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Prevention of Postnatal Bone Demineralization in Very Low-Birth-Weight Infants by Individually Monitored Supplementation with Calcium and Phosphorus

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ABSTRACT. Preterm infants are more prone to bone mineral deficiency the lower their birth weight. To achieve the intrauterine bone mineral accretion rate postnatally, 74 low-birth-weight infants (median birth weight, 980 g; range 430–1.580 g) were each supplemented enterally and/or parenterally with calcium and/or phosphorus in gradually increased amounts. The aim was to yield a simultaneous urinary excretion of Ca and inorganic phosphorus (Pi) at low concentrations (1–2 mmol/L) in spot urine specimens taken twice weekly. The hypothesis was that the intrauterine mineralization rate (4.5 mg cm^{-1}/100 g weight gain) would be achieved postnatally in very low-birth-weight infants, if they were supplemented with enough Ca and/or Pi to effect at least a low (1–2 mmol/L) simultaneous urinary excretion of both ions, as compared with infants who do not excrete both ions and would accrete the bone minerals at a lower rate. The change in bone mineral content was measured by single photonabsorption densitometry and related to weight gain during periods of 2 to 6 wk. Infants who simultaneously excreted Ca (>1.2 mmol/L) + Pi (>0.4 mmol/L) in more than half of the urine samples retrospectively showed the highest bone mineral accretion, 5.1 mg cm^{-1}/100 g weight gain, which was equivalent to the fetal mineralization rate (4.5). In this group the bone mineral status significantly contributed to the variance of the bone mineral accretion rate; severely demineralized infants showed a catch-up mineralization. A significantly lower rate (2.4) was observed in infants who excreted Ca + Pi in less than half of the urinary samples. Supplementation with Ca and Pi up to the point where both ions are simultaneously excreted with the urine at concentrations >1.2 and >0.4 mmol/L, respectively, offers a simple and safe way of achieving the fetal bone mineral accretion rate in preterm infants, taking into account their individual needs, the varying mineral content of breast milk, and the different compositions of special-care formulas. A further prospective study is needed to test the hypothesis. (*Pediatr Res* 35: 125–129, 1994)

Abbreviations

BMA, bone mineral accretion
BMC, bone mineral content
Pi, inorganic phosphorus
VLBW, very low-birth-weight

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Postnatal bone mineral deficiency is a condition that is well known (1–6) in preterm infants and that has gained in importance clinically since the rate of survival of VLBW infants has so greatly improved. Various factors were held to be responsible for bone mineral deficiency, such as deficiencies of vitamin D (7, 8), Ca (7, 9), Pi (10–13), Ca + Pi (14, 15), as well as parenteral nutrition (16–20), metabolic disease, physiotherapy, long-term ventilation and, finally, treatment with furosemide.

Schilling and co-workers (21) described the pivotal biochemical changes in breast milk- and formula-fed preterm infants and we have confirmed the findings many times (22): feeding with breast milk resulted in the phosphopenic type of rickets with severe hypophosphatemia and an absence of urinary Pi, together with hypercalciuria. In contrast, formula-fed infants were characterized by marginal hypocalcemia, no detectable urinary Ca, and showed secondary hyperparathyroidism together with hyperphosphaturia, *i.e.* the calcipenic type of rickets. The absence of Pi or Ca, respectively, from the urine, is explained by maximal tubular reabsorption of these ions, indicating a deficiency of Ca and Pi, respectively. The inorganic bone material is the crystalline mineral apatite, with the formula $Ca_5(PO4)_3(OH,F)$ (23). Owing to the different amounts and ratios of Ca and Pi in breast milk and special-care formulas for preterm infants, the limiting factor for bone mineralization was Pi in breast milk-fed and Ca in formula-fed infants. The corresponding ion in apatite was surplus and, therefore, excreted with the urine. The hypercalciuria observed in VLBW infants fed breast milk is a paradox because only one-third of the infant's requirement of Ca is administered by breast milk. The hypercalciuria indicates that the deficiency of phosphorus is even greater than that of calcium and that only a part of the small amount of Ca can be accreted as apatite. A supplementation with phosphate reduces calciuria to nearly zero and then calcium is the limiting factor. Therefore, VLBW infants fed breast milk need a supplementation with both Pi + Ca.

