Bol Med Hosp Infant Mex 2013;70(6):431-439

RESEARCH ARTICLE

Time of onset of osteopenia in preterm newborns in a neonatology service

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ABSTRACT

Introduction. Osteopenia is a decrease in bone density secondary to low bone mineralization and can present as rickets, osteomalacia and osteoporosis. The aim of this study is to detect when osteopenia is presented in preterm newborns (PTNB) of a neonatal ward.
Methods. We carried out an observational, prospective, comparative clinical trial (study cohort) that included 30 PTNB admitted from November 2010 to August 2011 and who met the selection criteria. Alkaline phosphatase levels were considered elevated from 280 IU/l. Serum Ca, P, and alkaline phosphatase were determined in all patients. X-rays of long bones at 2, 4, 6 and 8 weeks after admission were taken. Statistical analysis was performed using descriptive and inferential statistics. Significance levels were set at $p < 0.05$.
Results. The study population consisted of 30 PNB with a median gestational age of 29 weeks and median birth weight of 1055 g. Parenteral and enteral nutrition (mixed) was managed in all patients. Radiological changes suggestive of osteopenia were reported in 83.3% of patients during the first 2 weeks of study and at the end of the study in 86.7% of patients (n = 26). The median age of detection of osteopenia was 19 days of life.
Conclusions. Osteopenia of prematurity occurs at approximately the third week after birth. These results present a different picture from that reported in the literature since the time of reporting these data. Preventing bone disease should be done early.

Key words: preterm infants, osteopenia, appearance.

INTRODUCTION

Osteopenia or metabolic bone disease (MBD) of prematurity is a decrease in bone density secondary to low bone mineralization. It is multifactorial and presents itself as rickets, osteomalacia and osteoporosis. Any of the above may occur in the preterm newborn (PTNB). In rickets, serum levels of calcium (Ca), phosphorus (P) or both are diminished and the alkaline phosphatase (AP) level is increased. There are changes in the diaphyseal-cartilage junction such as increase in the width of the cartilage of growth, bulging in the shape of a cup, and signs of fraying.

Osteomalacia is characterized by the same biochemical changes as rickets including osteopenia and rare or no linear growth, but lacks the characteristics of rickets in the diaphyseal-cartilage junction. Osteoporosis is defined as decrease in the bone mass per volume unit with a normal proportion of mineral with respect to the bone matrix, *i.e.*, all is reduced and cannot be radiologically distinguished from osteomalacia because both are characterized by osteopenia. However, patients with osteoporosis have normal serum concentrations of Ca, P and AP. There is sometimes an association between osteoporosis and osteomalacia.[1]

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Received for publication: 6-10-13
Accepted for publication: 9-24-13

The incidence of osteopenia varies according to different medical centers. It has been reported in 30% of PTNB <1500 g and in 50% of those <1000 g of weight.[2]

Perinatal bone development is carried out by means of two processes that are inter-related: intramembraneous and endochondral. The intramembraneous process is carried out in the first bone where ossification begins and originates the differentiation of mesenchymal cells to produce pre-osteoblasts and later osteoblasts, with the subsequent formation of bone matrix. Bone trabeculae develop that later fuse and form the primary spongy layer. The osteoblasts cover the surface of the spongy layer and deposit new layers of bone matrix, whereas the remaining new bone is eliminated from other surfaces by the osteoclasts. On the other hand, during endochondral ossification there is a progressive bone replacement of the cartilaginous precursor. Ca salts begin to precipitate in diverse portions of the bone matrix.[3,4]

The etiology of osteopenia is multifactorial. We have mentioned different risk factors for its development such as prematurity, which is the most important. It is known that the Ca and P deposits substantially increase from week 24 of gestation forward. During this period, the fetus increases ~30 g/day, which represents a consumption of 310 mg/day of Ca and 170 mg/day of P. Two thirds of these requirements are acquired during this period.[3,5] Prolonged use of parenteral nutrition (PN) is one of the most frequent causes of osteopenia because the solubility of Ca and P limits the ideal contribution of these minerals, especially when the premature infant requires fluid restriction.[5,6] Another associated factor is bronchopulmonary dysplasia (BPD) mainly due to the prolonged use of diuretics and treatment with methylxanthines (both increase loss of minerals in the urine). Also, use of corticosteroids influences osteoblastic function by reducing the absorption of Ca and P.[7] Lack of mechanical stimulation and lack of movement of the extremities, as well as prolonged rest, favor increased activity of the osteoclasts[8-12] and neonatal sepsis. These pathologies are frequent in the neonatology services and are related with the patient's catabolic status.[12] Osteopenia has also been related with a poor transplacental transference of Ca and P, which frequently occurs in pregnancies complicated with preeclampsia.

