ORIGINAL ARTICLE

Impact of nutrient density of nocturnal enteral feeds on appetite: a prospective, randomised crossover study

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Objective: To determine whether the energy density of isocaloric nocturnal enteral feeds (NEF) influences daily nutrient intake in children.

Method: In a 6 week, randomised, crossover trial, the impact on spontaneous nutrient intake of manipulating the energy density of two isocaloric overnight feeds (1.0 kcal/ml and 1.5 kcal/ml) was compared in a group of 32 children aged 1–10 years (or 8–25 kg body weight) on long term, overnight enteral feeding at home. Total daily oral energy, protein, fat and carbohydrate intake were assessed using 3 day food diaries. Anthropometric data were also recorded during the study.

Results: Spontaneous intakes of energy, protein, fat and carbohydrate from food were 20–30% greater when receiving the lower nutrient density feed (1 kcal/ml). This was due to a gender effect; males consumed twice as much protein from food than females and had slightly higher (but not significant) energy and fat intakes when on the larger volume feed. All children increased in weight, height and mid-upper arm circumference in the 6 week period.

Conclusions: Children appear to tolerate and grow equally well, irrespective of the nutrient density and volume of NEF taken. However, it appears that children will consume a more energy and nutrient dense oral diet when given their NEF as a higher volume/lower nutrient density feed. This is particularly so for boys, while for girls the volume of NEF or feed concentration appeared to have no impact on quantity of oral diet taken. However, further blinded studies with larger subject numbers would be useful to support these findings.

Home enteral feeding is increasingly used to provide nutritional support to children with chronic disorders. In 2003, at least 5400 children were receiving home enteral tube feeds in the UK.¹ Consequently, the development of specialised paediatric formulas has expanded rapidly, with a variety of formulas available, providing between 1.0 kcal/ml and 1.5 kcal/ml. Most children are on overnight continuous tube feeds, an unphysiological method of nutritional delivery. It is therefore surprising that there are few studies on the effect of overnight tube feeding on daytime appetite in children. One study of newborn infants with protein energy malnutrition, demonstrated an improved diurnal calorie intake following nocturnal enteral feeds (NEF) with a calorie supply over the normal requirements for age.² However, the role of nutrient density and feed volume in enteral tube feeding supplements in determining children's oral food intake has not been reported.

There is evidence in adults that energy dilute foods are more satiating than energy dense foods.^{3–6} One study in lean and obese women demonstrated that when visual and oral cues were bypassed by infusing food nasogastrically as a bolus, increasing the volume but not energy content affected satiety, while the reverse had no effect on satiety.³ This would suggest that an isocaloric amount of an energy dense feed (1.5 kcal/ml) might have less depressant effects on appetite than a 1.0 kcal/ml feed. In addition, there is evidence that under ad libitum conditions, adults tend to consume a constant weight of food rather than a constant energy intake.⁷

It has also been shown in adults that increasing the volume of liquid food by the addition of water or air affects the satiating impact independent of energy content.^{7–9} Doubling the volume of a liquid food without increasing the energy content, has been shown to increase satiety, but doubling the energy content without changing the volume does not.¹⁰ This implies that in adults, volume consumed is an important determinant of satiety. Increasing volume may result in greater gastric

distension and feelings of fullness, and can subsequently lead to reductions in energy intake.

In children, a study looking at the effect of energy density and food volume on satiety showed that preschool children consumed a higher volume of food when given a low energy density meal compared to a high energy density meal despite a comparable energy intake.¹¹ Another study comparing food intake in children, young adults and the elderly demonstrated that all age groups ate less after a high-fat, high-carbohydrate (energy dense) preload.¹²

Neither adult nor paediatric studies have tested the hypothesis that provision of identical amounts of nutrient administered by nocturnal tube feed will result in lower diurnal food intake when the overnight feed is given in a more dilute, higher volume. This has important, practical implications when choosing the energy density of a feed.

METHODS

Subjects

Inclusion criteria were: (i) children aged 1–10 years or weight 8–25 kg; and (ii) 50–80% of estimated energy requirements taken as overnight enteral tube feeds. Exclusion criteria were: (i) severe hepatic or renal failure; (ii) malabsorption, inflammatory bowel disease or short bowel syndrome; (iii) inborn errors of metabolism; (iv) children on special diets (eg, milk free); or (v) children unable to take an oral diet.