The calcipenic type of postnatal bone demineralization develops in VLBW infants fed a special-care formula enriched with Ca + Pi, because of the low net absorption of Ca.

The hypothesis that we arrived at was that the intrauterine mineralization rate (4.5 mg cm^{-1}/100 g weight gain) (24) would be achieved postnatally in VLBW infants, if they were supplemented with enough Ca and/or Pi to effect at least a low (1–2 mmol/L), simultaneous urinary excretion of both ions, as com-

pared with infants who do not excrete both ions and would accrete the bone minerals at a lower rate. To test this hypothesis we undertook prospectively the study reported here.

MATERIALS AND METHODS

Supplementation procedure. For enteral supplementation, solid Ca gluconate (food quality, Merck, Darmstadt, Germany) and Ca glycerophosphate (food quality, Merck) were used and Ca gluconate 20% (Sandoz, Nürnberg, Germany) and Na_2 glucose-1-phosphate (1 mmol/mL, Leopold, Graz, Austria) were used for intravenous administration. The amounts of enteral and/or parenteral Ca and/or Pi were at first 2 mmol/kg a day and then increased weekly (0.5–1 mmol/kg a day) until morning spot urinary specimens, which were taken twice weekly, contained both Ca + Pi concentrations between 1 and 2 mmol/L. During the study, the doses were adjusted to reach this goal.

We deliberately did not choose a randomized placebo controlled trial but supplemented all VLBW infants in order to study our concept of individually adjusted supplements. This design would provide us with one group of infants who excrete Ca + Pi together with urine and a second group who would not. A better mineral accretion rate of the infants excreting Ca + Pi would support and equal mineralization in both groups would falsify our hypothesis.

Ca and Pi were measured by standard methods during the daily routine (25, 26). The lower limits of the method for detecting Ca was 1.2 and 0.4 mmol/L, respectively, for Pi. The coefficient of variation was 2.3% for Ca and 4% for Pi. The study was approved by the Committee on Human Experimentation of the University of Ulm.

Photon absorption densitometry. BMC was measured in the middle of the right humerus at 3 (range, 2–6)-wk intervals by single photon absorption densitometry as described previously (24). The coefficient of variation was 3%. BMC is best correlated with body weight (24). The change in BMC, therefore, was related to the change in body weight (mg cm^{-1}/100 g) over the same period.

Patients. All VLBW infants admitted to our unit were eligible for the study. Infants were excluded when they died or were transferred to other hospitals during the first 28 d. Seventy-four VLBW infants (birth weight, median 970 g, range 430–1.580; gestational age, median 28 wk, range 24–33) were supplemented with Ca and/or Pi (as planned) and observed for a total of 104 periods (median = 2 periods, range 1–5) of 3 wk (range 2–6). The wide range of observational periods resulted from the variation in birth weight and duration of stay in hospital. The bone mineral accretion rates during these intervals (mg cm^{-1}/100 g weight gain) were grouped according to the type of Ca/Pi urinary excretion observed during these periods: group 1, periods when more than half of the urinary specimens contained both Ca (>1.2 mmol/L) and Pi (>0.4 mmol/L); group 2, periods when fewer than half of the urinary specimens contained both Ca + Pi. When data from more than one period was available in one infant, one period was randomly selected for data analysis and statistical comparison. Data were only selected from periods when the parenterally supplied amount of Ca/Pi contributed less than 10% of the total administered dose.

The infants were fed with their own mother's milk when available, this being individually substituted with Alfaré (3–6 g/dL, Nestlé. Munich, Germany) to provide enough energy and protein in case of low plasma amino acid concentrations (<1800 μmol/L). Otherwise, cow's milk-based, special care formulas (Meb, Milupa, Friedrichsdorf, Germany; Humana O Frühnahrung, Humana Milchwerke e. G., Herford, Germany) were used (Table 1). All infants received 1000 IU of vitamin D_3 orally daily after the first week of life. Enteral feedings were started on the first day of life and complemented by parenteral nutrition during the first days.

Confirmative statistical analysis was limited to the evaluation of the hypothesized differences in BMA between group 1 and group 2 (Mann-Whitney test).

