Risk factors associated with low bone mineral content in very low birth weight infants

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ABSTRACT

Introduction: We report part of the findings of a study conducted to determine the correlation between bone mineral content (BMC) and biochemical bone markers in very low birth weight (VLBW) infants.

Methods: This was a cross-sectional study, carried out between August 2001 and June 2004 in the neonatal intensive care unit of Hospital Universiti Kebangsaan Malaysia. Whole body BMC was measured by dual energy X-ray absorptiometry in 41 VLBW infants.

Results: The mean BMC/kg body weight was 25.8 (standard deviation [SD] 11.2) g per kg. The BMC of these infants had significant negative correlation with their birth weight (r equals -0.31, p-value equals 0.048). There was no significant difference in the mean BMC between different races and gender. The infants were divided into two groups based on the course of prematurity: "non-complicated" and "complicated" groups because of the lack of "healthy reference population" data for normal BMC values in premature infants. The "non-complicated" group (30) had received ventilator assistance for less than seven days, tolerated full enteral nutrition before the age of two weeks, had no sepsis or necrotising enterocolitis and did not receive regular diuretic or steroid treatment. The cut-off level for a desirable BMC per kg in VLBW infants was obtained from a value corresponding to one SD below the mean of the "non-complicated" group, i.e., 17.4 g per kg. Eight (19.6 percent) infants had BMC less than this value. Multilinear regression analysis of demographical characteristics, maternal factors, neonatal complications and nutrition received revealed that heavier birth weight (p-value equals 0.007) and longer duration of parenteral nutrition (p-value equals 0.03) were associated with lower BMC.

Conclusion: VLBW infants who required parenteral nutrition for longer periods were at higher risk to having poorer bone mineralisation.

Keywords: bone mineral content, dual energy X-ray absorptiometry (DEXA), parenteral nutrition, very low birth weight infants

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INTRODUCTION

Metabolic bone disease (MBD) is one of the complications of premature, very low birth weight (VLBW) infants (birth weight of less than 1,500 g). This condition comprises a variety of disturbances ranging from mild undermineralisation to frank radiological rickets with fracture.[1] The term osteopaenia is usually used to define a mild to severe degree of hypomineralisation of the skeleton when compared with the foetal accretion rate. The term rickets is reserved for cases in which there are definite radiological features of rickets in the metaphyses of long bones.[2]

The main aetiological factor appears to be insufficient mineral intake; namely, calcium and phosphorus.[3-5] The maximum foetal accretion rates for both minerals occur during the third trimester, when 80% of the total foetal skeletal calcium and phosphorus is retained. Therefore, infants who are born prematurely have very low storage of these minerals. Poor mineralisation has been found in 30% of VLBW infants and in more than 50% of those weighing less than 1,000 g at birth.[6,7] It is important to recognise and prevent this condition as Fewtrell et al found that the linear growth of children with neonatal metabolic bone disease was significantly reduced, even at the age of 12 years.[8]

The diagnosis of MBD has been based on different criteria including clinical signs, radiological changes, bone mineral content (BMC), biochemical markers, and post-mortem analysis of bone structure and mineral composition.[5] Dual energy x-ray absorptiometry (DEXA) provides accurate and precise determination of BMC in preterm and term infants.[9-11] The radiation dose is low

(3 mRem), making it suitable for longitudinal studies. Presently, this is the method of choice in measuring BMC. The objective of the study was to determine the factors associated with low BMC in VLBW infants.

METHODS

This was part of a study investigating the correlation between biochemical markers of bone turnover and BMC in VLBW infants. The study was carried out from August 1, 2001 to June 30, 2004. The inclusion criteria were all infants with birth weight of 1,500 g or less admitted to the Neonatal Intensive Care Unit (NICU) of Hospital Universiti Kebangsaan Malaysia (HUKM) and survived to discharge during the study period, and whose parents had given informed consent. Infants with multiple congenital anomalies, hereditary bone disease such as osteogenesis imperfecta, and conditions known to have abnormal growth pattern such as skeletal dysplasia, were excluded. Infants with cholestatic jaundice were also excluded because the condition may affect the interpretation of the biochemical results.

