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ORIGINAL CONTRIBUTION

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Body composition in preterm infants fed standard term or enriched formula after hospital discharge

Summary *Background* Most preterm infants are still preterm and have a low birth weight when they are discharged from the hospital. An important issue is whether the long-term consequences of early growth restriction can be diminished by nutritional intervention in preterm infants after discharge from the hospital. *Aim* To evaluate differences in growth and in weight gain composition of preterm infants fed standard term formula (SF) or enriched formula (PDF) after discharge from hospital during the first 2 months of life. *Methods* Thirty-three healthy preterm infants, birth weight < 1750 g at gestational age < 35 weeks, were randomised to SF or PDF at the time of discharge from hospital. Anthropometric variables were studied longitudinally and body composition was measured using dual energy *x*-ray absorptiometry (DEXA) twice, before hospital discharge and two months later. Weight gain composition was calculated as the difference between the two determinations. *Results* Seventeen infants were fed SF and 16 PDF. Anthropometric variables and whole body composition were similar at birth, at the start of the nutritional study (mean age 45 days), and at the end of the study 2 months later. Over the whole study period, weight gain and weight gain composition were similar in the two groups. Sex did not appear to influence weight gain and weight gain composition. In infants with growth restriction at discharge there was a significant reduction of weight gain, fat mass gain, and bone mineral content deposition independently of the formula provided. *Conclusions* There is no immediate effect on preterm infants of a nutrient enriched formula compared with a standard formula on growth, weight gain, or weight gain composition.

Key words preterm infant – body composition – dual energy *x*-ray absorptiometry – weight gain – postdischarge formula

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Introduction

Despite increasingly aggressive hospital nutritional management, most preterm infants are still preterm and have a low birth weight when they are discharged from hospital. In addition the percentage of infants with a length below the reference range for corrected gestational age at discharge is several times greater than at birth [1, 2]. Various studies have indicated that the window for catch-up growth in growth-retarded babies is limited and that if such growth has not taken place in infancy, the chances that it will occur later diminish [3–5]. In humans, the importance of nutrition in early life is now well known, and the term "programming" has been proposed to emphasise that early nutrition should be considered not simply in terms of providing immediate nutritional needs but also because of certain biological effects that may have lasting or lifelong significance [5]. Epidemiological data also suggest that small size, both at birth and at 1 year of age, is associated with higher rates of diabetes, hypertension, cardiovascular diseases, and stroke later in life [6, 7]. An important issue is whether the long-term consequences of early growth restriction

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can be diminished by nutritional intervention in preterm infants after discharge from hospital – in other words, are the early weeks or months after term a critical period for catch up growth, and can they safely be influenced by nutritional manipulation?

As it appears difficult to avoid nutritional deficits and growth retardation before discharge, several studies in very low birthweight infants have evaluated the effect of postdischarge feeding regimens on growth, bone mineralisation, and biochemical markers of nutritional adequacy, with controversial results [8–15]. Measurement of body composition is fundamentally important in the nutritional care of preterm infants, and up to now there are no data on weight gain composition in preterm infants fed on formula after hospital discharge. Our aim in this study was to evaluate differences in growth and weight gain composition, using dual energy *x*-ray absorption (DEXA), in preterm infants fed on a standard term formula or enriched formula after the discharge from hospital during the first 2 months of life.

Methods

General study design

The study was prospective, blind, randomised, and controlled. We studied healthy preterm infants of birth weight < 1750 g and gestational age < 35 weeks, with no clinical problems. They were studied longitudinally twice using DEXA, to determine body composition and to calculate weight gain composition (as the difference between the two determinations).

The first study was performed just before discharge, when full enteral feeding had been attained and the infant's clinical status allowed us to perform the DEXA examination. The second study was performed at the age of 2 months.

