supplements may be because children do not take them or because they reduce their food intake as a result of taking them. Because of concerns about the inaccuracies in the diet diaries, we have not attempted to assess this further. However, these influences are likely to be similar across different disease groups, and we suggest that trials to assess the effectiveness of nutritional supplements should be done in children with any chronic disease associated with poor nutritional status and growth failure.

Conclusion

The results of this trial have important implications for the nutritional management of children with cystic fibrosis. We have shown that when children with suboptimal nutrition receive regular dietary advice, their nutritional status is similar whether or not they have supplements. Although oral protein energy supplements may have a place in the treatment of malnourished children, possibly during episodes of acute weight loss, they should not be regarded as an essential part of clinical care.

We thank the children with cystic fibrosis who participated in this trial and their families; Tim Cole, Jim Littlewood, John Reilly, and members of UK CF Dietitians Interest Group for advice on this study; and Larry Lands for allowing us to use the habitual activity estimation scale.

Contributors: All authors read and approved the paper. Every author contributed to the drafting and reviewing of the paper. RLS, VJP, DA, and RMW developed the study protocol. RLS was the lead investigator. VJP was the trial coordinator, analysed the results, and wrote the first draft of the paper. DA was the trial statistician and guided the analysis. RMW was the dietetic adviser and chief recruiter in the lead centre. JER collected all the data and assisted in the analysis. VJP is the guarantor. Gill Lancaster, Centre for Medical Statistics and Health Evaluation, University of Liverpool, was the auditor and provided the randomisation schedule.

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Competing interests: VJP, RMW, JER, and several of the dietitians involved in this study have previously received travel expenses to attend conferences from the following manufacturers of oral protein energy supplements: SHS International, Liverpool, UK; Ross Laboratories, IL, USA; Nutricia, Trowbridge, UK; Nestle UK, Croydon.

Ethical approval: Ethical approval was granted by the North West Multi-centre Research Ethics Committee and by the local research ethics committees of all the collaborating centres.

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