Refining low protein modular feeds for children on low protein tube feeds with organic acidemias①,☆,☆☆,☆☆☆

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ABSTRACT

Children with inherited metabolic disorders (IMD) who are dependent on tube feeding and require a protein restriction are commonly fed by ‘modular tube feeds’ consisting of several ingredients. A longitudinal, prospective two-phase study, conducted over 18 months assessed the long-term efficacy of a pre-measured protein-free composite feed. This was specifically designed to meet the non-protein nutritional requirements of children (aged over 1 year) with organic acidemias on low protein enteral feeds and to be used as a supplement with an enteral feeding protein source.

Methodology: All non-protein individual feed ingredients were replaced with one protein-free composite feed supplying fat, carbohydrate, and micronutrients. Thirteen subjects, median age 7.4y (3–15.5y), all nutritionally tube dependent (supplying nutritional intake ≥ 90%, n = 12; 75%, n = 1), and diagnosed with organic acidemias (Propionic acidaemia, n = 6; Vitamin B12 non-responsive methyl malonic acidaemia, n = 4; Isovaleric acidaemia, n = 2; Glutaric aciduria type1, n = 1); were studied. Nutritional intake, biochemistry and anthropology were monitored at week − 8, 0, 12, 26 and 79.

Results: Energy intake remained unchanged, providing 76% of estimated energy requirements. Dietary intakes of vitamins, minerals and essential fatty acids significantly increased from week 0 to week 79, but sodium, potassium, magnesium, decosahexanoic acid and fibre did not meet suggested requirements. Plasma zinc, selenium, haemoglobin and MCV significantly improved, and growth remained satisfactory. Natural protein intake met WHO/FAO/UNU 2007 recommendations.

Conclusions: A protein-free composite feed formulated to meet the non-protein nutritional requirements of children aged over 1 year improved nutritional intake, biochemical nutritional status, and simplified enteral tube feeding regimens in children with organic acidemias.

1. Introduction

Enteral feeds for children with severe organic acidemias, (propionic acidaemia, [PA]; vitamin B12 non-responsive methyl malonic acidaemia, [MMA B12nr]; isovaleric acidaemia, [IVA]; glutaric aciduria type 1, [GA1]); dependent on tube feeding are complex. Protein-free composite feeds supplying adequate macro and micronutrients are unavailable for children over 12 months of age, necessitating feeding regimens to consist of multiple ingredients to meet the non-protein nutritional requirements. Adaptation of enteral formulations designed for other clinical conditions may lead to nutritional imbalance, sub-optimal growth and body composition in children who are at risk of metabolic decompensation. It is essential to provide an age appropriate, protein-free composite feed to supplement sources of natural and precursor-free L-amino acid supplements for enteral feeds in this vulnerable group.

Our hypothesis was that an age appropriate protein-free composite feed (supplemented with fat, carbohydrate, vitamins, minerals and essential fatty acids) formulated for children over the age of 1 year with IMD would improve nutritional status and simplify enteral tube feeding regimens for children requiring low protein diets with organic acidemias. The protein-free composite feed was designed to accompany a protein containing feed, which supplied the protein source.

We have previously reported the short-term efficacy and tolerance

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of a powdered pre-measured protein-free composite feed [Basecal 200 Vitafllo Ltd. Liverpool UK], containing fat, carbohydrate and micronutrients designed for children with organic acidemias, over 1 year of age. The children required a protein restriction, and were tube feeding dependent. In this open, extension study, we report the nutritional efficacy and caregiver feed preparation data after the protein-free composite feed formulated for children aged over 1 year of age had been used for 18 months when patients were fully transitioned onto the protein-free composite feed. This protein-free feed provided energy and an important source of carbohydrate, fat, essential fatty acids, vitamins and minerals. The protein requirements were provided by a separate feed and we were not aiming to study the impact on protein nutrition.

