Bone mineral content in bronchopulmonary dysplasia

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SUMMARY Fourteen preterm infants who developed bronchopulmonary dysplasia diagnosed radiologically were compared with a group of similar infants who did not. The two groups were of comparable maturity and birth weight. The clinical histories indicated that those infants with bronchopulmonary dysplasia had had longer periods of supplemental oxygen, more frequent treatment with dexamethasone, and a higher mean total dosage of frusemide.

Bone mineral content in the mid-forearm was measured by photon absorptiometry at or near the postconceptional age of 40 weeks in all cases; no significant difference was found between the two groups, although both were severely undermineralised when compared with infants born at full term. In both groups mean daily calcium intake (about 70 mg/kg/day) was about half the daily intrauterine accretion of calcium.

Impaired skeletal mineral absorption is common in preterm infants after prolonged intensive care.¹ In such cases the deficit in bone mineral content (BMC) can be measured accurately by photon absorptiometry,² and we have shown that at a postconceptional age of 40 weeks the deficit in BMC in the mid-forearm compared with that in the arms of full term infants measured at birth is about 20%.^{3 4}

Inability in postnatal life to match intrauterine skeletal mineral absorption may be exacerbated by several factors including prolonged intravenous nutrition with its inherent limitation on mineral intake⁵; fluid restriction, resulting in decreased intake of calcium and phosphorus; physiological losses of calcium and phosphorus in stool and urine, which limit the quantities retained; chronic acidosis⁶; and treatment with steroids⁷ and diuretics.⁸ These factors are more common in infants undergoing prolonged intensive care, who often develop bronchopulmonary dysplasia (BPD).

Although there have been reports of radiologically diagnosed bone disease occurring in conjunction with chronic neonatal lung disease,^{9 10} only once to our knowledge has its severity been measured by photon absorptiometry.¹¹ As part of a larger study of bone mineral absorption in neonates we compared otherwise similar groups of preterm infants with and without BPD to ascertain whether undermineralisation was more severe in those with BPD.

Patients and methods

This retrospective study was confined to infants who had undergone photon absorptiometry of the forearm at or near the postconceptional age of 40 weeks. Informed consent was obtained from the parents and the study approved by the hospital ethical committee.

Over a period of 26 months 14 infants who needed ventilation for hyaline membrane disease developed radiological and clinical evidence of BPD. Using established criteria,¹² a paediatric radiologist (RA) graded their chest radiographs as showing either moderate or severe BPD. Fourteen infants of similar maturity and birth weight who were in the unit during the same period were identified and formed the control group; they were selected because they too had been ventilated but their chest radiographs showed either mild or no changes of BPD. Table 1 shows the sex, gestational age, birth weight, and duration of stay in the unit of each infant.

The number of days of ventilation and the number of days of supplemental oxygen were recorded for each infant. Table 2 gives these details together with the number of days of intravenous fluid replacement, acidosis (blood pH less than 7.30, usually respiratory in origin), and treatment with dexamethasone (0.1 mg/kg/dose) when these data were available. Only one infant in the control group

Table 1 Clinical details of infants studied

Case No	Sex	Gestational age (weeks)	Birth weight (g)	Stay in unit (days)
Group with BPD				
1	F	26	725	94
2	F	26	950	98
3	M	26	1010	84
4	M	26	1020	78
5	F	27	780	72
6	F	27	1125	91
7	M	27	740	70
8	M	27	1300	77
9	M	28	1000	60
10	M	28	1000	55
11	F	29	1200	98
12	M	29	1550	105
13	M	30	1300	82
14	M	30	1770	70
Mean		27.57	1105	81.0
SD		1.45	300	14.9
SE		0.39	80	4.0
Control group				
15	F	26	840	80
16	M	26	900	70
17	M	27	725	65
18	M	27	1000	91
19	F	28	1150	32
20	F	28	1500	84
21	M	28	1250	84
22	M	28	1300	63
23	M	28	1350	64
24	M	28	1450	38
25	F	29	1400	77
26	F	30	800	54
27	F	31	1100	52
28	M	31	1400	51
Mean		28.21	1155	64.6
SD		1.58	263	17.8
SE		0.42	70	4.7

received dexamethasone (for laryngeal oedema). Table 3 shows the number of doses of frusemide (1–2 mg/kg) given to each infant; treatment with dexamethasone or frusemide, or both, was always stopped before discharge from the unit.