Study design

The study was a single centre, open, prospective, randomised, crossover study. It comprised two treatment periods, each lasting 21 days. Treatment L was a "low" nutrient density feed (1 kcal/ml) and treatment H a "high" nutrient density feed

Abbreviations: BMI, body mass index; EAR, estimated average requirement; NEF, nocturnal enteral feed; RNI, reference nutrient intake

Table 1 Clinutren Junior composition (1 kcal/ml and 1.5 kcal/ml dilutions)

Nutrients/100 ml	1 kcal/ml	1.5 kcal/ml
Energy (kcal)	100	150
Protein (g)	3	4.5
Carbohydrate (g)	13.7	20
Fat (g)	4	5.9

(1.5 kcal/ml). Both treatments delivered the same amount of nutrients; only the volume of feed differed. This was done using equivalent amounts of the same powdered casein-based, nutritionally complete paediatric enteral feed, Clinutren Junior (Nestlé, Vevey, Switzerland) (table 1) but with differing dilutions.

The subjects were given between 50% and 80% (median 70%) of their estimated energy requirement (Schofield equation¹³) via an overnight tube feed. The amount of nutrient intake delivered by overnight feed was individualised for each subject based on nutritional requirements, and remained constant throughout the study.

Following parent/carer consent, subjects were randomised (using randomly generated numbers in sealed envelopes) to either group 1 (treatment L, then H) or group 2 (treatment H, then L). The allocation sequence was computer generated by an external company. There was no washout period as no carryover effect was anticipated. Nineteen subjects (eight male) were randomised to group 1 and 13 subjects (seven male) to group 2.

Ethical approval was given by the Ethics Committee of South Birmingham Health Authority and informed consent was obtained from parents/carers.

Feed preparation

Following recruitment, subjects were visited at home at the start of the study and at 21 days (crossover point). The investigator (AD) demonstrated the feed preparation technique on the first visit and parental technique was checked on the second visit. Powder was weighed on Salter electronic scales (Salter, Tonbridge, Kent, UK; accurate to 5 g), emptied into a

standard 1 litre measuring jug and cooled boiled water added in the appropriate volume.

Dietary intake data

Parents completed a 3 day food diary at the end of each study period (days 19–21 and 40–42). Food was described using common household measures (eg, tablespoons) and weights from food labels. Total daily energy, protein, fat and carbohydrate intake was assessed using Microdiet version 9 (Salford University, Manchester, UK), a computer program based on McCance and Widdowson's 'The composition of foods'.¹⁴ Energy intake was calculated as a percentage of estimated average requirement (EAR) and protein as a percentage of reference nutrient intake.¹⁵ Differences between the two treatments were assessed by comparing median total daily energy intake (across subjects) for the last 3 days of each treatment. This was considered as a valid surrogate marker for appetite.

Nocturnal tube feed intake

The actual volume of feed given overnight was recorded daily. From this, the quantity of administered feed as a percentage of the amount prescribed was calculated.

Anthropometric data

Subject weight, height and mid-upper arm circumference were recorded at the start, crossover (day 21) and end of the study (day 42) by the investigator (AD). Weight was measured to the nearest 10 g using Seca electronic scales (Seca, Hamburg, Germany). Height was measured to the nearest 1 mm using a portable measuring stick (Growth Foundation, London, UK). Mid-upper arm circumference was measured to the nearest 1 mm using non-stretch tape (Shakir strips).

Adverse events

Subjects were asked to record any gastrointestinal symptoms throughout the study such as vomiting, abdominal pain and abnormal stools (change in frequency or consistency).

Subject withdrawal

Forty subjects were initially recruited, but eight subjects withdrew from the study. Reasons for withdrawal were: inability to tolerate the higher feed volume (one), removal of the nasogastric tube due to improved oral intake (one) and

Figure 1 Nutrient intake from food on treatment L minus treatment H.

