Bone mineral accretion rate and calcium intake in preterm infants

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SUMMARY Thirty six preterm infants (20 boys) of 25 to 32 weeks' gestation were observed from birth to around 40 weeks' postconception. When oral feeding became possible, nine received mother's own breast milk (group B), 15 formula feed (group F), and 12 formula feed supplemented with calcium (5 ml 10% calcium gluconate/100 ml feed) and phosphorus (0.5 ml 17% potassium phosphate similarly) (group S). All received a daily supplement of 400 IU vitamin D. Intakes of calcium, phosphorus, vitamin D, energy, and fluid volume were recorded. When oral feeding started, and near 40 weeks' postconception, bone mineral content of the forearm was measured by photon absorptiometry; weight and crown-heel length were also measured.

After logarithmic transformation of the measurements, there were no significant intergroup differences between the mean rate constants for weight or crown-heel length describing growth during the observation period. The mean rate constant for mineral accretion (M) was significantly higher in group S than in both the others. Pooling all data, M was significantly correlated with calcium intake but not with any other variable. Mineral supplementation of feed can reduce but not cure osteopenia of prematurity.

By applying single photon absorptiometry to the mid forearm of neonates,¹ we have previously shown the existence of a substantial deficit in bone mineral content, relative to full term infants observed at birth, in most preterm infants when they reach a postconceptional age of 40 weeks.^{2,3}

Bone mineral content of cortical bone is dependent on both density of mineralisation and bone size in the measurement region. Infants with extremely low birth weight (ELBW) (that is, birth weight less than 1000 g) have recently been shown to be at a disadvantage in both respects.³ At about 40 weeks they are underweight by 45%, shorter by 20%, and undermineralised by 55% relative to full term controls observed at birth; taking into account their reduced body size, at 40 weeks ELBW infants are still undermineralised by 35%. Preterm infants with birth weights in excess of 1000 g have also been shown to be undermineralised at 40 weeks by about 20% when body size reduction is taken into account.² Numerical values of relative undermineralisation observed in such studies, based as they were on localised measurements of the peripheral skeleton, do not necessarily apply to the skeleton as

a whole; none the less, a mineral deficit in the forearm bones of a preterm infant is usually indicative of more widespread osteopenia.

Radiographically detectable osteopenia of prematurity has reportedly been ameliorated by vitamin D supplementation.⁴ However, radiological assessment detects only the most severe cases. In contrast, our measurements of the effects of vitamin D supplementation of randomly selected preterm infants did not show a significant improvement in the rate of postnatal mineral accretion when the vitamin D intake was raised from the standard 400 IU/day to 1000 IU/day (J James, PJ Congdon, A Horsman, *et al.* Unpublished observations). In the same study, infants given 1 α -hydroxyvitamin D had a slightly raised rate of mineral accretion but still did not reach values comparable with those attained in utero.⁵

There is, however, some evidence that bone mineral accretion can be accelerated by mineral supplementation,⁶ and given the lack of response to vitamin D supplements we consequently gave calcium and phosphorus supplemented feeds to some of the preterm infants in our neonatal unit. In this

paper we present observations of changes in bone mineral content in preterm infants some of whom were given breast milk, the remainder being offered either normal feeds or feeds supplemented with calcium and phosphorus, the aim being to determine whether mother's milk or increased mineral intake conferred detectable benefits with respect to mineral accretion rate and general growth parameters.

Patients and methods

This study was authorised by the local ethical committee and commenced in September 1986, being carried out over a period of 17 months. During that period, all white infants of less than 33 weeks' gestation who were born in The General Infirmary, Leeds, or transferred to our neonatal unit during the first week of life, were considered eligible for the study. Those who were transferred back to their referring hospitals before the initial assessment could be performed were excluded.

Parents of 36 infants consented to the recruitment of their child into the study, having been approached soon after the birth. Gestational age (completed weeks) and birth weight were noted in each case. Gestational age, calculated from maternal menstrual history and confirmed by either external examination⁷ or ophthalmoscopic examination of the lens,⁸ ranged from 25 to 32 weeks and birth weight from 650 to 2000 g. Descriptive statistics for observations at birth are contained in table 1 for each of the three dietary groups described below.