After discharge, infants were seen at home every 3 weeks. On each occasion the infants were weighed naked on an electronic baby scale (SECA, model 727, Hamburg, Germany) to the nearest 5 g. Crown-heel length (on an infant length-board to the next succeeding 0.1 cm) and head circumference (using a paper insertion tape to the next succeeding millimetre) were also determined. All measurements were performed by one person (CP). Regular telephone contact was maintained between visits.

This study was approved by the human ethics committee of the University of Liege. Informed parental consent was obtained.

Feeding

Before discharge, those infants whose parents had decided not breast-feed them were randomised to be fed a standard term formula (SF; Nutrilon Premium; Nutricia) or postdischarge formula (PDF; Premilon; Nutricia). Both formulas were given ad libitum in ready to feed form. The compositions of the formulas are shown in Table 1. Instructions were given to shake each bottle before feeding. Volume intakes were recorded by the parents at each meal the day before the examination at home and collected on the two occasions by the visitor.

DEXA scanning

Body composition was measured with the QDR 2000 bone densitometer (Hologic Inc, Waltham, Massachusetts, USA). Scans were analysed using infant whole body software V5.65P [16]. The principle of the DEXA measurements in term and preterm infants has been described previously [16–18].

From the difference in body composition values between the second and the first examinations, we determined body weight gain and weight gain composition. Increases in lean body mass, fat mass, and bone mineral content were expressed per kg/d and compared in infants fed SF or PDF [19–20].

Weight gain (g) and gain in lean body mass (g), fat mass (g), bone mineral content (mg), and bone area (cm^2) were calculated as the difference between DEXA 2 and DEXA 1. Data are given as per cent of the weight gain or as kg per day. Bone mineral density, calculated as bone mineral content per unit area of bone, is highly dependent on anthropometric variables; we therefore prefer to refer to bone area raised to the power of 1.5 – that

Table 1 Composition of study formulas (per 100 ml)

	Postdischarge formula Per 100 ml (*per 100 kcal*)	Standard term formula Per 100 ml (*per 100 kcal*)
Protein (g)	1.8 (2.4)	1.4 (2.1)
Casein	0.7 (0.9)	0.6 (0.9)
Whey	1.1 (1.5)	0.8 (1.2)
Fat (g)	4.1 (5.5)	3.6 (5.5)
Linoleic acid	0.5 (0.7)	0.4 (0.6)
α-Linolenic acid	0.05 (0.1)	0.08 (0.1)
Carbohydrate (g)	7.5 (10.1)	7.1 (10.8)
Lactose	6.0 (8.1)	7.1 (10.8)
Glucose syrup	1.5 (2.0)	–
Maltodextrin	–	–
Energy (kcal)	74 (100)	66 (100)
Minerals (mg)		
Calcium	80 (108)	54 (82)
Phosphorus	40 (54)	27 (41)
Magnesium	6 (8)	5 (8)
Sodium	24 (32)	18 (27)
Potassium	73 (99)	65 (98)
Iron	1.1 (1.5)	0.5 (0.8)
Zinc	0.7 (0.9)	0.4 (0.6)

Postdischarge formula Premilon (Nutricia)
Standard term formula Nutrilon Premium (Nutricia)

is, bone mineral content (mg)/(bone area (cm^2))$^{1.5}$. This allows us to obtain a measure of apparent volumetric bone mineral density independent of anthropometric variables during the first year of life [20].

Statistics

The data were analysed using PC statistical software (Statistica, version for Window 5.0, 1995, Statsoft, Tulsa, Oklahoma, USA). The data on the two types of feed were compared using paired and unpaired Student's *t* tests. Differences were considered significant at $p < 0.05$. Values was expressed as mean (SD).

In addition, analysis of variance was also performed in order to estimate the specific effects of sex and length growth restriction on weight gain and weight gain composition during the study.

Results

Thirty-three healthy preterm infants (17 girls and 16 boys) were included in the study. Their anthropometric characteristics at birth and at the DXA examinations are shown in Table 2.

