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# Effect of early nutritional intake on long-term growth and bone mineralization of former very low birth weight infants

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ABSTRACT

*Background:* Preterm infants are at risk for impaired bone mineralization and growth in length later in life due to inadequate nutritional intake in the early postnatal period.

*Objective:* To investigate whether increased nutritional supplementation of calcium, phosphate and protein in Very Low Birth Weight (VLBW) infants during the first 14 days after birth was associated with improvement in length and bone development until 9–10 years of age.

*Design:* Observational follow-up study of VLBW infants (birth weight < 1500 g or gestational age < 32 weeks) born in two consecutive years (eligible infants: 2004 n: 63 and 2005: n: 66). Cohort 2005 received higher intake of calcium, phosphate and protein with parenteral nutrition compared to Cohort 2004. Anthropometric data were collected during standard follow-up visits until five years, and additionally at 9–10 years of age including measurements of bone mineral content, bone mineral density of the whole body and lumbar spine determined by dual-energy X-ray absorptiometry. Long-term growth trajectories of both cohorts were evaluated separately for participants born appropriate (AGA) and small for gestational age (SGA), stratified by gender. Multivariate linear regression was used to examine the effect of nutritional intake and clinical covariates on length and bone mineralization.

*Results:* Both cohorts achieved a catch-up in length to SDS within the normal range by 6 months (length SDS: estimated mean (95% confidence interval (CI): 6 months: Cohort 2004: −0.7 (−1.1, −0.3) Cohort 2005: −0.5 (−0.8, −0.2)). Bone mineral content and density were within the normal range and not different between the cohorts. SGA children achieved a catch-up in length at 5 years with bone mineralization comparable to AGA children. Only for girls birth weight was significantly associated with length SDS (per gram: β 0.001; 95% CI (0.000, 0.003); $p = 0.03$) There was no evidence of an association between early nutritional intake and bone mineralization.

*Conclusion:* Children born as appropriate or small for gestational age preterm infants are able to catch up in length after the postnatal period, and achieve a normal length and bone mineralization at age nine–ten years. An improvement of calcium and phosphate intake during the first 14 days after birth was not associated with improvement in length and bone development.



## 1. Introduction

Achieving growth and development comparable to healthy term born infants has been a challenge for the treatment of preterm born infants for many decades [1]. As the survival of Very Low Birth Weight (VLBW) infants has increased significantly during the last years, it is important to evaluate their long-term outcomes, especially since recommendations and policies with regard to nutritional intake have been changed to improve postnatal growth [2–4].

*Abbreviations:* AGA, appropriate for gestational age; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; BW, birth weight; DEXA, dual energy X-ray absorptiometry; GA, gestational age; LS, Lumbar spine scan; SDS, standard deviation score; TCA, term corrected age; SGA, small for gestational age; VLBW, Very Low Birth Weight infants; WB, Whole body scan.

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While early cohort studies demonstrated that VLBW infants experienced a significant growth retardation during the early postnatal period without catch-up to the initial birth percentile, more recent studies showed that improvement of early nutritional intake diminishes the cumulative nutritional deficit and thereby may prevent growth retardation [5–7]. Growth and skeletal development seem to be closely related [8–10]. Adequate bone mineralization is necessary for optimal development of the bones [11–13]. Given the difficulties associated with meeting the nutritional needs of VLBW infants and to provide sufficient nutritional supply of minerals, VLBW infants are especially at risk of impaired bone mineral content [14–17]. While early studies showed that exclusive feeding of human milk in preterm infants leads to deficiencies of calcium and phosphate, it is nowadays generally recommended to fortify human milk with additional minerals, protein and vitamins [18–20]. Furthermore, parenteral supplementation of calcium and phosphate has been improved through the inclusion of organic phosphate in parenteral nutrition (PN) [21].

Only a few studies have evaluated long-term bone development of VLBW children until childhood and adolescence [22–30]. Their findings were diverse but most of the studies showed that these former preterm infants remained smaller later in life, some with lower bone mineralization, others with low mineralization but normal in proportion to their small body size. Several studies found impaired bone mineral content in boys compared to girls [22,31]. Despite the low content of minerals, human milk seemed to have a positive effect on bone development [32,33]. All of the participants of these studies received diets that provided nutrients markedly below the current recommendations and therefore the results may not be representative for the population of preterm infants treated nowadays. A more recent randomized trial in VLBW infants found a positive effect of post- discharge feeding on BMC in comparison to human milk and term formula at the corrected age of 6 months, irrespective of gain in weight and length [34].

Previously we reported the short-term outcome results for two consecutive year-cohorts of VLBW infants that differed with regard to the nutritional intake during the first two weeks of life [35]. The second cohort received a higher intake of protein, energy as well as calcium and phosphate and this was associated with improved weight gain during the early postnatal period and at the corrected age of two years there was a tendency of improved growth in length. A secondary analysis revealed that this was mainly based on improvement in boys. Small for gestational age (SGA) infants had a higher postnatal weight gain than appropriate for gestational age (AGA) born infants [35]. For the current study we describe the long-term growth in length for the surviving infants of the original cohorts and analyze the effect of the postnatal nutritional intake on length and bone mineralization at the of age 9 to 10 years. We hypothesized that increased nutritional intake would lead to improved length and bone mineralization.