2. Methods

2.1. Study design

An 18-month, longitudinal prospective open-label, intervention, extension study using a protein-free composite feed (study feed) developed for children over 1 year of age. The introduction of the study feed in the first 6 months (phase 1) has been reported [1]. In phase 2, patients with organic acidemias on tube feeds were studied for a further 12 months, when all individual modular energy sources were replaced with only one ingredient, the study feed.

2.2. Study formulation (Table 1)

The pre-measured study feed has a nutritional profile that meets the nutritional requirements of children over 1 year of age when reconstructed at 1 kcal/ml. It contains carbohydrate, fat (including long chain polysaturated fatty acids), vitamins, minerals, and trace elements. It does not contain fibre. Each sachet (43 g) mixed with 200 ml water, provides 200 kcals (1 kcal/ml).

2.3. Inclusion criteria

Children were recruited if they had a proven organic acidemia, aged over 1 year of age or weighed between 8 and 31 kg, and were taking a modular feed providing ≥ 75% of enteral feed intake. All children had taken part in study phase 1 [1].

2.4. Phased introduction of study feed (Table 2)

At the start of the study, when analysis is based on the follow-up subjects (n = 13), enteral feeds consisted of a median of 4 ingredients comprising of: a natural protein source, precursor-free L-amino acids (disorder specific) and energy modules (either an infant energy module [± additional energy modules] or individual energy modules).

2.4.1. Phase 1 (week 0–26)

In this phase, the aim was to ensure children tolerated the study feed. This feed replaced the infant protein-free composite feed (Energivit [Nutricia Ltd]). However, to maintain a constant energy intake supporting metabolic stability, other energy sources [glucose polymer (n = 8) and 50% fat emulsion (n = 1)] remained in the feed recipes. All precursor-free L-amino acids were changed to pre-measured sachets. (Vitafllo International Ltd)

2.4.2. Phase 2 (week 27–79)

The study protein-free composite feed completely replaced the remaining energy sources (glucose polymer and 50% fat emulsion).

2.5. Protein prescription

Changes were made to protein (intake/sources) as children increased in age (e.g. natural protein source changed from infant formula to standard enteral feed). Natural protein was prescribed according to WHO/FAO/UNU (2007) [2] safe levels of protein intake for MMA/PA and IVA and in GA1 according to European guidelines [3]. In MMA/PA, an additional 15 to 20% of total protein intake was prescribed from MMA/PA precursor-free L-amino acids (AA); in GA1, lysine-free, low tryptophan AA supplements were prescribed according to GA1 European guidelines [3]. No precursor-free AA supplements were prescribed for patients with IVA.

2.6. Dietary analysis

For 3 days during week 79, caregivers recorded the volume of modular feed consumed and any oral food and drink intake (n = 1) by weighing dietary intake. Dietary analysis was calculated using the software program Electronic Dietetic Manager (EDM 2000™ Microman 2000 PO box 3721 Newport Pagnell UK) and McCance and Widdowson’s ‘The Composition of Foods.’ [4]. The intake of energy, total protein (natural protein and protein equivalent from precursor-free L-amino acids), fibre, calcium, magnesium, iron, zinc, selenium, sodium, potassium, vitamin B12, vitamin D, essential fatty acids (DHA and AA) and fluid was assessed. Each nutrient (except protein, essential fatty acids (DHA and AA), fluids and fibre) was compared as a percentage of the DH 1991 reference nutrient intakes (RNI) or estimated average requirement (EAR) for energy [5]. Protein intake was compared.
with the WHO/FAO/UNU safe levels of protein intake [2] and fibre with the Scientific Advisory Committee on Nutrition [6]. Nationally agreed definitions for DHA and AA intake for children in the UK are not available. A comparison was made with World Health Organization [7] global recommendations.