Table 2 Subject characteristics

	Group 1 (treatment L then H), n = 19	Group 2 (treatment H then L), n = 13
Gender	8 M; 11 F	7 M; 6 F
Median age (years)	4.5	4.6
Median weight (kg)	14.6	15.2
Median height (cm)	95.4	101.5
Median mid-upper arm circumference (cm)	15.0	15.6
Diagnostic group		
Liver/small bowel transplant	5	5
Cystic fibrosis	3	3
Cardiac	3	0
Cancer	2	3
Neurological	2	1
Haematological	2	0
Surgical	1	1
Respiratory	1	0

inadequate record keeping (six). Seven of the eight subjects were withdrawn before crossover such that there were equal numbers of patients on each feed at withdrawal; four (three male) were on feed L, and four (one male) on feed H. With the exception of one subject, withdrawal was not feed related. Data on 32 subjects were therefore available for analysis.

Statistical analysis

With 32 subjects it would be possible to detect with 90% power a difference of 10% between the two regimens in the primary

study parameter (mean total dietary energy intake over the last 3 days) using a paired *t* test with a 5%, two-sided significance level. A sample size of 40 subjects allowed for a potential 20% withdrawal rate.

Groups were compared for energy, protein, fat and carbohydrate intake and for anthropometric measurements using Wilcoxon signed rank tests suitable for crossover studies and Mann–Whitney tests to compare differences between genders. These non-parametric tests were also used to compare the two time periods of the study in respect of nutrient and energy intake. For between dietary group comparisons, the within individual differences were reasonably normally distributed, so general linear model analysis of variance was used to test for effects of age, gender and order of treatment (HL or LH). Results are presented as medians with ranges in parentheses.

RESULTS

Subjects

Thirty two children (15 male), with median age of 4.5 years (range 1.2–12.2 years), median weight of 14.8 kg (range 7.8–26.7) and body mass index (BMI) of 15.4 kg/m² (range 11.2–19.5) were recruited (21 white, 10 Asian and one Afro-Caribbean) (table 2). Children presented from a range of medical specialties. All children were medically stable during the study. Children were taking a 1 kcal/ml or 1.5 kcal/ml standard whole protein enteral tube feed at commencement of the study to provide 50–80% of their daily calorie intake and all children had been established on overnight feeding for at least 1 year. Seventeen children had a nasogastric tube and 15 had a gastrostomy.

Table 3 Nutrient composition of oral food intake and enteral tube feed consumed

	Kilojoules	% EAR* energy	Protein (g)	% RNI† protein	Fat (g)	Carbo- hydrate (g)	Volume (ml)	% recommended volume
Oral food intake								
L								
Median	1365	20	9.0	48	15.4	35.1	–	–
Range	(135–4832)	(3–68)	(1–42)	(3–288)	(3–46)	(1–164)	–	–
H								
Median	987	15	7.0	36	11.8	28.1	–	–
Range	(110–3560)	(2–50)	(1–27)	(6–186)	(1–41)	(4–120)	–	–
L–H‡								
Median	344	5	3.0	10	4.2	10.8	–	–
95% CI§	(139 to 567)	(2.3 to 8.7)	(1.2 to 5.3)	(6.5 to 29.8)	(1.3 to 7.0)	(3.2 to 18.8)	–	–
p Value§	0.001	0.002	0.001	0.001	0.005	0.006	–	–
Enteral tube feed								
L								
Median	2575	45	18.4	103	24.5	84.0	613	100
Range	(1260–5145)	(19–86)	(9–37)	(46–219)	(12–49)	(41–168)	(300–1225)	(86–107)
H								
Median	2680	47	19.1	111	25.1	85.1	426	100
Range	(1260–5603)	(19–83)	(9–40)	(46–211)	(12–52)	(40–178)	(200–889)	(85–108)
L–H‡								
Median	–63	–1.0	–0.5	–2.0	–0.2	–0.4	1.47 (L/H)¶	0.5
Range	(–1483 to 256)	(–22 to 5)	(–8 to 2)	(–55 to 13)	(–13 to 3)	(–44 to 12)	(1.4 to 1.5)	(–14 to 17)
Total diet (oral+tube feed)								
L								
Median	4004	65	29.6	158	38.3	130.6	–	–
Range	(1753–8236)	(27–140)	(13.0–63.5)	(66–413)	(15.7–80.9)	(59.2–270.3)	–	–
H								
Median	3959	63	27.4	161	39.4	121.9	–	–
Range	(1723–9114)	(33–130)	(13.9–68.7)	(79–345)	(15.1–92.7)	(55.7–274.2)	–	–
L–H‡								
Median	281	4	2.2	12	4.1	9.9	–	–
95% CI§	(38 to 491)	(0.7 to 7.8)	(0.5 to 4.7)	(2.5 to 26)	(1.0 to 6.9)	(2.1 to 17.6)	–	–
p Value§	0.03	0.03	0.02	0.02	0.01	0.02	–	–

L, low nutrient density feed; H, high nutrient density feed.