Most infants received intravenous fluids immediately after birth and, if fluids were required for three days or more, total parenteral nutrition was then implemented using standard solutions supplying up to 60 mg/kg/day calcium, 40 mg/kg/day phosphorus, and 200 IU/day vitamin D. When the infants were able to tolerate oral feeds they were allocated to one of three dietary groups: breast milk, formula fed, and supplemented groups denoted by B, F, and S, respectively.

Mothers who wished to feed their infants with breast milk were allowed to do so. The infants in this group, B, received expressed milk until able to feed at the breast. Nine infants (seven boys) out of the 36 participants in this study were fed in that way throughout the individual period of observation. Each received an oral daily supplement of 400 IU vitamin D.

Those infants whose mothers did not wish to breast feed were given standard cows' milk formula feeds, including the standard daily supplement of 400 IU vitamin D, with or without additional mineral supplementation. The unsupplemented feed contained calcium and phosphorus in concentrations in the ranges 44 to 61 and 27 to 50 mg/100 ml respectively and was received by 15 infants (six boys) comprising group F. The additional supplement was allocated on a random basis and consisted of 5 ml 10% calcium gluconate plus 0.5 ml 17.4% dipotassium hydrogen phosphate added to each 100 ml bottle of ready made feed. Concentrations of calcium and phosphorus in the supplemented feed, which was received by 12 infants (seven boys) comprising group S, were in the ranges 86 to 102 and 46 to 62 mg/100 ml of prepared feed respectively; dilution caused a reduction in energy content of about 5%.

Infants in group S were screened for hypercalcaemia or hyperphosphataemia on a weekly basis. No deleterious effects of this form of supplementation were observed. When the supplemented infants were discharged from the neonatal unit, mineral supplements were discontinued in view of the potential errors and dangers involved in adding mineral supplements at home. The infants then received standard cows' milk formula feed.

For each infant, calcium, phosphorus, vitamin D, energy, and fluid intakes were assessed for every day in the period between the two absorptiometric scans (see below). Calcium and phosphorus concentrations in breast milk were taken to be 25 and 17 mg/100 ml respectively, based on analyses of pooled samples from eight mothers. Most of the informa-

Table 1 Descriptive statistics for gestational age and weight at birth in the breast milk group (B), the formula fed group (F), and the group of infants given calcium and phosphorus supplemented feeds (S)

	Group B (n=9)		Group F (n=15)		Group S (n=12)	
	Gestational age (weeks)	Birth weight (g)	Gestational age (weeks)	Birth weight (g)	Gestational age (weeks)	Birth weight (g)
Mean	28.22	1219	29.67	1254	30.17	1426
SD	1.64	288	2.16	316	1.85	296
Minimum	25	925	26	950	27	650
Maximum	30	1750	32	2000	32	1800

tion about intakes was obtained from dietary records; however, for each infant discharged from the neonatal unit before the second scan, the dietary intakes after discharge were estimated from a diet history taken when the second scan was performed. Mean values of calcium and phosphorus intakes in mg/kg/day, vitamin D intake in IU/day, energy intake in MJ/kg/day (except in group B) and fluid intake in ml/kg/day were evaluated for each infant. Individual total calcium and phosphorus intakes were divided by individual observation periods to

provide average rates of nutrient intake in g/week. Descriptive statistics for the dietary variables are given in table 2.

In all infants within seven weeks of birth, and in most (29 out of 36) within three weeks of birth, bone mineral content was measured at the middle of the right forearm by photon absorptiometry as described in previous publications.^{1 2} The radiation exposure involved in this procedure is very small, and only a narrow area of the forearm is irradiated during a scan; skin entrance dose is 0.03 mGy per

Table 2 Descriptive statistics for estimates of dietary intakes of calcium, phosphorus, vitamin D, energy, and fluids for the three dietary groups between the first and second absorptiometric scans