2.7. Anthropometric measurements

Weight, height/length, z-scores were collected at outpatient clinic appointments. In children ≥ 2 years of age, weight was estimated by: standing and sitting Seca electronic scales (accurate to two decimal places); and height by a calibrated stadiometer (accurate to one decimal place). In children < 2 years of age, measurements were taken naked: weight by Seca infant scales accurate to two decimal places, supine place). In children < 2 years of age, measurements were taken naked: height by a calibrated stadiometer (accurate to one decimal place). In children ≥ 2 years of age, weight was estimated by:

2.8. Illness episodes

The number of hospital admissions, reason for admission and length of stay were recorded from phase 1 (week 0–26) and phase 2 (27–79).

2.9. Nutritional blood biochemistry

Venous blood samples were collected for glucose, electrolytes, full blood count, plasma selenium glutathione peroxidase, zinc, iron, ferritin, vitamin B12, plasma MMA, and C-reactive protein (CRP) at week 8, 0, 12, 26. At week 79, venous samples were taken for full blood count, zinc, selenium, ferritin and CRP. Additionally, a random urine test analyzing sodium and potassium concentrations was collected at week 79, as dietary sodium intake was low in phase 1. Blood samples were taken after a minimum of 3 h fasting.

2.10. Statistics

The median nutritional intake from the different feeding regimens was compared at baseline, week 26 and week 79. The statistical tests used were non-parametric paired Wilcoxon signed rank tests. The same statistical tests were applied to analyse for significant differences in biochemistry, haematology and anthropometric results.

3. Results

3.1. Subjects (Table 3)

Thirteen children (6 boys, 7 girls) were followed from phase 1. Confirmation of the organic acidaemia by DNA analysis is available for nine of the thirteen subjects. One subject had confirmation via skin biopsy and isovaleric acid incorporation analysis; the remaining three subjects were diagnosed by routine biochemical testing. Their median age (range) was 7.4y (3–15.5y). All had organic acidaemias: PA n = 6; MMA B12nr, n = 4; IVA n = 2; and GA1, n = 1. Eight children were of Asian Pakistani origin, one Afro-Caribbean, one Arabic, one Bangladeshi and two European. All children received ≥ 75% of their enteral nutritional intake via tube feeds (nutritional intake: ≥ 75%, n = 12; 75%, n = 1).

Two children, both with PA were withdrawn from the study after completing phase 1 (one died post liver transplantation and one required long term hospital intensive care management).
Table 4
Comparison of daily nutritional intake and reference nutrient intakes, median (range) for all nutrients measured at baseline, phase 1 (when study feed replaced one ingredient), and phase 2 (when all modular ingredients were replaced).