The majority of the time, rickets occurs in the PTNB due to deficiency of the mineral substrate of the bone rather than by vitamin D deficiency. It is more common in PTNB who are fed only breast milk.[13-15]

Osteopenia or MBD—with or without radiological evidence of rickets—occurs between the third and the twelfth weeks of age in the PTNB and is usually also associated with low birth weight.[1] Osteopenia is usually subclinical and occurs prior to the presence of fractures. On several occasions, this is the reason for diagnosis.[12,16-18]

Another marker of decreased bone mineral substrate is AP, an enzyme derived from matrix vesicles located in the membrane of osteoblasts and which increase with osteopenia secondary to rickets or osteomalacia in the PTNB. It has also been associated with linear growth up to the age of 12 weeks (in small groups of PTNB).[15,19-22]

In this last study it was found that the cut-off point was ≥1200 IU of AP, with a high incidence of low concentrations of serum P and high urine concentrations of the same element and serum elevation of Ca among PTNB with and without MBD. This suggested the association of P deficiency with growth retardation.[22] It was also appreciated that PTNB fed with breast milk (containing smaller amount of Ca and P compared to the industrialized formula) had higher levels of AP than those fed with industrialized formula for preterm infants during the first 9 weeks of extrauterine life. In the group with AP ≥1200 IU, weight gain, height and head circumference were decreased in the neonatal period, and at the age of 9-18 months only height and weight were decreased with respect to the group with lower AP activity.[21]

Kovar et al. introduced the use of serum AP for the detection of fractures in the PTNB.[20] In contrast, Faerk et al. found no relationship between the increase in AP and bone changes observed by absorptiometry.[23] Infants with osteopenia may have a large anterior fontanel, craniotabes (sign of "ping pong ball"), widening of the wrists, costochondral rosary, fractures of long bones and ribs and, over time, linear growth arrest, depending on the type of osteopenia. Radiologically all presented decrease in bone density. Miller reports that l0% of PTNB <1000 g, at the average age of 76 days, present fractures.[15] Brooke and Lucas found that 57% of PTNB <1200 g had fractures, and the main cause was the low amounts of Ca and P.[3]

The use of vitamin D for the treatment of osteopenia has not been proven. The quantity of 400 IU daily does not improve the absorption of Ca and P, and a quantity >800 IU could produce hypervitaminosis and is not recommended. The mineral supplement should be continued once initiated until there are radiological signs of improve-

ment.[4] In general, the medical literature mention diagnosis and treatment at the time osteopenia occurs and not when it should be prevented.[2,4,11,16,18]

In the Neonatology Service of the Medical Unit of High Specialty, General Hospital Dr. Gaudencio Gonzalez Garza (UMAE HG Dr. GGG) of the National Medical Center La Raza (CMNR), a large number of NB are seen; ~380 a year. Of these, >60% are premature, and virtually 100% are managed with PN. The literature mentions the presence of osteopenia from the third or fourth week of extrauterine life or even later.[1,6] However, it has been empirically observed with greater frequency at about the third week. Thus, a need arose for this study to report on the experience in the UMAE HG Dr. GGG of CMNR. According to the results, more precise bases and criteria for the initiation of management of minerals could be established —such as Ca, P and others—so as to possibly prevent the occurrence of this pathology.

The objective of this study was to detect the time at which osteopenia occurs in the premature infant (rickets, osteomalacia or osteoporosis) in the Neonatology Service of the UMAE HG Dr. GGG, CMNR.

SUBJECTS AND METHODS

An observational, prospective, comparative and clinical (cohort) study was carried out. We included 30 PTNB from the UMAE HG Dr. GGG Neonatology Service of the CMNR who were consecutively admitted from November 2010 to August 2011 and met the selection criteria.

We included all PTNB <34 weeks confirmed gestational age at the time of admission to the service within the first 72 h of extrauterine life with the expanded Ballard method for extremely premature NB.[24] In cases of doubt, this method was also used even at greater extrauterine ages than mentioned. Inclusion criteria were as follows: with or without mechanical ventilation, PN or fasting, infants who received maternal breast milk or special formula for preterm infants (from the first day of birth up to a maximum of 2 weeks extrauterine age), presence or not of BPD, and with or without a history of necrotizing enterocolitis. Parents or guardians provided informed consent prior to study admission.