	Calcium			Phosphorus			Vitamin D		Energy (MJ/kg/day)	Fluids (ml/kg/day)
	mg/kg/day	g	g/week	mg/kg/day	g	g/week	IU/day	IU		
Group B (n=9):										
Mean	52.31	7.35	0.713	36.87	5.14	0.501	400	27820	—	187.6
SD	7.62	3.47	0.264	5.91	2.42	0.192	—	5656	—	20.9
Minimum	39.40	2.38	0.415	29.10	1.75	0.303	400	15988	—	149.4
Maximum	67.30	12.98	1.218	49.90	8.80	0.907	400	35196	—	216.7
Group F (n=15):										
Mean	92.49	7.52	1.035	63.51	5.29	0.721	483.9	25467	0.483	177.6
SD	20.32	3.25	0.361	15.71	2.73	0.313	79.7	7630	0.041	15.7
Minimum	51.30	2.72	0.464	41.80	1.59	0.232	311.0	12757	0.400	146.6
Maximum	113.30	12.40	1.621	92.20	10.17	1.329	595.0	42115	0.556	202.0
Group S (n=12):										
Mean	136.60	12.57	1.690	81.99	7.44	0.994	518.1	26984	0.482	184.3
SD	36.83	5.10	0.374	15.56	3.38	0.267	70.7	9717	0.038	11.0
Minimum	95.60	6.81	1.147	64.70	3.95	0.675	359.0	14644	0.396	167.7
Maximum	233.30	19.86	2.255	112.70	15.45	1.774	618.0	40916	0.544	204.8

Table 3 Descriptive statistics for observations at the time of the first scan. Weight, crown-heel length, and bone mineral content were measured in the mid forearm at that time for the three dietary groups. Natural logarithms are denoted by *ln*

	Postconcep- tional age (weeks)	Weight		Crown-heel length		Bone mineral content	
		g	<i>ln</i>	cm	<i>ln</i>	mg/cm	<i>ln</i>
Group B (n=9):							
Mean	30.29	1188	7.062	38.87	3.658	95.56	4.540
SD	0.72	247	0.203	2.60	0.066	19.90	0.213
Minimum	29.00	910	6.813	35.20	3.561	70.81	4.260
Maximum	31.29	1600	7.378	43.30	3.768	126.41	4.840
Group F (n=15)*:							
Mean	31.92	1252	7.105	39.28	3.669	101.06	4.599
SD	1.45	317	0.236	2.35	0.060	19.26	0.192
Minimum	29.29	825	6.715	35.30	3.564	71.62	4.271
Maximum	35.00	2000	7.601	43.20	3.766	140.93	4.948
Group S (n=12):							
Mean	31.76	1342	7.190	39.92	3.685	101.03	4.604
SD	1.64	214	0.161	2.12	0.055	14.73	0.160
Minimum	28.29	950	6.856	34.60	3.544	66.55	4.198
Maximum	34.00	1700	7.438	43.10	3.764	121.98	4.804

*n=14 for crown-heel length.

investigation. Postconceptional ages at the time of the first scan ranged from 28 to 35 weeks. Weight (in g) and crown-heel length (in cm) were measured at the same time. A crown-heel length measurement was not taken in one case. Descriptive statistics for observations performed at this time are contained in table 3.

Between the postconceptional ages of 37 and 43 weeks bone mineral content, weight, and crown-heel length were measured again. Crown-heel length was not measured in one case; this was a different infant from the one in whom crown-heel length was not measured on the first scan. The interval between the first and second scans ranged from 3.7 to 12.6 weeks (mean 8.0 weeks). Descriptive statistics for observations performed at the time of the second scan are contained in table 4.

STATISTICAL ANALYSIS

Individual values of weight, crown-heel length, and bone mineral content were converted to logarithms to the base *e* because previously published intra-uterine data indicated that logarithmic transformation is appropriate⁵; individual infants were assumed to follow exponential growth curves for all three variables during the postconceptional age range covered by these investigations. Individual rate constants (that is, rates of change of the natural logarithms of the measurements) were calculated by dividing the changes in the logarithms by the

corresponding time intervals of observation (in weeks) between the first and second scans. Student's *t* test was used to evaluate the significances of observed mean changes within and mean differences between groups; significances of differences in mean rate constants between groups were evaluated similarly. Paired *t* tests were used in comparisons of the preterm infants with full term infants observed previously and matched for postconceptional age at the time of photon absorptiometry.