| Nutrients                  | Mean nutrient intake (range) | Significance Pre-study to phase 1 | Significance Baseline to phase 2 | % reference nutrient intake | Significance Pre-study to phase 1 | % reference nutrient intake | Significance Baseline to phase 2 |
|----------------------------|-----------------------------|-----------------------------------|-----------------------------------|-----------------------------|-----------------------------------|-----------------------------|----------------------------------|
|                            | Pre-study (week 8)          | Phase 1 (week 26)                 | Phase 2 (week 79)                 | Baseline (week 8)           | Phase 1 (week 26)                 | Phase 2 (week 79)            | n = 13                           |
| Energy kcal/kg/d           | 59 (32–82)                  | 61 (34–87)                        | 58 (33–62)                        | 61 (34–87)                  | 61 (34–87)                        | 76 (47–103)                  | 76 (48–86)                       | p = 0.87                        |
| Total protein g/kg (natural and precursor-free l-amino acids) g/kg/d | 1.2 (0.7–1.5)               | 1.2 (0.8–1.4)                     | 1.0 (0.6–2.1)                     | 1.0 (0.8–2.1)               | 1.0 (0.8–2.1)                     | 1.29 (78–153)                | 1.29 (78–153)                    | p = 0.002                        |
| Natural protein** g/kg/d   | 0.85 (0.5–1.2)              | 0.85 (0.5–1.2)                    | 0.9 (0.6–1.1)                     | 0.9 (0.6–1.1)               | 0.9 (0.6–1.1)                     | 94 (56–141)                  | 94 (56–141)                      | p = 0.8                         |
| Precursor-free L-amino acids g/kg/d | 0.35 (0.2–0.7)       | 0.4 (0.2–0.6)                     | 0.2 (0–1)                         | 0.2 (0–1)                   | 0.2 (0–1)                         | 0/na                        | 0/na                            | p = 0.002                        |
| Calcium mg/d***            | 693 (426–848)               | 718 (498–1102)                    | 804 (599–1673)                    | 804 (599–1673)              | 804 (599–1673)                    | 145 (89–242)                 | 145 (89–242)                     | p = 0.75                         |
| Iron mg/d***               | 12 (6–17)                   | 12 (6–18)                         | 13.7 (10–27)                      | 13.7 (10–27)                | 13.7 (10–27)                      | 142 (87–232)                 | 142 (87–232)                    | p = 0.75                         |
| Zinc mg/d***               | 10.5 (6–14)                 | 11.5 (6–17)                       | 13.7 (10–26)                      | 13.7 (10–26)                | 13.7 (10–26)                      | 149 (92–240)                 | 149 (92–240)                     | p = 0.75                         |
| Selenium μg/d***           | 30.2 (15–46)                | 35.5 (17–68)                      | 41 (29–71)                        | 41 (29–71)                  | 41 (29–71)                        | 148 (87–247)                 | 148 (87–247)                     | p = 0.75                         |
| Phosphorous mg/d***        | 508 (308–749)               | 553 (291–832)                     | 634 (445–1231)                    | 634 (445–1231)              | 634 (445–1231)                    | 144 (93–214)                 | 144 (93–214)                     | p = 0.75                         |
| Potassium mmol/d***        | 26.9 (16–46)                | 28 (15–48)                        | 37 (26–63)                        | 37 (26–63)                  | 37 (26–63)                        | 91 (28–164)                  | 91 (28–164)                      | p = 0.75                         |
| Vitamin D μg/d***          | 13 (8–17)                   | 15.7 (12–24)                      | 16 (11–29)                        | 16 (11–29)                  | 16 (11–29)                        | 179 (114–242)                | 179 (114–242)                    | p = 0.75                         |
| Magnesium mg/d***          | 100 (67–173)                | 121 (57–278)                      | 145 (102–392)                     | 145 (102–392)               | 145 (102–392)                     | 77 (43–144)                  | 77 (43–144)                      | p = 0.75                         |
| Vitamin B12 μg/d***        | 2.7 (1.7–3.6)               | 3.0 (2–5)                         | 3.0 (3–6)                         | 3.0 (3–6)                   | 3.0 (3–6)                         | 339 (200–580)                | 339 (200–580)                    | p = 0.002                        |
| Sodium mmol/d***           | 20 (8–33)                   | 25 (9–36)                         | 31 (22–42)                        | 31 (22–42)                  | 31 (22–42)                        | 61 (29–110)                  | 61 (29–110)                      | p = 0.002                        |
| Arachidonic acid (mg)§§    | 0 (0–91)                    | 96 (32–128)                       | 95 (45–121)                       | 95 (45–121)                 | 95 (45–121)                       | 107 (58–131)                 | 107 (58–131)                     | p = 0.002                        |
| Fluid ml/kg/d§§§           | 1087                        | 1100                              | 1200 (900–1890)                   | 1200 (900–1890)             | 1200 (900–1890)                   | 68 (39–89)                   | 68 (39–89)                       | p = 0.2                          |
| Fibre g/d§§§               | 4 (0–12)                    | 4 (0–12)                          | 4 (0–12)                          | 4 (0–12)                    | 4 (0–12)                          | 20 (0–60)                    | 20 (0–60)                       | p = 1                            |