*Estimated average requirement; †reference nutrient intake; ‡median value derived from individual measurements (not difference between overall median values given);

§Wilcoxon signed rank test, 95% confidence interval (CI) for median; ¶ratio of volume L and volume H not difference (L–H) as in remainder of table.

Table 4 Median difference in nutrient intake between genders: oral food intake

	Low nutrient density (L) feed		High nutrient density (H) feed		L-H*		p value† (CI)‡ L-H male vs female
	Male	Female	Male	Female	Male	Female	
Kilojoules							
Median	1604	920	958	1000	611	219	0.06
Range	(630–3286)	(134–4830)	(420–2700)	(110–3561)	(–197 to 1570)	(–751 to 1529)	(–760 to 21)
%EAR‡ energy							
Median	26	19	14	15	8	3	NS
Range	(13–54)	(3–68)	(6–47)	(3–50)	(–3 to 30)	(–12 to 22)	(–12.2 to 0.6)
Protein (g)							
Median	14.6	7.1	7.3	6.8	5.3	1.1	0.02
Range	(4.1–28.2)	(0.4–41.7)	(2.8–22.9)	(0.8–29.0)	(–0.4 to 16.4)	(–4.2 to 14.8)	(–7.5 to 0.5)
%RNI§ protein							
Median	81	42	36	37	21	8	0.03
Range	(28–194)	(3–288)	(14–134)	(6–186)	(–3 to 113)	(–21 to 102)	(–43 to –2)
Fat (g)							
Median	18.4	10.5	12.2	11.3	7.2	1.4	0.09
Range	(6.2–40.2)	(2.9–45.5)	(4.4–29.9)	(0.8–40.7)	(–5.8 to 17.3)	(–14.1 to 18.9)	(–10 to 0.9)
Carbohydrate (g)							
Median	54.5	31.3	22.7	28.1	16	5.3	NS
Range	(18.1–98.9)	(1.0–164)	(11.7–89.6)	(3.6–120)	(–26.9 to 54.3)	(–21.3 to 44)	(–21.3 to 7.3)

*Median value derived from individual measurements (not difference between overall median values given); †Mann–Whitney test, 95% confidence interval (CI) for difference in medians; ‡estimated average requirement; §reference nutrient intake.

Energy and nutrient intake

Both tube feeds were isocaloric differing only in the volume of added water. There was a significantly higher (20–30%) nutrient intake from food while on feed L compared with the higher nutrient density feed H (table 3; fig 1).

As nutrient intake from NEF was comparable on both feeds, the differences between total intake on feed L and H were due to differences in oral intake. Children were generally compliant with taking the recommended quantity of feed. The median intakes on both L and H were 100% of that prescribed, and median volumes on feed L were 1.47 times higher than on feed H (expected difference 1.5 times, based on 1 kcal/ml and 1.5 kcal/ml feeds) (table 3).

When the differences between treatment L and H with respect to energy, protein, fat and carbohydrate intake from food were considered in multi-factor analysis as cited above, there was no evident influence of the age of children or by the order of treatment so details are omitted for brevity. However, a gender effect was present with boys consuming more protein than girls on feed L (high volume, energy dilute feed) compared

to feed H ($p = 0.02$; CI –7.5 to 0.5; 95% CI for difference in median). Boys consumed twice as much protein from food when on feed L compared to girls and had higher but not significant energy, fat and carbohydrate intakes (table 4).

When total dietary intake (food+NEF) was calculated, a similar difference between boys and girls was seen (energy $p = 0.02$, protein $p = 0.01$, fat $p = 0.05$) (table 5).

Carbohydrate intake however, did not appear to differ significantly between boys and girls. There was no noteworthy difference between the two time periods in respect of the energy and nutrient characteristics.