Results

With one exception, there were no significant intergroup differences in the mean values of gestational age and weight at birth (table 1). Infants in group B had a significantly lower mean gestational age (28.22 weeks) than those in group S (30.17 weeks; *p*<0.05).

The data in table 2 show the disadvantage of breast feeding and the effectiveness of supplementation with regard to mineral intakes. As percentages of the mean mg/kg/day value in the group F, calcium and phosphorus intakes were 57% and 58% respectively in group B and 148% and 129% respectively in group S. Intergroup differences in the mean values of intake expressed as mg/kg/day were all highly significant (*p*<0.01); with the exception of the difference in phosphorus intake between groups B and F, differences between intakes expressed as

Table 4 Descriptive statistics for observations at the time of the second scan. Weight, crown-heel length, and bone mineral content were measured in the mid forearm at that time for the three dietary groups. Natural logarithms are denoted by *ln*

	<i>Postconcep- tional age (weeks)</i>	<i>Weight</i>		<i>Crown-heel length</i>		<i>Bone mineral content</i>	
		<i>g</i>	<i>ln</i>	<i>cm</i>	<i>ln</i>	<i>mg/cm</i>	<i>ln</i>
Group B (n=9):							
Mean	40.22	2685	7.850	46.99	3.845	96.12	4.528
SD	1.67	811	0.332	4.53	0.097	29.60	0.284
Minimum	37.00	1350	7.208	39.70	3.681	66.38	4.195
Maximum	42.86	3760	8.232	53.30	3.976	158.35	5.065
Group F (n=15)*:							
Mean	39.18	2399	7.753	46.20	3.830	98.53	4.575
SD	1.11	580	0.256	3.59	0.079	16.88	0.185
Minimum	37.14	1400	7.244	39.10	3.666	60.88	4.109
Maximum	40.86	3400	8.132	51.80	3.947	126.80	4.843
Group S (n=12):							
Mean	39.13	2453	7.782	46.43	3.836	116.68	4.742
SD	1.66	562	0.222	2.72	0.059	20.26	0.203
Minimum	37.29	1850	7.523	41.00	3.714	64.95	4.174
Maximum	42.71	3600	8.189	51.80	3.947	148.49	5.001

*n=14 for crown-heel length.

g/week were also significant ($p<0.05$). Mean calcium:phosphorus ratio (based on the mg/kg/day figures) was higher in group S (1.67) than in the other two groups (1.42 in group B and 1.46 in group F).

Values given in table 2 for vitamin D intake do not include the component present in the mother's milk fed to group B. The mean intake (IU/day) in group S was higher by about 7% than the mean in group F; this difference is mainly an indirect result of the fact that infants in group S tended initially to be slightly heavier and therefore were offered more feed than those in group F (see the mean weight values in tables 3 and 4). Mean energy intake (MJ/kg/day), however, did not differ between groups F and S (table 2; data were not available for group B), nor were there significant differences between the three groups with respect to fluid intake.

It was anticipated from the way the study was performed that there would be no systematic differences between the groups at the time of the first scan. Results at this time are given in table 3. Although the postconceptional age was significantly lower in group B than in group F ($p<0.01$) and group S ($p<0.05$), the differences between the means were small (less than 1.7 weeks). There were no significant intergroup differences between the mean values of weight, crown-heel length, and bone mineral content, or between the mean values of the logarithms of those measurements at the time of the first scan.

Results at the time of the second scan are given in table 4. Mean values of postconceptional age at that

time did not differ significantly between groups and occupied the range 39.13 to 40.22 weeks. Group B was the heaviest (mean 2685 g) but there were no significant weight (or $\ln$ weight) differences between groups. Group B was also the longest (mean crown-heel length 46.99 cm) but again there were no significant intergroup differences. Similar mean values of bone mineral content were attained at this time by groups B and F, although the variance was greater in the former. Both mean bone mineral content and its logarithmic equivalent, however, were significantly higher in group S than in group F ($p<0.02$ and $p<0.05$ for bone mineral content and its natural logarithm respectively). The figure summarises the results obtained at the times of the first and second scans.