n/a not available, * estimated average requirement ** WHO/FAO/UNU 2007 recommendations *** reference nutrient intake, § food and agriculture organization of united nations (FAO), §§ based on Holliday Segar formula for 20 kg child, §§§ SACN2015, $ no vitamin D RNI available for children > 3 yr.
Twelve children had a gastrostomy tube/button and one had a nasogastric tube. Eleven families had one caregiver who spoke and read English fluently. Diagnosis was mainly in the neonatal period (including three siblings of index cases), but 2 were diagnosed later in infancy (7 months \( n = 1 \) and 10 months \( n = 1 \)).

### 3.2. Feed preparation changes (Table 2)

The number of enteral feed ingredients decreased significantly in phase 2: median number of ingredients baseline, \( n = 4 \); phase 1, \( n = 3 \); and phase 2, \( n = 3 \) (\( p = 0.05 \)). In phase 2, no caregivers used scales or scoops to measure ingredients.

#### 3.3. Nutrient intake (Table 4)

##### 3.3.1. Energy, protein and fluid intake

Energy intake (median of 76%) as a percentage of the estimated average requirement (EAR) for age \( 5 \) remained unchanged between baseline, phase 1 and phase 2. The energy intake was closely controlled to avoid excessive weight gain.

##### 3.3.2. Protein intake

The median natural protein intake remained constant at 0.9 g/kg/day throughout the 18-month study period. Total protein intake expressed as g/kg/day significantly decreased, (\( p = 0.002 \)) associated with decreasing natural protein requirements with age (WHO/FAO/UNU 2007) \( 2 \) and a corresponding decrease in precursor-free L-AA (\( p = 0.002 \)) from baseline to week 79. Natural protein intake was provided from a standard paediatric feed Nutrini multisource (Nutricia Ltd., Trowbridge, UK), meeting safe levels of protein intake. Precursor-free amino acids supplemented natural protein intake, providing an additional 15 to 20% of total protein intake.

##### 3.3.3. Vitamin, mineral and long chain fatty acid intake (Table 4)

From baseline to week 79 there was a significant increase in the median daily intake of: calcium (\( p = 0.02 \)), iron (\( p = 0.02 \)), zinc (\( p = 0.0005 \)), selenium (\( 0.005 \)), phosphorous (\( 0.001 \)), vitamin B12 (\( p = 0.003 \)), potassium (\( 0.005 \)), magnesium (\( p = 0.005 \)), and sodium (\( p = 0.001 \)). The intake of both docosahexaenoic acid (DHA) (\( p = 0.0001 \)) and arachidonic acid (AA) (\( p = 0.0005 \)) significantly improved. Nutrients failing to meet reference intakes were potassium (74%), magnesium (89%), sodium (80%), docosahexaenoic acid (DHA) 57% and fibre (20%).

In phase 1, dietary intake of only magnesium (\( p = 0.02 \)), sodium (\( p = 0.002 \)), Vitamin B12 (\( p = 0.01 \)), Vitamin D (\( p = 0.04 \)), docosahexaenoic acid (DHA) (\( p = 0.01 \)) and arachidonic acid (AA) (\( p = 0.001 \)) significantly improved. All except sodium (72%), DHA (48%) and fibre (20%) failed to meet reference guideline intakes.

#### 3.4. Nutritional biochemical and haematology results (Table 5)

Over the 18-month period (baseline to week 79), there was a significant increase in plasma zinc (\( p = 0.03 \)), selenium (\( p = 0.01 \)), haemoglobin (\( p = 0.05 \)) and MCV (\( p = 0.005 \)). All the other measured analytes, ferritin and CRP remained within the reference ranges and were unchanged. Median urinary sodium was 80 mmol/L (22 – 300) and potassium was 41 mmol/L (13–236), with an appropriate ratio of 2:1.

In phase 1, only plasma selenium (\( p = 0.002 \)) and whole blood glutathione peroxide (\( p = 0.02 \)) significantly improved (baseline to week 26).

