Biochemical and osteodensitometric correlations in diagnosis of metabolic bone disturbances of prematurity

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Abstract

The incidence of osteopenia of prematurity varies between 30-60%. The biochemical examinations have a high degree of relativity in diagnosis. Radiological changes appear late. Dual energy X-ray absorptiometry allows a better quantification of bone mass. ***Objective:*** *To evaluate the bone mineral content of premature infants by dual X-ray absorbtiometry and to correlate the values obtained with biochemical values.* ***Method:*** *55 premature infants and 20 term newborns were included in a prospective study. We measured calcemia, phosphatemia, alkaline phosphatase and total bone mineral content at 40 weeks corrected age for premature infants and 4 days of life for term newborns.* ***Results:*** *25 premature infants had low DXA parameters. There was a highly positive correlation between hypofosfataemia and DXA values and a highly negative correlation between alkaline phosphatase and DXA values.* ***Conclusions:*** *Biochemical investigations are useful tools for the monitoring of bone mineralization and diagnosis of metabolic bone disease.*

Keywords: *osteopenia of prematurity, hypophosphatemia, bone mineral content, dual absorptiometry*

Presentation

Osteopenia and rickets are common in verz premature infants. They are clinically evident late. Dual X-ray absorptiometry is an accurate technique for diagnosis. Because of difficulties in transporting preterm infants to DXA investigation, biochemical measurements would be useful for monitoring bone mineralization.

Background

Bone mineral disease affects 30-60% of very low birth weight infants, especially those with a birth weight under 1,000 grams[1,2]. Osteopenia of prematurity, caused by phosphate deficiency in very premature newborns fed with human milk, is well recognized. The clinical onset of the disease occurs between 5-15 weeks postnatal age[3]. It is often asymptomatic, but can produce respiratory failure with the impossibility of disconnection from the ventilator or pathological fractures[1,2]. Radiological changes are similar to those of deficiency rickets of infancy and they are visible in the skull, spine and ribs. Unfortunately, they become obvious at a late stage, when bone mineralization is reduced by at least 20%[3]. Biochemical parameters (calcium and phosphorus) are inconsistently changed and they are not clear indicators of the disease severity[4]. Some authors show that serial determinations of phosphorus represent a good method for the detection and monitoring of the disease[5], and repeated dosing of alkaline phosphatase could be predictive for it, even if its values are fluctuating in premature infants[6].

Dual energy X-ray absorptiometry allows a better quantification of bone demineralization. Over the past 10 years, it has become the method of choice for diagnosis and treatment monitoring[7,8,9]. However, access to

Table 1 The anthropometric characteristics of the two groups

	Term newborns	Premature infants	P value
	N=20	N=55	
Gestational age (weeks)	39,3+/-0,72	30,2+/-1,9	0,00001
Birth weight (g)	3433,3+/-465	1258,6+/-196	0,00001
Postnatal age at DXA examination (weeks)	39,3+/-0,72	39,5+/-1,1	0,5231
Weight at DXA Examination (g)	3169+/-387	2665,2+/-169	0,00001
Length at DXA Examination (cm)	53,7+/-1	46,6+/-1	0,00001

Table 2 Values of biochemical and DXA parameters

	Term newborns	Premature infants	P value
	N=20	N=55	
Total calcium (mEq/l)	4,87+/-0.15	4,91+/-0,18	0.606
Phosphorus (mg/dl)	6,33+/-1.08	4,77+/-0,22	Kw=0,001
Alkaline phosphatase (u.i./l)	126+/-52	217+/-28	0,0005
BMC (g)	46,26+/-10.11	13,043+/-3,57	Kw=0,00001
BMD (g/cm2)	0,519+/-0.016	0,474+/-0,026	0,00001

this investigation is limited, because of the difficulties in transporting very small infants to the DXA machine. The parameters of this investigation, bone mineral content and bone mineral density, differ from one author to another depending on the type of machine and software used and the explored areas of the skeleton[9,10,11,12]. In this sense, biochemical parameters could be more useful in the routine practice of neonatal departments.

The aim of this paper is to evaluate the predictive value of biochemical parameters in relation to DXA parameters in the diagnosis of metabolic bone disease of prematurity.

Patients and methods

The prospective study included 75 newborns born in the "Dominic Stanca" Maternity, between 2002-2004. They were grouped as follows: 55 premature infants with a gestational age of 30,2+/-1,9 weeks and a birth weight of 1258,6g+/-196g; 20 term newborns, the control group, without pathological perinatal events, with a gestational age of 39,3+/-0,72 weeks and a birth weight of 343,3+/-465g. All the characteristics of the 2 groups are given in Table 1.