Mean values of the time interval between birth and the first scan were 2.1, 2.3, and 1.6 weeks for groups B, F, and S, respectively and were not significantly different from one another. For the three groups together, the mean was 2.0 weeks with individual time intervals ranging from 1 day to 7.0 weeks. The interval was less than three weeks in 78% of cases and less than two weeks in 58%. During that period, some infants gained while others lost weight. The rate of weight change for all infants averaged (SEM) -25 (17) g/week and was not significantly different from zero. Individual changes in weight ranged from -280 g to $+300$ g. Such changes are consistent with common clinical experience of preterm infants.

Absolute changes in the mean values of the measurements can be derived from tables 3 and 4. The mean (SD) interval between the first and

Figure Mean (SEM) of weight, crown-heel length, and bone mineral content of the mid forearm in the three dietary groups at the times of the first and second absorptiometric scans. B=breast milk, F=formula, and S=supplement.

second scans varied between groups however, it was 9.94 (2.02) weeks in group B, 7.26 (1.87) weeks in group F, and 7.37 (2.20) weeks in group S. Significant differences between the mean interval in group B and both the other groups ($p < 0.02$) make interpretation of absolute changes difficult. Instead, rates of change of the measurements were compared.

Results derived from individual rates of change of the measurements and individual rate constants are given in tables 5 and 6 respectively. Values in table 5 are the weekly changes in the raw measurements and were evaluated only as a guide to the growth rates. Statistical tests were not performed on those results as it is known that the rate of change of each of the three variables is itself an increasing function

Table 5 Rates of change (weekly changes in measurements) for weight, crown-heel length, and bone mineral content of the mid forearm in the three dietary groups. Results apply to the period between the first and second scans

	Rates of change		
	Weight (g/week)	Crown-heel length (cm/week)	Bone mineral content (mg/cm/week)
Group B (n=9):			
Mean	144.6	0.790	-0.027
SD	45.9	0.251	2.027
Minimum	61.3	0.385	-3.126
Maximum	222.5	1.055	+2.541
Group F (n=15)*:			
Mean	153.9	0.998	-0.560
SD	47.0	0.409	1.782
Minimum	75.0	0.550	-3.234
Maximum	238.1	2.289	+2.510
Group S (n=12):			
Mean	148.5	0.905	2.349
SD	37.6	0.206	2.013
Minimum	80.7	0.631	-1.118
Maximum	211.1	1.356	+5.235

*n=13 for crown-heel length.

Table 6 Rate constants (weekly changes in natural logarithms of measurements) for weight, crown-heel length, and bone mineral content of the mid forearm in the three dietary groups. Results apply to the period between the first and second scans and were used for evaluation of the significance of intergroup differences of the means

	Rate constants		
	Weight	Crown-heel length	Bone mineral content
Group B (n=9):			
Mean	0.0781	0.01836	-0.0018
SD	0.0132	0.00536	0.0207
SEM	0.0044	0.00179	0.0069
Group F (n=15)*:			
Mean	0.0881	0.02319	-0.0057
SD	0.0229	0.00848	0.0202
SEM	0.0059	0.00235	0.0052
Group S (n=12):			
Mean	0.0811	0.02112	0.0207
SD	0.0177	0.00523	0.0175
SEM	0.0051	0.00151	0.0051

*n=13 for crown-heel length.

of postconceptional age; the growth curves are exponential. Mean rate of weight gain was about the same in all three groups (about 150 g/week); within all three groups there was a wide spread in the individual rate of weight gain, with maximum values approximately three times the minimum values. Group B appeared to grow in length least rapidly (see below), mean values of the rate of increase of crown-heel length being similar in the other two groups (about 1 cm/week); again there was wide variability between individuals, with maximum values of the rate of crown-heel length increase being two to four times the minimum values. Based on the rate constants in table 6 there were no significant intergroup differences in weight increase or linear growth. For bone mineral content, however, the mean rate constant was significantly higher in group S than in both the other two groups ($p<0.01$ for groups S and F, and $p<0.02$ for groups S and B). There was no evidence within any group that the distribution of any rate constant was other than normal.