#### 3.5. Anthropometry

There were no significant differences in median height or weight z scores throughout the study. Median weight z score: baseline, 0.3 (– 3.1 to 2.5); phase 2, 0.2 ( – 2.3 to 1.8); height z score: baseline, – 1.3 ( – 2.6 to 1.5); phase 2, – 0.9 ( – 2.9 to 0.4).

#### 3.6. Hospital admissions

The median number of hospital admission days was: phase 1, 3 (range 2–12); and phase 2, 3 (range 1–86). The hospital admissions were associated with vomiting, chest infections or pancreatitis (\( n = 1 \)) causing metabolic decompensation. No admissions were reported because of feed changes.

#### 3.7. Medications

The median number of daily medications was 4, range (1–10): including L-carnitine (\( n = 13 \)), metronidazole (\( n = 7 \)), domperidone (\( n = 2 \)), ondansetron (\( n = 4 \)), omeprazole (\( n = 4 \)), and ranitidine (\( n = 1 \)). Six subjects were prescribed regular laxatives (movicol and lactulose) and 4 had fibre added to their feeds for constipation. One child was prescribed sodium supplements because of previous low blood concentrations. Only one child was routinely prescribed sodium benzoate due to frequent metabolic decompensation; no other patients were prescribed ammonia lowering drugs.

### 4. Discussion

In this longitudinal 18 month study, the use of a pre-measured protein-free composite feed designed for children aged over 1 year used in combination with protein sources (natural protein and precursor-free L-AA) to meet individualized protein requirements improved the nutrient intake and biochemical status in children with organic acidemias. Replacing individual energy and fat modules with one comprehensive protein-free composite feed simplified the feeding regimens, replacing individualized protein requirements with age

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**Table 5**

|                         | Pre-study (week – 8) | Phase 1 (week 26) | Statistical significance pre-study to phase 1 n = 13 | Phase 2 (week 79) | Statistical significance pre-study to phase 2 n = 13 | Reference range |
|-------------------------|----------------------|-------------------|------------------------------------------------------|-------------------|------------------------------------------------------|-----------------|
| Plasma zinc µmol/L. L   | 10.9 (8.9–14.6)      | 10.7 (7–15.3)     | p = 0.98                                             | 12.5 (7–16.5)     | p = 0.03                                             | 10–18           |
| Plasma selenium µmol/L   | 0.96 (0.6–1.2)       | 1.11 (0.8–1.4)    | p = 0.002                                            | 1.2 (0.9–1.5)     | p = 0.01                                             | 0.8–8.2         |
| Ferritin µg/L            | 34 (5.3–121)         | 39.2 (7.8–167)    | p = 0.12                                             | 38.5 (9–93)       | p = 0.8                                              | 32–233          |
| Vitamin B12 ng/L         | 957 (209–1049)       | 977 (166–2121)    | p = 0.95                                             | 760 (114–1500)    | p = 0.2                                              | 259–823         |
| Haemoglobin g/dl         | 122.9 (103–139)      | 123.8 (114–136)   | p = 0.84                                             | 130 (109–161)     | p = 0.05                                             | 112–130         |
| MCV g/L                 | 75 (65–83)           | 76 (68–84)        | p = 0.22                                             | 85 (73–94)        | p = 0.005                                            | 75–90           |
| C reactive protein mg/   | 2.6 (1–13)           | 2.9 (1–19)        | p = 0.9                                              | 2.3 (1–12)        | p = 0.9                                              | < 10            |
| L L                     |                       |                   |                                                      |                   |                                                      |                 |
| Urine sodium mmol/L     | –                    |                   |                                                      | 80 (22–300)       |                                                      | 40–220          |
| Urine potassium mmol/L  | –                    |                   |                                                      | 41 (13–236)       |                                                      | 10–60           |
and overall, lowered the number of core ingredients used.