Seventeen infants were fed SF and 16 PDF. At the start of the study, length growth restriction (> 2 SD below the mean of the Usher growth chart [21]) was present in 59 % and 50 % of the two groups, respectively. There was no drop out of infants during the study. There was no difference ($p < 0.05$) in anthropometric parameters and whole body composition between infants fed SF and PDF, at birth and at the start and end of the study (Table 2).

During the 2 months of the study, whole body composition changed significantly in the two groups. From the first to the second DEXA examination, there was a significant increase in relative fat mass content (% of body weight) from 9.6 (2.9)% to 21.9 (4.4)% in SF infants, and from 10.8 (5.4)% to 21.8 (4.8)% in PDF infants ($p < 0.01$). Apparent volumetric bone mineral density increased from 9.4 (0.8) to 10.2 (0.6) mg/cm^3 in SF infants, and from 9.4 (0.9) to 10.3 (1.1) mg/cm^3 in PDF infants ($p < 0.01$).

Over the whole period of study, milk intake was similar in the two groups, resulting in higher energy and protein supplies in infants fed the PDF without any effect on gain and weight gain composition (Table 3). The later variables were not influenced by gender, while, when length growth restriction at discharge was taken in account, a significant reduction in weight gain ($p = 0.05$), FM gain ($p < 0.05$) and BMC deposition ($p < 0.05$) was observed independent of the formula provided (Table 4).

Table 2 Anthropometric characteristics and body composition in infants fed term formula or postdischarge formula

	Postdischarge formula	Standard term formula
Number of infants	16	17
At birth		
Sex	8 M/8 F	8 M/9 F
Weight (g)	1294±295	1261±381
Length (cm)	38.4±2.6	38.0±3.5
Head circumference (cm)	27.7±2.0	27.4±2.5
Gestational age (weeks)	30±2	30±2
At 1st DXA examination		
Age (days)	45±21	45±25
Weight (g)	2210±237	2104±304
Length (cm)	43.9±1.4	43.7±2.2
Head circumference (cm)	32.5±1.2	32.3±1.7
LBM (g)	1969±207	1845±247
FM (g)	213±70	232±119
FM (%)	9.6±2.9	10.8±5.4
BMC (g)	28.0±3.4	27.8±4.8
BA (cm^2)	208±19	205±25
At 2nd DXA examination		
Age (days)	106±22	108±27
Weight (g)	4200±270	4030±539
Length (cm)	52.8±1.4	52.4±2.7
Head circumference (cm)	37.7±1.1	37.8±1.8
LBM (g)	3209±233	3082±414
FM (g)	923±220	884±242
FM (%)	21.9±4.4	21.8±4.8
BMC (g)	68.2±10.6	65.0±12.6
BA (cm^2)	351±21	344±42

Values are mean (SD). *BA* bone area; *BMC* bone mineral content; *FM* fat mass; *FM%* fat mass expressed as % body weight; *LBM* lean body mass

Table 3 Weight gain and weight gain composition in infants fed term formula or postdischarge formula

	Postdischarge formula	Term formula
N	16	17
Days between 1 and 2 DXA	61±5	63±8
Volume intake day 25 (ml kg/day)	171±24	174±22
Volume intake day 44 (ml kg/day)	177±20	173±20
Weight gain (g/kg/day)	10±2	10±2
Length (cm/week)	1.0±0.1	1.0±0.2
Head circumference (cm/week)	0.6±0.1	0.6±0.1
LBM (g/kg/day)	6.3±1.5	6.4±1.2
FM (g/kg/day)	3.5±1.0	3.4±1.1
BA (cm^2/kg/day)	0.7±0.1	0.7±0.1
BMC (mg/kg/day)	200±46	188±40

Values are mean (SD). *BA* bone area; *BMC* bone mineral content; *FM* fat mass; *LBM* lean body mass

Discussion

Our results suggest that there is no immediate effect of an enriched formula compared with a standard formula on growth, weight gain, and weight gain composition in preterm infants fed ad libitum in the first 2 months after