Oral fluid intake was used to derive energy and mineral intakes from manufacturers' data sheets. Table 3 lists the total calcium intake with corresponding mean daily intakes of fluid, energy, and calcium up to the day when photon absorptiometry was performed. Fluid intake was unknown in two cases.

We always supplement the milk with vitamin D (400 or 1000 IU daily) once oral feeds can be tolerated, and vitamin D intake is usually recorded throughout each infant's stay in the unit; the mean

daily intake over the period up to discharge was calculated for each infant and is also shown in table 3. No attempt was made to estimate vitamin D intake after discharge from the unit. Data were not available in three cases.

BMC in the mid-forearm was measured as previously described.^{2,4} Photon absorptiometry of the forearm in neonates entails a small skin entrance dose of 0.03 mGy (3 mrad) for each investigation; a 0.5 cm length of forearm is irradiated. The procedure was done in 24 of the infants at postconceptional ages ranging from 37 to 41 weeks, and the remaining four within six days of these limits. Results are expressed as mass of ash per unit length (mg/cm). Crown-heel length (cm), weight (g), and ulnar length (mm) were measured when photon absorptiometry was performed. Table 4 shows the results of the radiological grading for evidence of BPD, the results of photon absorptiometry, and anthropometric data. Blood samples were taken for assay of plasma concentrations of 25-hydroxy-vitamin D from 18 of the 28 infants on the day that absorptiometry was performed.¹³ These results are also shown in table 4.

When the data were normally distributed the mean, standard deviation (SD), and standard error (SE) of each measurement were computed for each group and the significance of the difference between the two group means calculated with the unpaired Student's *t* test. Otherwise only the means were calculated and a non-parametric test (Mann-Whitney U test or Wilcoxon rank sum test) used to calculate the significance of the differences between the two groups. Two tailed probabilities are quoted throughout.

Results

There were no significant differences in mean gestational age or birth weight between the infants with BPD and the controls (Table 1). Those with BPD spent significantly more time in the unit ($p < 0.02$; table 1) and required more days of ventilation ($p < 0.001$) and supplemental oxygen ($p < 0.001$; table 2) than the controls. Intravenous fluid replacement was undertaken significantly more often ($p < 0.01$) and acidosis occurred more frequently ($p < 0.005$) in the group with BPD than in the control group. Infants with BPD were treated more frequently with dexamethasone ($p < 0.005$; table 2); the mean total frusemide dosage was also significantly higher ($p < 0.05$; table 3).

The mean total calcium intake was significantly lower in the group with BPD than in the control group (6.46 g v 10.33 g; $p < 0.05$; table 3). The mean daily calcium intake in the group with BPD

Table 2 Number of days of ventilation, supplementary oxygen, intravenous fluid replacement, acidosis, and treatment with dexamethasone therapy

Case No	Ventilation	Oxygen	Fluids	Acidosis	Dexamethasone
Group with BFD					
1	32	84	45	22	24
2	23	65	30	29	30
3	49	98	38	37	9
4	20	56	19	15	11
5	17	28	34	15	9
6	24	27	32	13	0
7	26	88	42	18	0
8	12	22	41	8	22
9	31	20	—	—	—
10	22	85	40	30	8
11	21	26	24	10	31
12	37	36	38	14	0
13	18	36	29	14	38
14	37	69	44	14	7
Mean	26.4	52.9	35.1	18.4	14.5
Control group					
15	22	29	43	15	0
16	5	27	7	7	0
17	1	1	3	4	0
18	18	43	32	—	6
19	4	5	6	3	0
20	26	21	33	22	0
21	22	26	61	12	0
22	8	9	14	8	0
23	14	16	17	5	0
24	7	10	9	5	—
25	7	19	9	9	0
26	1	1	2	1	0
27	7	7	9	7	0
28	14	17	17	6	0
Mean	11.1	16.5	18.7	8.0	0.5

(expressed as mmol/kg/day) was also lower but not significantly so. Daily fluid and energy intakes were significantly lower in the group with BPD than in the control group ($p < 0.02$ and $p < 0.05$, respectively).