When a VLBW infant weighed at least 1,750 g, fed well and was not on oxygen therapy, the parents were approached for consent. Once consent was obtained, the infant was subjected to whole body BMC measurement. The BMC was measured using the DEXA technique using Small Subject Software of Norland Digital Model 394a 040 (serial number 6784) absorptiometer (Norland Fort Atkinson, WI, USA). The Norland scans were strictly pencil-beam scans and the radiation dose to the patient was very low (1–10 uSv) and comparable to the average daily dose from natural background radiation of 7 uSv. The procedure was performed with the infant wrapped in a layer of cotton blanket and placed in supine position on the scan platform. Scanning took place after a feed, when the infant was quiet and in most cases, asleep, to avoid movement artefact. No sedatives were used. Quality control was implemented by phantom scans on a daily basis.

The data were analysed using the Statistical Package for Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA). Chi-square test was used to compare the qualitative data. The independent t-test was used for normally distributed continuous data while Mann-Whitney U test was used for skewed data. Correlation among the qualitative variables was determined using Spearman correlation because the data on gestation and birth weight were skewed. Linear regression analysis model was used to test the significance of risk factors associated with low BMC. p-values of less than 0.05 were considered statistically significant.

RESULTS

During the study period, 167 VLBW infants were discharged from NICU, HUKM. 16 infants met the exclusion criteria. However only 41 (27.1%) of the eligible infants were enrolled into the study. Majority (46.4%) of the infants were not studied because the equipment to measure BMC was out of order at the time of discharge. The study infants (n = 41) were similar to the 110 eligible infants who were not enrolled into the study, with regard to ethnic distribution and mean gestational age. The study infants were heavier at birth and more were males. However, these were not statistically significant, with p-values of 0.08 and 0.07, respectively.

The BMC measurement was performed at mean postnatal age of 46.5 (standard deviation [SD] 19.4) days and mean corrected age of 37.5 (SD 0.6) weeks. The mean weight at BMC measurement was 2,013.7 (SD 526) g. The mean BMC was 25.8 (SD 11.2) g per kg body weight. There was a significant negative correlation between BMC and birth weight ($r = -0.31$, $p = 0.048$). There was no correlation between BMC and gestational age ($r = 0.2$, $p = 0.21$) or weight at BMC measurement ($r = -0.24$, $p = 0.14$). There was no significant difference in the mean bone mineral content between different races and gender. The small for gestation (SGA) infants had a higher mean BMC/kg (32.3), compared to the appropriate for gestation (AGA) infants (23.7); however, this was not statistically significant ($p = 0.09$).

The infants were divided into two groups based on the course of prematurity: "non-complicated" and "complicated" groups, because of the lack of "healthy reference population" data for normal BMC values in premature infants. The "non-complicated" group (n = 30) had received ventilator assistance for less than seven days, tolerated full enteral nutrition before the age of two weeks, had no sepsis or necrotising enterocolitis (NEC), and did not receive regular diuretic or steroid treatment. The remaining 11 premature infants belonged to the "complicated" group. The "complicated" group had a significantly lower mean BMC/kg (18.2, SD 3.0) compared to the "non-complicated" VLBW infants (29.6, SD 12.2), ($p = 0.0005$). Their median gestation was lower compared to the "non-complicated" group ($p = 0.02$). There was no significant difference in median birth weight and intrauterine growth between the two groups.

Defining "low" BMC in VLBW infants was approached as follows: the cut-off level for a desirable BMC/kg in VLBW infants was obtained from a value corresponding to one SD below the mean of the "non-complicated" group. This value was 17.4 g/kg. Eight infants had BMC/kg body weight lower than this value. These infants were then compared to the rest of the VLBW infants ("normal" BMC group) to evaluate the effect of the course of prematurity on BMC.

Various factors that may affect the difference in BMC between the two groups were compared (Table I). The median birth weight and days on assisted ventilation

Table I. Comparison of infants' characteristics and neonatal complications between infants with "normal" and "low" BMC.