Table 4 Weight gain and weight gain composition in infants without or with length growth restriction* (GR) fed on standard term formula or postdischarge formula

	Postdischarge formula		Standard term formula		
	No GR	GR	No GR	GR	p Value[a]
N	8	8	7	10	
Weight gain (g/kg/day)	11.4 ± 0.6	9.1 ± 1.0	10.1 ± 1.7	9.9 ± 1.9	**0.05**
LBM (g/kg/day)	6.9 ± 1.7	5.9 ± 1.1	6.3 ± 1.5	6.5 ± 0.9	
FM (g/kg/day)	4.3 ± 0.6	3.0 ± 1.0	3.6 ± 1.1	3.2 ± 1.1	**0.025**
BA (cm^2/kg/day)	0.80 ± 0.09	0.67 ± 0.15	0.73 ± 0.12	0.71 ± 0.14	
BMC (mg/kg/day)	227 ± 38	182 ± 43	201 ± 51	182 ± 29	**< 0.025**

Values are mean (SD). * > 2 SD below mean on Usher growth chart [21]. [a] Significant effect of growth restriction at discharge from hospital by analysis of variance. *BA* bone area; *BMC* bone mineral content; *FM* fat mass; *LBM* lean body mass

hospital discharge. On the other hand, growth restriction at the time of discharge appears to affect subsequent growth and body composition.

We have shown in our previous studies that body and weight gain composition can be determined accurately using DEXA technology, allowing direct measurements of lean body mass, fat mass, and bone mineral content [19, 20]. With this in mind, we studied preterm infants after hospital discharge for a further 2 months, to analyse the different effects of a standard or an enriched formula given at a time of high growth velocity. During that period, the mean weight gain was about 2000 g, corresponding to about 90 % of the weight achieved at discharge. From our previous studies, this value would be sufficient to detect significant changes of about 1.0 g/kg for weight gain and lean body mass gain, 0.8 g/kg/d for fat mass gain, and 30 mg/kg/d for bone mineral content gain [19, 20]. On this basis, we found no significant differences in anthropometric variables or body composition between the two groups of infants fed standard formula or postdischarge formula during their first 2 months after hospital discharge. Additional analyses suggested that growth achieved by the time of discharge could be one of the major determinants of subsequent growth during the early postdischarge period.

Infants were fed at libitum and measurement of the intake volume was obtained at two different occasions during the study. There is still debate over the regulation of volume intake in newborn infants. Some previous investigators have suggested that babies regulate their milk intake in relation to the energy or nutrient density [14, 22, 23] while others found that milk consumption was unaffected or just mildly affected [15] by formula composition [8]. In our study, volume intake did not appear to be affected, suggesting a significantly higher energy supply in PDF fed infants contrasting with the absence of weight gain difference between groups. This discrepancy may be the result of the difficulties to obtain accurate measurements of feeding intake at home, as well as to some awareness of the parents to a sufficient daily volume intake at the days of intake measurement.

Weight gain and weight gain composition were in the range of the values previously observed in term infants [20]. However, in contrast to the data observed in term infants during the first two month of life [20], volumetric bone mineral density increased significantly in both groups, suggesting a progressive resolution of the relative osteopenia observed in preterm infants at discharge. Nevertheless, due to the low threshold level necessary for bone detection with DEXA, the BMC gain is related to mineral accretion but also to bone matrix increase during the study. Thus the BMC gain cannot be directly converted into calcium retention according to the calcium content of hydroxyapatite [19, 24].

Despite the vast body of work published on the nutrition of preterm infants, there is no clear information on their nutritional management after discharge from hospital. This issue is becoming increasingly important with the progressive improvement in survival of preterm infants of ever smaller birth weights and increasingly early discharge. In contrast to feeding in hospital, feeding after discharge for these ex-premature infants is based on less clear scientific evidence. It seems likely that the nutrition of these infants after discharge from hospital will continue to be important for their future growth and development, also with respect to possible morbidity during adult life.