The group with BPD had a lower mean vitamin D intake than the control group (306 v 472 IU daily); this difference was significant ($p < 0.05$). The mean plasma 25-hydroxyvitamin D concentrations around the postconceptional age of 40 weeks were comparable and not significantly different between the two groups; in the group with BPD one infant had a value below 25 nmol/l whereas four controls had values below that limit.

At about 40 weeks the infants with BPD were on average lighter than the controls (table 4); the difference (about 430 g) between the group means was significant ($p < 0.05$). There were no significant differences between the two groups in mean crown-heel length, ulnar length, or BMC. Even when the

extreme cases were contrasted the mean BMC did not differ significantly between those with and without BPD; mean (SE) BMC in nine infants classified as having severe radiological changes associated with BPD was 98.0 (5.5) mg/cm, and in 10 controls with no radiological evidence of BPD the corresponding value was 105.1 (11.4) mg/cm. Although significant differences between groups could not be shown, the mean BMC was only about 100 mg/cm in both the BPD and control groups; in contrast, the mean value in full term infants measured at birth with the same apparatus has been shown to be 194.0 (3.7) mg/cm.⁴

Discussion

During pregnancy the placenta provides the fetus with a readily available source of calcium and phosphorus. It has been estimated that the accretion of calcium in utero is about 130 mg/kg/day during

Table 3 Total number of doses of frusemide and intake of calcium and average daily intake of fluid, energy, calcium, and vitamin D

Case No	Total intake		Daily intake			
	Frusemide (No of doses)	Calcium (g)	Fluid (ml/kg)	Energy (kJ/kg)	Calcium (mmol/kg)	Vitamin D (IU)
Group with BPD						
1	22	5.72	172		1.17	252
2	8	5.34	152	26.0	2.62	230
3	109	9.55	160	22.9	1.92	176
4	29		137			853
5	7	3.65	157	20.3	1.14	453
6	7	3.86	149	17.7	1.15	582
7	50	7.49	140	20.6	1.50	213
8	0	8.96	138	19.0	1.71	220
9		8.60	132	19.9	1.86	
10	60	4.44	137		2.34	195
11	2					
12	49	12.93	135	19.9	1.81	143
13	0	1.38	133	15.5	0.99	281
14	114	5.60	134	17.7	1.40	77
Mean	35.2	6.46	144.3	20.0	1.63	306
SD			12.6	2.9	0.51	
SE			3.5	0.9	0.15	
Control group						
15	11	14.45	143	23.7	1.81	475
16	1	13.92	165	26.0	2.14	478
17	0	7.63	219	33.7	3.16	384
18		9.23	157	19.6	1.78	618
19	0	7.24	167	27.5	1.26	911
20	28	9.31	165	21.8	1.75	552
21	4	3.42	140	14.1	0.79	97
22	0	13.33	167	29.9	2.10	374
23	6	11.86	139	20.5	1.88	490
24	21	11.96	139	22.4	1.90	424
25	9					
26	0	15.48	187	31.3	2.66	464
27	3	6.11	165	26.4	1.41	592
28	6	10.35	153	22.4	1.77	273
Mean	6.8	10.33	162.0	24.6	1.88	472
SD			22.3	5.3	0.59	
SE			6.2	1.5	0.16	

the last trimester of pregnancy, resulting in the deposition of about 25 g of calcium in the fetal skeleton.¹⁴ Because many premature infants have nutritional problems it is not surprising that inadequate skeletal mineral absorption is common. Although skeletal changes associated with neonatal bone disease can sometimes be detected radiologically,¹⁵ the more sensitive technique of photon absorptiometry has shown that the bones of almost all premature infants are deficient in minerals by the time they reach the postconceptional age of 40 weeks.^{3, 4}

There are compelling theoretical reasons for believing that inadequate skeletal mineralisation

should be more pronounced in infants who develop BPD. As we have shown, these infants are generally more ill and require longer periods of ventilation and supplemental oxygen with restriction of fluids, and hence lower calcium and phosphorus intakes. Although we did not attempt to carry out balance studies, in both the BPD and control groups the average daily calcium intake over the study period was far less than would be expected in utero. Furthermore, the calcium available for absorption into bone was considerably less than the intake because retention was probably no more than 50%.¹⁶ Calcium retention in the group with BPD was probably further reduced by treatment with