	BMC ≥ 17.4 g/kg n = 33 (%)	BMC < 17.4 g/kg n = 8 (%)	p-value
Gender			
Male	18 (55)	7 (88)	0.12
Female	15 (45)	1 (12)	
Race			
Malay	23 (69.6)	2 (25)	0.06
Chinese	6 (18.2)	5 (62.5)	
Indian	2 (6.1)	0	
Others	2 (6.1)	1 (12.5)	
Median birth weight (g)	1,300	1,440	0.02
Median gestation (weeks)	31	31.8	0.82
Intrauterine growth			
AGA	23 (56.1)	8 (100)	0.16
SGA	10 (43.9)	0	
Respiratory distress syndrome	23 (70)	6 (75)	0.76
Sepsis	13 (39)	3 (38)	0.92
Necrotising enterocolitis	5 (15)	1 (13)	0.85
Patent ductus arteriosus	7 (21)	2 (25)	0.82
Intraventricular haemorrhage	6 (10)	3 (27)	0.32
Median ventilation (days)	2	5.5	0.02
Median parenteral nutrition (days)	7	10	0.55

BMC: bone mineral content

significantly contributed to the difference in BMC between the groups. Maternal calcium supplementation and illness as well as type of nutrition and supplements received by the infants were not significantly different between the two groups. When the risk factors were subjected to multiple regression analysis, birth weight and duration of parenteral nutrition were statistically significant, p-values being 0.007 and 0.03, respectively.

DISCUSSION

DEXA is currently the "gold standard" for determining BMC because of its high precision and accuracy.[12,13] However, normative data of BMC for preterm infants are limited.[14–16] We found that the BMC of VLBW infants had a significant negative correlation with their birth weight. The weight at the time of BMC measurement also had negative correlation with BMC, though not significant. This was in contrast with findings by two other studies which found the reverse.[5,17] However, the heavier weight in an infant could be caused by accumulation of fluid or fat deposition rather than lean mass, which has a better correlation with BMC.[17] The finding of no difference in mean BMC between genders was comparable to results obtained by other studies.[11,17] Faerks et al found that gender had no influence on BMC at term gestation in 127 premature infants.[17]

The difference between adults and premature newborns is that no "healthy reference population" exists. A significantly lower BMC in premature infants at term corrected age compared with term born infants has been described in several studies.[18,19] Even though our study was not designed as a comparison study, we used the data obtained to identify risk factors associated with a lower BMC in these infants. For this purpose, we chose a diagnostic cut-off value of one SD below the mean BMC in the relatively well "non-complicated" VLBW to arbitrarily divide the infants into the "low" and "normal" BMC/kg groups. Subsequently we compared the potential risk factors of low BMC between the two groups.

Based on the cut-off BMC value of 17.4 g/kg, eight (19.6%) of the VLBW infants had "low" BMC. When multilinear regression analysis was performed, heavier birth weight and longer duration of parenteral nutrition were associated with lower BMC. Previous studies found that the frequency of MBD is directly correlated with postnatal morbidity, e.g. bronchopulmonary dysplasia, NEC, delay in full feeding and prolonged parenteral nutrition.[20,21] The amount of calcium and phosphorus delivered in parenteral nutrition solutions is unable to match the intrauterine accretion.[21,22] Their bone minerals accretion is further compromised by periods of fasting, use of diuretics and steroid, and chronic illness.

Rigo et al and Faerk et al showed that BMC is directly correlated with body weight and linear growth.[5,17] Prevention of MBD should then focus on promotion of adequate growth. Lucas et al, in a randomised trial on the nutrition for preterm infants after discharge, found that there was a significant increase in linear growth and weight gain in the infants who had received the mineral-enriched diet.[23] The use of a special nutrient-enriched post-discharge formula had a significant positive effect on bone growth and mineralisation during a period of rapid skeletal development.[24]

To improve the bone mineralisation of VLBW infants, we recommend optimising the amount and accretion of bone minerals in parenteral nutrition and enteral feeds. They should also be discharged home with nutrient-enriched formula or human milk fortifier to ensure adequate growth and bone mineralisation. We realised that the results of this study have to be interpreted with caution. Throughout the study period, the equipment used to measure BMC was intermittently out of order for a cumulative period of one year. This forced us to adopt a convenient sampling method in the selection of the samples, thus predisposing to selection bias. The arbitrary method of determining the "low" and "normal" levels of BMC should also be taken into account in future studies. In summary, this study showed that the VLBW infants who required parenteral nutrition for a longer period seem to be at a higher risk of having poorer bone mineralisation compared to their peers.

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