Table 1. *Composition of formulas*

	Humana 0 Frühnahrung per L	Meb per L	Alfare per 100 g of powder
Ca (mmol)	13	12.5	10
Pi (mmol)	12	13.3	1.29
Protein (g)	23	14	16.5
Maltodextrin (g)			44.9
Starch (g)			6.0
Lactose (g)	86	87	0.8
Fat (g)	33	38	24.0
MCT (g)*			11.5
Energy (kJ)	3100	3160	2010

* MCT, medium-chain triglycerides.

RESULTS

The amount of supplemented Ca and/or Pi was gradually increased until a low urinary excretion of both Ca + Pi was achieved. This goal was reached in only 30 of 74 studied periods (group 1). In this group, median bone mineral accretion was 5.1 mg cm^{-1}/100 g weight gain, which is equivalent to the intrauterine rate (4.5) (24). During the 44 periods, when simultaneous excretion of both Ca + Pi was not observed in more than half of the urine samples (group 2), BMA was significantly lower (mean 2.4) than during periods when this goal was reached (group 1) (one-tailed probability; $p = 0.012$) (Table 2).

BMA was proportional to the number of urine samples containing both Ca + Pi (Fig. 1). The wide range of BMA in group 1 prompted us to look for factors that contribute to this variation. The BMC at the beginning of an observational period was significantly correlated with BMA during the next weeks; infants who had a BMC above the 50th percentile value for their body weight achieved only a low BMA or even lost bone mineral, whereas infants with low BMC yielded a more than average BMA (Fig. 2).

Further analysis revealed a coincidence of high BMA, a high percentage of Ca + Pi positive urine samples and a low mineral status at the beginning of an observational period (Fig. 2).

DISCUSSION

The mineralization of skeletal tissue in vertebrate organisms is a complex and not completely understood process (27–30). The crystalline structure of apatite requires the presence of both Ca + Pi in sufficient concentrations to form new crystallites. Conducive to the deposition of calcium phosphate minerals is an elevation of local Ca + Pi concentration (25), but nothing is known about the plasma concentrations of either ion necessary to achieve the apatite accretion rate of the fetus in the preterm infant. In addition, what is a normal bone mineral accretion rate in VLBW infants? The only naturally provided yardstick for bone mineralization in preterm infants is the intrauterine bone mineral accretion rate during the same postmenstrual period. Intrauterine BMC is strongly and linearly related to body weight and, from cross-sectional data, the mineral accretion rate was calculated as 4.55 mg cm^{-1}/100 g weight gain (24).

Greer and co-workers tried to achieve intrauterine mineralization rate in preterm infants by feeding a special-care formula highly enriched with Ca (1400 mg/L) + Pi (750 mg/L) but then observed in some of their infants a zero rate or even a decrease in BMC (15). These varying results are probably explained by the considerable variation of the, on average, low Ca net absorption from cow's milk-based formulas in preterm infants (31–40). The enteral supplementation, therefore, should be given individually to prevent demineralization in insufficiently supplemented

Table 2. *Bone mineral accretion rate in VLBW infants supplemented individually with Ca and/or Pi, grouped according to urinary Ca/Pi excretion*

	Type of urinary Ca and Pi excretion	
	Group 1	Group 2
BMA (mg cm^{-1}/100 g weight gain)		
Median	5.1*	2.4*
Range	−2.2–13.3	−19.1–14.4
Periods	30	44
Interval between two BMC measurements (wk)		
Median	3.9	3.8
Range	2.2–6.0	2.3–6.0
Birth weight (g)		
Median	885	1005
Range	430–1520	530–1580
Gestational age (wk)		
Median	27.5	28.5
Range	25–32	24–33
Postmenstrual age (wk)†		
Median	51.6	50.4
Range	46.5–63.2	41.5–72.2
Postnatal age (wk)†		
Median	11.1	6.7
Range	1.8–23.7	2.0–24.2
Body weight (g)†		
Median	2519	2295
Range	1455–4620	1293–4222
Daily weight gain (g)†		
Median	18.2	18.0
Range	9.0–40	7.5–30
Ca‡ (mmol kg^{-1} d^{-1})		
Median	4.2	5.6
Range	2.4–8.5	2.0–9.0
Pi‡ (mmol kg^{-1} d^{-1})		
Median	2.3	2.3
Range	1.6–7.5	1.6–7.5
Bone M status§ (mg/cm)		
Median	−20	−13
Range	−56–15	−48–71

* Significant difference between group 1 and group 2; one-tailed probability, $p = 0.012$.