An important issue is whether the long-term consequences of early growth restriction can be diminished by nutritional intervention in preterm infants after discharge from the hospital, in other words, whether the early weeks or months after term are a critical period for catch up growth, and whether they can safely be influenced by nutritional manipulation. As it appears difficult to avoid nutritional deficits and growth retardation before discharge, several studies in very low birthweight infants have evaluated the effect of postdischarge feeding regimens on growth, bone mineralisation, and biochemical indices of nutritional adequacy.

The concept of a postdischarge formula was introduced by Lucas *et al.*, who in 1992 reported a randomised double blind trial on the effects on growth and bone mineralisation of a nutrient enriched formula compared with a standard formula in a limited number of infants [8]. At 9 months, infants fed the nutrient enriched formula had significantly improved weight gain and linear growth and a trend toward improved head growth. From that time, conflicting results have been reported. For example, two recent studies which involved a relatively large population suggested that any growth benefit of a nutrient enriched formula occurred mainly during the early postdischarge period and particularly in very low birthweight infants and boys [13–15].

In contrast with the growth results, there is relative unanimity over the metabolic effects of increasing the protein supply. Nutritional interventions that increase protein and mineral supplies from discharge up to 6 month of age induce metabolic stress, promoting an increase in blood urea and probably in plasma amino acid concentrations that could be harmful to the child [9, 13–15].

All thee studies had somewhat questionable methodology in terms of the inclusion criteria or their selection of major end points. The inclusion of premature infants with a birth weight below 1650 to 1800 g for a gestational age below 34 to 37 weeks did not allow the selection population at high risk of long-term growth impairment, such as preterm infants with length restriction by the time of discharge. The results of our present study suggest that predischarge growth significantly affects early postdischarge growth.

The analysis of growth indices during a short period of time as a principal objective may not allow sufficient time for a clear evaluation of the potential for catch up growth resulting from a change in the protein and mineral density of the formula. Considering that preterm infants whose size is not appropriate for postconceptional age at the time of discharge show up to 80 % spontaneous catch up growth [1], a better approach could be to evaluate the prevalence of a persistent growth deficit in a selected high risk population, compared to reference curves, at 2 to 3 years of age. However, with a relative risk of 20 % and a target reduction of 50 %, more than 200 infants would need to be included in such a study.

Thus neither our present study nor a review of available reports on postdischarge nutrition supports the view that nutritional manipulation is beneficial to improving catch up growth in very low birthweight infants. These studies do, however, suggest that enriched formulas may involve potentially deleterious and prolonged metabolic stress. Up to now, breast feeding or the use of a standard formula has been encouraged at the time of discharge in very low birthweight infants who are appropriately grown for corrected gestational age, as it has in infants with minimal growth restriction. For very low birthweight infants with significant growth restriction at the time of discharge, further studies need to be performed to evaluate their nutritional requirements during the first postdischarge weeks or months, and to determine the long-term implications of nutrient enrichment on longitudinal growth, peak bone mass, and health status at adulthood.