Correlations between rate constants for weight, crown-heel length and bone mineral content were evaluated. Within the groups, there were only two significant correlations, both involving weight and crown-heel length: in group B, $r=0.80$ ($p<0.02$) and in group F, $r=0.62$ ($p<0.05$). Pooling results in the three groups, again only the correlation coefficient between the rate constants for crown-heel length and weight was significant ($r=0.60$; $p<0.0002$). The rate constant for bone mineral content was not significantly correlated with the rate constant for either crown-heel length or weight.

For calcium and phosphorus, individual intakes expressed both as mg/kg/day and g/week (averaged over the period between the two scans) were available. In the case of calcium, pooling the results in the three groups, the rate constant for bone mineral content was significantly correlated with the intake expressed as mg/kg/day ($r=0.43$; $p<0.01$) and as g/week ($r=0.36$; $p<0.05$). In the case of phosphorus, the corresponding associations were not significant ($r=0.22$ and $r=0.09$ respectively).

None of the rate constants for weight, crown-heel length, or bone mineral content (again pooling the results in the three groups) was significantly correlated with energy intake (MJ/kg/day) or fluid intake (ml/kg/day). The correlation coefficient between the rate constant for bone mineral content and vitamin D intake (IU/day) was 0.30 ($0.05<p<0.1$); the vitamin D intake was not correlated with any other variable at the significance level $p<0.1$. All possible correlations within each group were also evaluated. There were no associations significant at the level $p<0.05$.

It was possible to match, on the basis of postconceptional age at the time of observation, nine of the infants in group S with nine full term white infants observed in previous studies.² The matching tolerance was less than one week; seven of the nine pairs were also sex matched. The matching exercise was limited to group S because the expected difference between preterm and full term infants in the mean value of bone mineral content was least in that group. Paired *t* tests were used to examine the significance of differences in the group mean values of weight, crown-heel length, and bone mineral content between the preterm and full term infants. Mean postconceptional age was almost identical in the two groups (39.7 weeks). The preterm infants were significantly lighter (preterm mean 2579 g; full term mean 3470 g; $p<0.01$) and shorter (preterm crown-heel length mean 46.8 cm; full term mean 51.0 cm; $p<0.01$). Despite the fact that supplementation promotes bone mineral accretion, the mean value of bone mineral content in the preterm infants was significantly less than in the matched full term controls (preterm bone mineral content mean 113.9 mg/cm; full term value 211.0 mg/cm; $p<0.001$).

Discussion

Osteopenia of prematurity results from postnatal failure to match the rate of skeletal mineral accretion achieved in utero.^{5,6} It is likely that reduced accretion is at least partly a consequence of relative lack of mineral (calcium and phosphorus) in the diet. Supportive evidence for this view is provided by the observation that the mineral supply is particularly deficient in human milk (see table 2), a feed which has previously been shown to be associated with poor calcium retention and an increased risk of osteopenia.⁹⁻¹¹ Furthermore, despite the insensitivity of radiological assessment of skeletal mineralisation,¹² studies based on radiographic examination have shown a very high prevalence of rickets in extremely low birthweight infants fed human milk.¹³ Higher activities of alkaline phosphatase in blood, indicative of metabolic bone disease, have also been recorded in premature infants fed human milk.¹⁴