† Mean value calculated for the interval between the first and second BMC measurement.

‡ Total amount provided by milk and supplement.

§ Bone mineral status = BMC at the beginning of an observational period minus the 50th percentile value in newborn infants of the same body weight at birth.

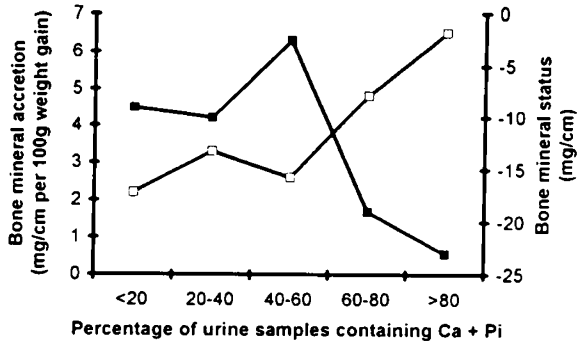

Fig. 1. Correlation between the bone mineral accretion rate (□—□) and the percentage of urine samples containing both Ca + Pi and the bone mineral status (■—■) (BMC at the beginning of an observational period minus the 50th percentile BMC value at birth in newborn infants of the same body weight).

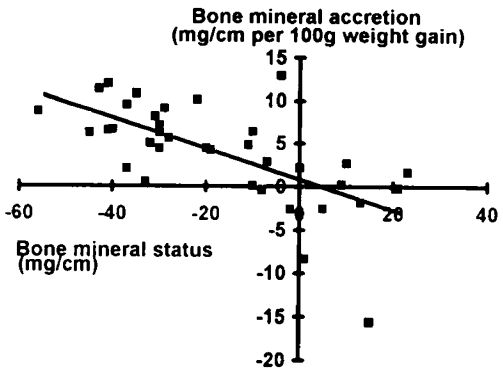

Fig. 2. Correlation between the bone mineral accretion rate and the bone mineral status (BMC at the beginning of an observational period minus the 50th percentile BMC value at birth in newborn infants of the same body weight) in preterm infants excreting Ca + Pi in more than 50% of spot urine samples (group 1); BMA = −0.178 BM status + 0.83, $r^2 = 0.42$; $p = 0.00001$.

infants and also to avoid the potential risk of nephrocalcinosis through overdose. The individual measurement of enteral Ca net absorption is a time-consuming procedure, unsuitable for clinical routine. The easy-to-do measurement of Ca and Pi in urine spot specimens seemed to us to be a simple way of monitoring the supplementation. In VLBW infants fed every 2 to 3 h, we found that measurements of <1.2 mmol of Ca and <0.4 mmol of Pi, respectively (the lower limits of detectability with our method), in a spot urine specimen were representative for all spot urine specimens delivered over 24 h. We also observed, 1 d thereafter, a urinary excretion of Ca and/or Pi as a rapid response to sufficient supplementation. We therefore took the absence of Ca and/or Pi from the urine as a sign of Ca and/or Pi deficiency, which we then enterally and/or parenterally compensated for until low urinary concentration showed a slight surplus.

The positive correlation between the percentage of Ca + Pi positive urinary samples and the BMA rate and the significant difference in BMA between the infants who excreted Ca + Pi together in more than 50% or fewer than 50% of the measured urine samples supported our hypothesis that the supplementation of preterm infants with Ca and Pi to yield postnatally an intrauterine BMA can be monitored by measuring the urinary concentrations of both ions.

A high BMA was also correlated with a low BMC at the beginning of an observational period (Fig. 2). A stepwise linear regression even revealed that the BMC at the beginning contributed more than the Ca + Pi excretion to the variance of BMA. But this correlation makes sense only in connection with a simultaneous sufficient supplementation with minerals and the coincidence of high BMA rates, high Ca + Pi excretion rates and a low starting BMC can be easily explained by the design of our study. The supplements were increased so slowly that the simultaneous excretion of Ca + Pi was not achieved until a median postnatal age of 11 wk. During this long period the infants did not receive sufficient amounts of Ca + Pi to achieve the intrauterine BMA. In some infants the bones were even demineralized in order to have some material for the mineralization of the newly grown parts of the skeleton. But eventually the supplement met requirements and then the infants with the lowest BMC yielded the higher BMA, *i.e.* a catch-up mineralization took place.