References

1. Rigo J, Boboli H, Franckart G, Pieltain C, De Curtis M (1998) Surveillance de l'ancien prématuré: croissance et nutrition. Arch Pédiatr 5:449–453
2. Lucas A (1996) Nutrition, growth, and development of postdischarge preterm infants. In: Posthospital Nutrition in the Preterm Infant. Report of the 106th Ross Conference on Pediatric Research, pp 81–89
3. Hack M, Merkatz IR, McGrath SK, Jones PK, Fanaroff AA (1984) Catch-up growth in very low birth weight infants. Am J Dis Child 138:370–375
4. Fitzhardinge PM, Steven EM (1972) The small-for-date infant. I. Later growth patterns. Pediatrics 49:671–681
5. Lucas A (1991) Programming by early nutrition in man. In: Bock GR, Whelan J (eds) The Childhood Environment and Adult Disease. Ciba Foundation Symposium No 156. Chichester: John Wiley, pp 38–55
6. Barker DJP (1993) Fetal nutrition and cardiovascular disease in adult life. Lancet 341:938–941
7. Eriksson JG, Forsen T, Tuomilehto J, Jaddoc VW, Osmond C, Barker DJ (2001) Early growth and coronary heart disease in later life: longitudinal study. BMJ 322:949–953
8. Lucas A, Bishop NJ, King FJ, Cole TJ (1992) Randomised trial of nutrition for preterm infants after discharge. Arch Dis Child 67:324–327
9. Chan GM (1993) Growth and bone mineral status of discharged very low birth weight infants fed different formulas or human milk. J Pediatr 123:439–443
10. Bhatia J, Rassin DK (1991) Feeding the premature infant after hospital discharge: growth and biochemical responses. J Pediatr 118:515–519
11. Wauben IPM, Atkinson SA, Shah JK, Paes B (1998) Growth and body composition of preterm infants: influence of nutrient fortification of mother's milk in hospital and breastfeeding posthospital discharge. Acta Paediatr 87: 780–785
12. Brunton JA, Saigal S, Atkinson SA (1998) Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. J Pediatr 133:340–345
13. Cooke RJ, McCormick K, Griffin IJ, McCormick, Wells JC, Smith JS, Rovinson SJ, Leighton M (1998) Feeding preterm infants after hospital discharge: effect of dietary manipulation on nutrient intake and growth. Pediatr Res 43: 355–360
14. Cooke RJ, McCornick K, Griffin IJ, Embleton N, Faulkner K, Wells JC, Rawlings DC (1999) Feeding preterm infants after hospital discharge: effect of diet on body composition. Pediatr Res 46: 461–464
15. Carver JD, Wu PYK, Hall RT, Ziegler EE, Sosa R, Jacobs J, Baggs G, Auestad N, Lloyd B (2001) Growth of preterm infants fed nutrient-enriched or term formula after hospital discharge. Pediatrics 107:683–689

16. Picaud JC, Rigo J, Nyamugabo K, Milet J, Senterre J (1996) Evaluation of dual energy x-ray absorptiometry (DXA) for body composition assessment in piglets and term human neonates. Am J Clin Nutr 63:157–163
17. Koo WWK, Walters J, Bush AJ, Chesney RW, Carlson SE (1996) Dual-energy-x-ray absorptiometry studies of bone mineral status in newborn infants. J Bone Miner Res 11:997–1002
18. Rigo J, Nyamugabo K, Picaud JC, Gerard P, Pieltain C, De Curtis M (1998) Reference values of body composition obtained by dual energy x-ray absorptiometry in preterm and term neonates. J Pediatr Gastroenterol Nutr 27: 184–190
19. Pieltain C, De Curtis M, Gerard P, Rigo J (2001) Weight gain composition in preterm infants with dual energy x-ray absorptiometry. Pediatr Res 49:120–124
20. De Curtis M, Pieltain C, Studzinski F, Moureau V, Gerard P, Rigo J (2001) Evaluation of weight gain composition during the first 2 months of life in breast- and formula-fed term infants using dual energy x-ray absorptiometry. Eur J Pediatr 160:319–320
21. Usher R, McLean F (1969) Intrauterine growth of liveborn Caucasian infants at sea level: Standard obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr 74:901–910
22. Brooke OG, Kinsey JM (1985) High energy feeding in small for gestation infants. Arch Dis Child 60:42–46
23. Fomon SJ, Filmer LJ, Thomas LN, Anderson TA, Nelson SE (1975) Influence of formula concentration on caloric intake and growth of normal infants. Acta Paediatr Scand 64:172–181
24. Rigo J, De Curtis M and Pieltain C (2001) Nutritional assessment in preterm infants with special reference to body composition. Semin Neonatol 6:383–391