Table 4 Observations at postconceptional age of 40 weeks

Case No	Radiological grade*	Weight (g)	Crown-heel length (cm)	Ulnar length (mm)	BMC (mg/cm)	25-Hydroxy vitamin D (nmol/l)
Group with BPD						
1	3	1775	40.2	57.5	94.1	
2	3	2170	44.3	64.0	86.3	
3	3	1980	40.6	67.0	121.4	198
4	2	2700	44.5	69.0	92.0	149
5	3	2570	45.5	73.0	66.0	
6	3	1400	40.2	61.0	111.8	58
7	3	1620	39.5	61.0	89.2	
8	2	1990	43.5	69.0	101.1	113
9	3	1900	40.9	66.0	102.3	
10	3	1400	39.1	56.3	109.2	
11	2	1650	42.1	63.0	96.7	69
12	2	2650	46.9	73.0	129.7	8
13	2	1830	42.3	67.0	97.0	52
14	3	1450	43.8	60.0	101.3	25
Mean		1935	42.39	64.77	99.86	84
SD		446	2.41	5.28	15.57	
SE		119	0.64	1.41	4.16	
Control group						
15	0	2520	46.0	72.5	79.6	
16	0	3000	41.5	67.0	126.1	82
17	0	1600	40.0	58.0	65.0	4
18	1	1840	40.5	60.5	90.4	
19	0	2730	45.1	75.0	100.2	107
20	1	1650	40.2	64.0	87.5	23
21	1	1520	40.0	62.0	79.3	18
22	1	2500	45.0	69.0	104.7	15
23	0	2800	47.5	74.0	127.5	201
24	0	3450	50.8	85.0	124.0	
25	0	2180	44.6	69.0	93.2	78
26	0	2700	45.7	72.5	68.7	
27	0	1800	42.0	65.0	82.9	105
28	0	2780	48.2	75.0	183.5	131
Mean		2362	44.08	69.18	100.90	76
SD		599	3.45	7.15	31.17	
SE		160	0.92	1.91	8.33	

*0 = normal, 1 = mild, 2 = moderate, 3 = severe BPD.

frusemide, which is known to increase urinary calcium excretions.⁸ Additionally, because steroids cause a reduction in the mineral content of bone in adults, it might be expected that treatment with dexamethasone would also have deleterious effects on the infant skeleton.⁷

Despite these expectations we did not detect a difference in BMC of the forearm between the BPD and control groups using the most sensitive technique available. When compared with full term infants at birth the preterm infants with BPD observed at 40 weeks were severely deficient in minerals, but this seems to be a consequence of their prematurity and not a secondary effect of treatment. Greer and McCormick reached a similar conclusion,

even though their controls were on average more mature and heavier than our infants with BPD.¹¹

Though inadequate intake of both calcium and phosphorus is likely to be a major cause of mineral deficiency in preterm infants,¹⁷ vitamin D deficiency is also associated with bone disease.¹⁸ Although the babies in our study ultimately received the recommended intake of 400 IU/day, this could not be achieved until oral feeds were tolerated in sufficient quantities. Some infants received more vitamin D than is recommended (Table 3), and in some cases when enteral feeding was delayed the daily average intake over the period of stay in the neonatal unit was well below the recommended value. Although plasma 25-hydroxyvitamin D concentrations were

similar in the two groups at the time that BMC was measured, when vitamin D intake was most likely to be optimal, those concentrations might not reflect earlier vitamin D state. Several infants had 25-hydroxyvitamin D values below the concentration regarded as indicating vitamin D deficiency (25 nmol/l). Within this set of data, however, no significant association between the plasma 25-hydroxyvitamin D concentrations and BMC could be shown.

The results of this study indicate that the skeleton is deficient in minerals in infants with BPD as a consequence of their prematurity. That such infants were not found to be more severely undermineralised than preterm controls without BPD was surprising. Both mineral and vitamin D intakes in preterm infants may be suboptimal during their stay in the neonatal unit, and both factors probably contribute to the development of neonatal bone disease, although the grossly deficient mineral intake (compared with the intrauterine accretion) may be the more important.¹⁷ It is reassuring to know that the current treatment of BPD with frusemide and dexamethasone does not seem to be detrimental.¹⁹

JRJ has a research grant from the Yorkshire Regional Health Authority. SR is supported by an award from the special trustees of the General Infirmary, Leeds. We thank E B Mawer for performing the vitamin D assays.

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Received 29 April 1987