## 2. Methods

### *2.1. Study population and design*

This observational follow-up study evaluated the long-term outcomes of growth and bone mineralization of a previously described prospective cohort study that was conducted in 2004 and 2005, in order to evaluate changes in the composition of parenteral nutrition (PN) [35,36]. Surviving participants of both cohorts who were eligible for the standard follow-up schedule provided to VLBW infants born prior to 32 weeks of gestation, or those with a birth weight below 1500 g were included in the study. (Eligible children: Cohort 2004: $n = 63$; Cohort 2005: $n = 66$). These children were invited for an additional outpatient clinic visit that included an evaluation of bone mineralization by dual energy X-ray absorptiometry (DEXA). The parents of all participants provided written informed consent for the additional investigation. The study was approved by the local ethics committee (2013/594) and registered within the Dutch Trial Registry (NTR = TC4842).

In accordance with the standard follow-up program, growth and general health status were recorded at the corrected ages of six months, and 1, 2 and 5 years. For the current study, we extended the follow-up by inviting children who were previously seen during the national follow-up program to return for further testing around the ages of nine and 10 years.

### *2.2. Nutritional protocol*

The 2004 and 2005 cohorts included preterm infants admitted to the level III neonatal intensive care unit (Radboud University Medical Center, The Netherlands) on the first day of life after it was estimated that parenteral nutrition would be needed for at least 5 days. Infants with major congenital malformations or asphyxia were excluded. The nutritional protocols for the two cohorts primarily differed in terms of the parenteral nutritional intake with higher amounts of protein, calcium and phosphate provided to the 2005 Cohort. (Table 1) Following the recommendation of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition the 2005 PN provided 3 mmol per kg per day of calcium and 1.92 mmol per kg per day of glycerophosphate [4,37]. According to the nutritional protocol of 2005, full PN was achieved four days following birth, while the maximum amount of PN in Cohort 2004 was achieved later, at day six. For both cohorts, enteral feeding was started on the first day of life and human milk was enriched with a commercially available fortifier (HMF) (Nutrilon Nenatal BMF, Nutricia, Zoetermeer, The Netherlands) from an intake of 50 ml per day onwards. HMF added 1.6 mmol/dL of calcium and 1.95 mmol/dL of phosphate. If human milk was not available, infants received a preterm formula (Nutrilon Nenatal Start, Nutricia, Zoetermeer, The Netherlands). The formula contained 2.5 mmol per dL of calcium and 1.6 mmol per dL of phosphate and 200 IE per dL of Vitamin D. The full nutritional protocol has previously been described in detail [35,36]. No major changes in clinical practice occurred and all infants received nutrition according to standard institutional protocols.

### *2.3. Anthropometric measurements and questionnaire*

At the last visit length and weight were determined, and the health condition evaluated using a questionnaire. We specifically focused on morbidities and the use of medication that could have affected growth and bone mineralization, for example corticosteroids, asthma and fractures. For the preceding follow-up visits anthropometric measurements

**Table 1**
Parenteral nutritional intake.

| | | D0 | D1 | D2 | D3 | D4 | D5 | D6 |
|---|---|---|---|---|---|---|---|---|
| 2004 | Fluid ml/kg/d | 60 | 80 | 100 | 120 | 140 | 160 | 180 |
| | CH g/kg/d | 4.9 | 5.9 | 6.8 | 7.8 | 8.83 | 11.7 | 13.7 |
| | AA g/kg/d | 0.5 | 1 | 1.5 | 2 | 2.25 | 2.5 | 2.5 |
| | Lipids g/kg/d | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3 |
| | EQ kcal/kg/d | 26 | 37 | 47 | 57 | 67 | 86 | 92 |
| | Ca mmol/kg/d | 0.17 | 0.17 | 0.33 | 0.50 | 0.66 | 0.83 | 1.08 |
| | P mmol/kg/d | 0.04 | 0.04 | 0.08 | 0.12 | 0.16 | 0.20 | 0.26 |
| 2005 | Fluid ml/kg/d | 80 | 100 | 125 | 150 | 150 | 150 | 150–180 |
| | CH g/kg/d | 8 | 9.6 | 11.7 | 13.8 | 13.8 | 13.8 | 13.8–16.8 |
| | AA g/kg/d | 0.75 | 1.5 | 2.25 | 3 | 3 | 3 | 3 |
| | Lipids g/kg/d | – | 1 | 2 | 3 | 3 | 3 | 3 |
| | EQ kcal/kg/d | 35 | 53 | 74 | 94 | 94 | 94 | 94–106 |
| | Ca mmol/kg/d | 0.75 | 1.5 | 2.25 | 3.00 | 3.00 | 3.00 | 3.00 |
| | P mmol/kg/d | 0.48 | 0.96 | 1.44 | 1.92 | 1.92 | 1.92 | 1.92 |

Standard protocol for parenteral nutrition of Cohort 2004 and Cohort 2005 with different standardized parenteral solutions. CH: carbohydrates; AA: amino acid; EQ: energy quotient. Ca: calcium; P: phosphateThe parenteral nutrition consisted of two standard prepared components, a mixture of amino acids/glucose/minerals and lipid emulsion plus vitamins. Amino acid solutions and lipid emulsion: Cohort 2004: Aminovenos N paed 10% (Fresenius Kabi), Intralipid 20% (Fresenius Kabi), Ca gluconate 10% (Braun Melsungen), Potassium phosphate (Braun melsungen) Cohort 2005: Primene (Clintec, Brussels), Intralipid 30% (Fresenius Kabi) Ca gluconate 10% (Braun Melsungen), Sodium-glycerophosphate (Glycophos; Fresenius Kabi).