Anthropometry

Children gained in weight (median = 0.4 kg), BMI (median = 0.8 kg/m²), height (median = 10 mm) and mid-upper arm circumference (median = 4 mm) in the 6 week period. All anthropometric measurements showed a significant improvement over the 6 weeks of the study ($p < 0.001$). There was no significant difference between feed L or H and no order of treatment effect on anthropometric gains.

Table 5 Median difference in nutrient intake between genders: total diet (oral+tube feed)

	Low nutrient density (L) feed		High nutrient density (H) feed		L-H*		p value† (CI)‡ L-H male vs female
	Male	Female	Male	Female	Male	Female	
Kilojoules							
Median	4829	3503	4444	3772	552	55.9	0.02
Range	(2969 to 7750)	(1751 to 8236)	(1819 to 7048)	(1722 to 9118)	(–176 to 1570)	(–1707 to 1449)	(–998 to –139)
%EAR‡ energy							
Median	69	57	63	63	8	1	0.04
Range	(46 to 140)	(27 to 113)	(35 to 130)	(33 to 125)	(–2 to 30)	(–35 to 20)	(–14.4 to –1.5)
Protein (g)							
Median	41.7	22.8	31.7	26.2	5.3	0.1	0.
Range	(22.1 to 59.9)	(13.0 to 63.5)	(13.9 to 50.8)	(14.2 to 68.7)	(–1.3 to 16.4)	(–8.9 to 14.1)	01 (–9.3 to –1.8)
%RNI§ protein							
Median	173	137	161	160	27	1	0.01
Range	(116 to 413)	(66 to 391)	(96 to 345)	(79 to 294)	(–9 to 113)	(–61 to 97)	(–51 to –9)
Fat (g)							
Median	43.9	34.7	41.7	35.8	6.5	0.5	0.05
Range	(30.4 to 80.9)	(15.7 to 76.7)	(17.5 to 69.3)	(15.1 to 92.7)	(–3.3 to 19.5)	(–24.2 to 18.7)	(–11.6 to 0.2)
Carbohydrate (g)							
Median	161	107	143	108	20.9	0.7	0.08
Range	(86 to 242)	(59 to 270)	(56 to 226)	(56 to 274)	(–18.1 to 56.5)	(–36.2 to 44.3)	(–28.9 to 1.9)

*Median value derived from individual measurements (not difference between overall median values given); †Mann–Whitney test, 95% confidence interval (CI) for difference in medians; ‡estimated average requirement; §reference nutrient intake.

What is already known on this topic

- In adults energy dilute foods appear to be more satiating than energy dense foods and volume consumed affects satiating impact independent of energy content.
- In children taking an oral diet there is a tendency to consume more on a low energy density meal than on a high energy density meal.
- Impact of energy density and volume of enteral tube feeds on appetite in children has not been studied.

Patient tolerance

The feed was generally well tolerated on both regimens. There was one reported incident of apparent feed related vomiting and abdominal pain on feed H but not L. There was no reported incidence of diarrhoea associated with either feed volume. Frequent bed-wetting was reported in four subjects on the larger volume feed (L).

DISCUSSION

This study shows that in contrast to adults and to the study hypothesis, children consume more food orally when given their NEF as a higher volume more dilute feed than a lower volume more energy dense feed. In a study of newborn infants with protein energy malnutrition, infants who received a NEF in addition to ad libitum oral feeding demonstrated an improved diurnal caloric intake.² This suggests that NEF somehow stimulates diurnal appetite. However, why children might eat more following a larger volume NEF than an equivalent energy feed in a smaller volume is unclear. Results in adult studies seem to suggest the opposite, although most involve oral diet and not enteral tube feeds.^{4 6–10} In one adult study involving enteral tube feeding, enteral feeds were given as preloads (bolus) immediately before an oral meal rather than as continuous NEF and provided only a small contribution to energy intake over the day.³ Unfortunately, no other studies have looked at the effect of different nutrient densities of NEF on diurnal appetite.

When results were broken down by gender, this study demonstrated that boys in particular consume more food orally when given their NEF as a higher volume more dilute feed than a lower volume more energy dense feed. Boys consumed twice as much protein orally while on the higher volume, more dilute feed. However, this trend was not seen in girls.