The term newborns were fed with mother's milk soon after birth. The premature infants were only given intravenous fluids in the first 2-3 days, then they were fed with human milk, starting with the third day of life. They were exclusively fed with human milk until they were discharged from our hospital. Vitamin D was administered starting with the 14th day of life (Vygantol 800ui/day), orally.

We determined calcemia, phosphataemia and alkaline phosphatase from a blood sample collected on the 4th day of life for term newborns and at 40 weeks corrected age for premature infants. Total calcium was determined with a Beckman flame photometer; phosphorus was determined by spectrophotometry and alkaline phosphatase by kinetic methods with para-nitrophenyl phosphate. Dual energy X-ray investigation was performed with a Lunar DPX-NT scanner, concomitantly with biochemical determinations. The coefficient of variation for "in vivo" determinations was 1,58 and the degree of accuracy was 99,4%. The parents' written informed consent was obtained.

Data were statistically processed using EPI INFO 6 program with $p<0,05$ significant, the Kruskall Wallis nonparametric test, and the correlation coefficient "r".

Results

The mean and standard deviation (SD) of biochemical and osteodensitometric parameters in the two groups are given in Table 2. We found no significant differences between calcium values in the two groups, while phosphorus was significantly lower and alkaline phosphatase significantly increased in premature infants compared to term newborns. Bone mineral density (BMD) and total bone mineral content (BMC) were significantly lower in preterm infants. A highly positive correlation between hypophosphataemia and BMD (r=0.76) and between hypophosphataemia and BMC (r=0.53) was found. We also found a highly negative correlation between alkaline phosphatase and BMD (r=-0.85) and between alkaline phosphatase and BMC (r=-0.74).

Bone demineralization was diagnosed in 25 of the 55 premature infants (45.4%). They had low BMD and BMC values. We considered the mean value -1SD as the lower limit of the two parameters. At 40 weeks corrected age, when the examination was performed, they had a significantly lower length and weight than term newborns. The premature infants with low mineral content had a significantly lower birth weight and gestational age than those without bone demineralization (Table 3).

Table 3 Anthropometric characteristics of premature infants with or without osteopenia

	Premature infants with osteopenia	Premature without osteopenia	P value
	N=25	N=30	
Gestational age (weeks)	29,4+/-1,9	31+/-1,5	0,026
Birth weight (g)	1129,4+/-228	1361,5+/-132	0,003

Pathological calcium values were present in 24 children, but only 10 of them had abnormal DXA values, and of the children with normal calcemia, 15 children had low DXA values. The sensitivity and specificity of calcium determination were 40% and 53%, respectively.

Hypophosphataemia (mean value -1SD) was present in 16 children and 15 of them had bone demineralization. 39 children had normal phosphorus values and 10 of them had low DXA values. The sensitivity and specificity of phosphorus determination were 60% and 96%, respectively.

Abnormal values of alkaline phosphatase (mean value +1SD) were found in 18 children and 14 of them had low DXA parameters. Of the 37 children with normal alkaline phosphatase values, 11 had bone demineralization. The sensitivity and specificity of alkaline phosphatase determination were 56% and 86%, respectively.

Discussions

The incidence of bone demineralization in our study was 45.4%, in children with a birth weight between 700-1,500g. The literature data show an incidence of 55% in premature infants under 1,000g and 23% in those under 1,500g[3,5]. The spearhead of diagnosis in metabolic bone disease is dual absorptiometry, but its parameters reported in the literature are different[7,9]. Using the same device and software, our values were similar to those obtained by Chen et al. for term newborns and lower for premature infants[11]. The DXA parameters were lower in premature infants but not all developed rickets. Literature data show that postnatal bone growth rate is different in preterm infants compared to term newborns[6,13].

Children with bone mineral disease can have normal, low or elevated calcium values; alkaline phosphatase has highly variable values that do not faithfully reflect osteopenia; in contrast, the monitoring of dynamic phosphataemia is useful for the detection and monitoring of the disease[5]. Backstrom et al. support that alkaline phosphatase and phosphataemia are useful indicators in the detection of osteopenia[3]. They find a high correlation of alkaline phosphatase with low mineral content with a specificity of 71%, while hypophosphatemia has a specificity of 96%. In our study the specificity of alkaline phosphatase was 87% and of hypophosphatemia was 96%.

Conclusions

In the absence of benchmarks for DXA exploration and under the conditions of the difficult access of very premature infants to DXA investigation, we conclude that the dynamic determination of phosphorus and alkaline phosphatase is a useful tool for the detection of bone mineral disease. ■

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