A reasonable approach to the treatment or prevention of osteopenia, therefore, is to increase dietary mineral intake. When offering a supplemented diet to a preterm infant, however, it has to be accepted that the skeletal response is likely to depend on both the size of the supplement and the formulation of the feed, with variations in mineral bioavailability causing variations in mineral absorption between different formulations.¹⁵ Whatever the

response is, it can be measured, albeit with considerable technical difficulty, by calcium balance studies because a large proportion of total body calcium is located in the skeleton. Using that approach, Day *et al* showed that addition of calcium lactate to infant milk feeds resulted in calcium retention equal to that attained in utero¹⁶; however, in their study ionic hypercalcaemia occurred in over half the treated patients and the disparity between calcium retention (160 mg/kg/day) and phosphorus retention (25 mg/kg/day) remains unexplained. A similar disparity is present in the results of a study performed by Moya and Domenech that was probably too short (three days) to provide a reliable estimate of longer term calcium retention.¹⁷ More recent studies, in which specially prepared feeds were used that are not routinely available, have shown that mineral supplementation of formula feeds may result in calcium retention comparable with that achieved in utero.^{18 19} Further evidence of the benefits of mineral supplementation has been provided by radiographic studies which showed fewer abnormal wrist radiographs in infants receiving mineral supplemented formula feed.²⁰

From a technical standpoint, it is preferable to measure changes in skeletal mineralisation using photon absorptiometry, rather than calcium balance or radiological techniques, because the method provides a precise and accurate direct measurement of the bone mineral content at the scan site.^{1 2} Absorptiometric data on the effect of human milk feeding on changes in bone mineral content are confusing. A significant fall in bone mineral content during human milk feeding has been shown,^{21 22} but a significant fall has been shown in formula fed infants too.²² The addition of mineral supplements to human milk feeds has been found to confer no extra advantage in promoting bone mineral accretion.²³

The first workers to report normalised rates of bone mineralisation, based on absorptiometric data, in preterm infants given supplemented feeds were Steichen and Tsang.⁶ Unlike the infants in our study, theirs received not only mineral but also vitamin D supplements; furthermore the groups were not accurately described and the control group unexpectedly had a significantly lower mean value of bone mineral content at 2 weeks of age than the supplemented group despite the fact that both received the same feed for the first six days of life. However, there is evidence that the very smallest infants do not do so well. A further study by the same group, in which the benefits of mineral and vitamin D supplementation in infants weighing less than 1500 g were investigated, showed that in two thirds of the infants bone mineral content increased,

while in one third of the cases bone mineral content fell.²⁴ Chan *et al* studied mineral supplementation in carefully selected infants who weighed less than 1600 g; they excluded from their study infants who were ventilated, those who received more than 50% ambient oxygen, those with sepsis or intraventricular haemorrhage and those who received total parenteral nutrition for more than five days.²¹ Thus infants most at risk of osteopenia due to nutritional compromise were excluded. None the less, in that study also, some infants appeared to respond to supplementation by increasing bone mineral content whereas others suffered a net loss of bone mineral. A more recent study using very high concentrations of mineral in formula feed (180 mg/100 ml calcium and 90 mg/100 ml phosphorus) showed a significant increase in bone mineral content, but the increase did not match the change expected in utero.²² The risk of mineral precipitation at such concentrations is quite high and supplementation to this level is well above present guidelines.²⁵ At the much lower concentrations used in our study, we found no evidence of mineral precipitation.

The selection of infants at reduced risk of osteopenia, the use of complicated formula feeds, and the concomitant use of vitamin D as well as mineral supplements, has made the interpretation of the results of previous studies and the choice of an optimal dietary regime in preterm infants difficult for the practising paediatrician. With this in mind, in our study we regarded all infants as eligible for study no matter how ill they were, we used a simple method of mineral supplementation using standard cows' milk formula, and we used no vitamin D supplement over and above the standard supplement of 400 IU/day. Furthermore, no attempt was made to increase mineral accretion rates to the values achieved in utero because sick preterm infants often do not match intrauterine rates of growth in weight and length.

Under those conditions, we have shown that mineral supplementation of formula feeds confers a small but significant benefit in terms of mineral accretion rate, with rates of weight and length increase being independent of the dietary regimes studied. No side effects such as acidosis²⁶ and necrotising enterocolitis²⁷ occurred in the supplemented group. Although fat malabsorption has previously been shown in infants given mineral supplemented milk,^{28 29} there was no evidence of reduced weight gain in our supplemented infants. We therefore conclude that mineral supplementation of formula feed at the levels used in our study is a worthwhile and safe approach to the reduction of osteopenia of prematurity in all infants whose mothers choose not to breast feed.

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