Larger subject numbers and a longer study period may have enabled a more definitive result, particularly with respect to the female subjects who showed no significant difference in oral intake on either feed. Some qualitative measure of satiety and abdominal symptoms (nausea, bloating) may also have provided additional information. While treatment sequence was random and externally controlled, neither the subjects nor the researcher were blinded to the treatment sequence. This may have influenced food intake or reporting of food intake and led to potential source of bias. In addition, while boys on the low energy density feed had a greater intake of food, there was no significant difference in growth and feed tolerance between groups. This questions the clinical significance of the greater nutrient intake which may be a reflection of the inaccuracies of food diaries and the short duration of the study; more significant changes in growth might be expected over a longer duration. Despite these limitations, as the first study to look at the effect of nutrient density and feed volume of NEF on oral intake in children, it does provide an interesting

What this study adds

- This is the first study to examine the effect of different nutrient densities of nocturnal enteral feed on diurnal food intake.
- In contrast to adults and to common assumptions, children appear to consume more nutrients orally when given nocturnal enteral feeds as a higher volume, more dilute feed.
- Male children in particular appear to consume a more energy and nutrient dense oral diet when given their NEF as a higher volume more dilute feed than as a lower volume nutrient dense feed.

comparison to results found in adult studies and studies of oral diet and appetite.

Research suggests that nutrients delivered as enteral tube feeds or parenteral nutrition are less effective in relieving appetite sensations or suppressing food intake than orally ingested nutrients even if estimated energy requirements are met.^{16 17} A study comparing the effect of diurnal, nocturnal and 24 h tube feeding on oral intake and appetite found that tube feeding has little effect on satiety irrespective of the timing of the schedule.¹⁸

The mechanisms responsible for the poorer satiating ability of artificial feeding methods relative to food intake are not clearly understood, but the bypassing of the upper gastrointestinal tract and associated cephalic response by these methods of nutrient delivery may be important.¹⁶ This still does not fully explain why children in this study had higher daily oral energy intakes following a larger volume NEF. It might be possible that the more energy dense feed despite being lower in volume is more viscous and therefore more satiating as has been shown in other studies.¹⁹ In addition, there is evidence that subjects behave differently in longer term studies in naturalistic environments (compared to short-to-medium term laboratory studies), where increased energy density appears more effective at decreasing food intake and less effective at elevating energy intake²⁰ as was seen in this study.

Nocturnal tube feeding is used for many children with chronic or acute illnesses to increase energy and nutrient intake and improve growth and development. It minimises disruption to the child's daily activities and enables them to take oral diet during the day. During this study, the volume of NEF was changed to see if this had any significant effect on daytime appetite. Results showed a trend for children, particularly boys, to consume a more energy and nutrient dense oral diet when given their NEF as a higher volume more dilute feed. This has implications for dieticians when choosing appropriate feeds for children on NEF. Intuitively, most people would assume that a lower volume feed is likely to have a lesser effect on daytime appetite. The results of this study refute this popular assumption.

Further research looking at larger numbers of children on long term NEF are needed to establish a recommendation for routine management and to maximise nutritional status for children on NEF.

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IMAGES IN PAEDIATRICS

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Emergence of *Scedosporium apiospermum* in patients with cystic fibrosis

The ubiquitous *Scedosporium apiospermum* is a saprophytic filamentous fungus that causes a wide range of human infections that affect virtually every organ in the body. *S apiospermum* has been described as one of the major fungal agents of chronic colonisation of airways in patients with cystic fibrosis (CF).¹ This organism is the second most frequent filamentous fungus that can be found in patients with CF after *Aspergillus fumigatus*. The prevalence of *S apiospermum* from bronchial secretions of patients with CF is reported to be 0.7–9%.^{1–3} Although this fungus is usually considered a simple endobronchial colonising agent in CF without pathological effects for the host, there have been some reported cases of invasive infections due to *S apiospermum* in patients with CF, including one case after lung transplantation.^{1,4} However, the pathogenicity of this organism in CF is still not well established.

Figure 1 *Scedosporium apiospermum* growth on Sabouraud Dextrose Agar (SAB) at 22°C for 4 weeks.

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