The net absorption of Ca from cow's milk-based formulas is low in preterm infants, varies considerably interindividually and reaches only 50% at 60 d postnatal age (36). Our findings are consistent with the concept of a maturation of Ca absorption. In group 1, the median dose of Ca required to yield a urinary excretion of Ca was 4.2 mmol/kg/d and varied considerably between 2.4 and 8.5. The median age was 11.1 wk. The infants in group 2, however, were younger (6.7 wk) and their Ca absorp-

tion must have been lower than in group 1, because even a higher dose of Ca (5.6) did not reach the target of a continuous urinary excretion of Ca.

The gradual increase of supplementation was obviously too slow, because the simultaneous excretion of Ca + Pi in more than half of the urine specimens (group 1) was only achieved in 30 of 74 studied periods and not until a median postnatal age of 11 wk. Average daily Ca (Pi) accretion was calculated from the content of fetal bodies at different gestational ages as 3.2 (2.5) mmol/kg (22, 41–44). Assuming a rather good 50% Ca net absorption, the enterally fed preterm infant should receive a total of 6.4 mmol of Ca kg^{-1}/d in order to meet the requirement at the beginning of supplementation. The Ca supplement required depends on the Ca-concentration of the type of milk provided. It should bring the milk Ca content up to 6.4 mmol/kg. In case of a continuing lack of urinary Ca excretion, the daily Ca dose should be increased each week by 2 mmol kg^{-1}. Phosphorus supplementation (1–2 mmol/kg) is mainly necessary in the breast milk-fed infant. Special-care formulas for preterm infants are sufficiently enriched with phosphorus.

The principle of Pi supplementation guided by urinary concentrations cannot be applied to infants with Pi-losing nephropathy. Here, Pi is excreted at low plasma Pi concentrations that do not allow normal mineralization (45). The same could be true for Ca in infants receiving a long-term treatment with furosemide that impairs the tubular reabsorption of Ca.

The bone mineral accretion rate clearly correlated with the percentage of Ca + Pi-positive specimens and was highest in group 1. Confirming the wide variation of net Ca absorption we observed that a wide range of Ca was necessary to bring about slight urinary excretion (46). The daily doses of Ca + Pi were added to the total daily milk volume in order to provide Ca + Pi simultaneously and constantly, around the clock. By doing this, the increase in osmolarity of the milk was kept as low as possible. No cases of intestinal obstruction or necrotizing enterocolitis were observed.

Ca added in large amounts to milk form insoluble Ca soaps and impair fat absorption, but a preliminary report showed the same weight in all infants independent of the amount of supplemented Ca (46).

Nephrocalcinosis and urolithiasis have been said to be a result of Ca/Pi supplementation but are not likely to occur when the dose is monitored individually and increased gradually until urinary excretion starts in low concentrations. Twenty-four supplemented infants were examined longitudinally for nephrocalcinosis by ultrasound. Only one infant, who had received long-term treatment with furosemide, developed nephrocalcinosis (47).

We have presented evidence that our proposal offers a simple, effective and safe way of preventing bone demineralization in VLBW infants while taking into account individual needs and varying amounts of Ca and Pi in breast milk as well as formulas of differing compositions. However, although our study was prospectively designed and the gradually increased Ca/Pi supplements were administered as planned, we retrospectively classified the infants as group 1 and group 2. Therefore, a further prospective trial is needed to test our hypothesis.

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Announcement

VII International Congress of Pediatric Dermatology

The VII International Congress of Pediatric Dermatology will be held in Buenos Aires, Argentina, from September 26th to October 1st, 1994. The main themes will be Atopic Dermatitis, Nutritional Disorders, AIDS, and Genodermatoses. For further information, please contact Dr. Adrián M. Pierini, President, VII International Congress of Pediatric Dermatology, Arenales 1446 Ap. 1 B, (1061) Buenos Aires, Argentina, phone (54.1) 814-4068, fax (54.1) 812-9255.