Over 18 months, there was a significant improvement in the intake of essential fatty acids, vitamins and minerals (calcium, iron, zinc, selenium, phosphorus, vitamin B12, potassium, magnesium, sodium and docosahexaenoic and arachidonic acid), which led to an improvement in biochemical nutritional status for plasma zinc, selenium, hae-moglobin and MCV. These results were better than what we reported in phase 1 of this study. However, in phase 2 (out of controlled study conditions) we were able to replace all energy supplied by glucose polymer supplements with the nutrient supplemented protein-free composite feed leading to further improvements in nutrient intake. It is essential that patients with organic acidemias on low protein diets receive optimal nutrition from enteral feeds. They have frequent and unpredictable hospital admissions due to metabolic decompensation and require glucose-polymer based emergency feeds (with a low nutrient density) during intercurrent illness. This interrupts macro and micro-nutrient supply.

The nutrient composition of the study feed may require further optimization. Magnesium, potassium and sodium intakes were still below the UK RNI [5]. Only one child, with PA received sodium containing nitrogen scavenger drugs. Although, random sodium and potassium urine analysis in phase 2 suggested an overall satisfactory biochemical status, dietary intakes would imply some children might be borderline deficient. The long-term clinical consequences of these sub-optimal intakes are unknown. Magnesium is physiologically important for skeletal development and maintenance of electrical potential in nerve and muscle membranes [8]. Potassium is required for lean muscle synthesis, normal cell function and maintenance of total body fluid volume, acid and electrolyte balance. The WHO guideline on potassium intake for adults and children [9] suggested a conditional recommendation of at least 90 mmol/day, with an adjustment downwards for children based on their energy requirements.

The study feed did not contain a source of fibre. In MMA and PA, the amount and optimal blend of fibre(s) that should be added to enteral feeds is unknown. Mixed fibre supplements in enteral feeds normalising transit time, improves gut barrier function, and increases production of short chain fatty acids especially propionate [10]. It is possible that adding mixed fibres, particularly those containing neutral sugars to enteral feeds, may increase concentrations of propionate from short chain fatty acids, which may be detrimental in children with PA and MMA [11–14]. More information is required about the composition of gut flora in children with OA before optimal fibre(s) amounts and composition can be defined [15,16]. A high number of our study group had chronic issues with constipation and were prescribed regular laxatives.

There were a number of limitations with this study. Due to the rarity of the conditions, it only included a small number of children. We did not measure biochemical fatty acid status. We have also not examined organic acids, protein status or amino acid status as this was not the purpose of this study. Plasma sodium and potassium are not sensitive indices of total body sodium and potassium. Although we did take measurements for urinary sodium and potassium, this was only performed at week 79, and only a single, random sample was taken rather than a 24-h collection to measure 24-h excretion as recommended by the World Health Organization report [17]. Overall this study cohort was followed up consistently, blood sample timing standardized and any feed changes monitored closely.

This long term follow up study successfully demonstrated that a pre-measured protein-free composite feed used in combination with an enteral protein source for children aged over 1 year with organic acidemias on low protein enteral feeds, significantly improved nutrient intake, biochemical nutritional status and simplified the feed making process. However, further changes to the nutrient composition of this protein-free composite feed are necessary to deliver the optimal nutritional intake in this group of children, whose nutrient intake may be frequently disrupted as a consequence of illness and metabolic decompensation.

Conflict of interest

The study was funded as part of PhD grant. The authors: Daly A, Evans S, MacDonald A have received honoraria, consulting fees from various nutritional companies (Nutricia Ltd., Vitallo Ltd., Merck Serono, Bio Marin, Firstplay dietary foods, Mevalia, Cambrook Foods). Santra S, Chahal S declare no conflict of interests

Transparency declaration

‘The lead author confirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with the ethics committee) have been explained. The reporting of this work is compliant with STROBE guidelines.’

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