We excluded PTNB with major congenital malformations such as disorders of neuronal migration, complex congenital heart disease, esophageal atresia, or congenital hypoparathyroidism or congenital hyperparathyroidism, congenital hypothyroidism or congenital hyperthyroidism, anemia (Hb <8 g/dl), and any type of liver disease. If any of the above was detected at any point during the study, the patient was excluded. Patients were also excluded if the family decided to withdraw the patient from the study.

Diagnosis of osteopenia was based on the radiological reduction of bone density of the humerus or femur associated or not with other radiological changes such as width of growth cartilage, bulging in a cup shape and signs of fraying as well as low or normal serum Ca levels, low or normal P serum levels and an increase of AP (rickets or osteomalacia).

Hypocalcemia was considered when Ca serum levels reported were <7 mg/dl. Hypophosphatemia was considered when serum P levels were <3.7 mg/dl and hyperphosphatemia with P serum levels of >8.2 mg/dl. AP serum levels >280 IU/l were considered to be elevated.

Parenteral Ca was provided with Ca gluconate at l0%, P as potassium phosphate and both were administered enterally through the contribution of the minerals mentioned in special formulas for premature infants.

Serum Ca, P and AP levels were determined for all patients included in the study at 2, 4, 6 and 8 weeks from the time of their admission. Radiographs of the long bones (femur and humerus) were taken during the same weeks with a portable X-ray apparatus (model 4564 100 X0381, Polymobil III, Siemens, Spain). Evaluations were done by an expert radiologist.

Serum Ca and P were determined by endpoint dichromic analysis. Ca present in the sample binds to the O-cresolphthalein complex to form a purple color complex in saline solution. Normal values for the PTNB are 7-10.8 mg/dl. For P, the method relates how much of the unreduced phosphomolybdate complex is proportional to the quantity of inorganic P in the sample.

Normal values in the PTNB range from 3.7-8.2 mg/dl. AP in serum was determined by methodology initially proposed by Bowers and McComb—using p-nitrophenyl phosphate as a substrate—and optimized by Tietz with the inclusion of a buffer to provide a metal ion and a 2-amino,2-methyl,1-propanolol buffer. The reference values in this determination for our patients are from 150-280 IU/l.

The age of appearance of osteopenia was considered to be from the day it was diagnosed for the first time in each patient. Weight, length and head circumference were

also determined during the study. Data obtained were recorded in a special format for data collection.

The analysis of the results was done using descriptive statistics (median and interquartile range for non-normally distributed variables) and mean and standard deviation of frequencies for normally distributed variables. Inferential statistics were done using the Friedman test and in case of normal distribution, repeated samples analysis. When indicated, the Wilcoxon range test was done; $p < 0.05$ was considered significant.

For statistical analysis, SPSS v.15 (Chicago, IL) was used. This work was approved by the Committee of Education and Medical Research and by the Bioethics Committee, both of the UMAE HG Dr. GGG of the CMNR.

RESULTS

The population studied was comprised of 30 PTNB who met the inclusion criteria. They were followed for 8 weeks; 60% ($n = 18$) were males (Table 1).

Among the admitting diagnoses, sepsis occupied first place with nine patients (30%); in second place, respiratory distress syndrome with eight patients (26.7%) and with a lower frequency, persistence of ductus arteriosus, pneumonia, intrauterine growth delay and prematurity for precise management of PN.

Of the 30 patients studied, only five received prenatal steroids (16.7%) although 20 were children of mothers with preeclampsia (66.6%). Of the 30 patients, 29 were managed with mechanical ventilation (96.7%) from 1 day to 105 days (median 30.5 days) (Table 2).

All patients received parenteral nutrition that was initiated within the first 48 h after admission. Intake of Ca increased with the length of hospitalization days with a significant difference. This was not the case for P (Table 3).

Intake of vitamin D <400 IU per day was reported in ten patients (33.3%); the remainder ($n = 20$) had an intake >400 IU (66.7%). All patients were managed with mixed feedings (parenteral and enteral) with different durations (Table 4).

There were 60% of patients who received nutrition with milk (PreNAN, Nestlé, Mexico) ($n = 18$) and 40% with Enfamil (Mead Johnson, Evansville, IN) for premature babies ($n = 12$); 73% of the patients received maternal milk combined with either of the formulas mentioned. Median weight during the weeks of study demonstrated a significant difference. The same was seen for height and head circumference (Table 5).

For detection of osteopenia, Ca, P and AP serum values were taken into account as well as x-rays of the long bones. These studies were carried out every 2 weeks for 8 weeks. There was an increase in the AP values upon admission (95 IU/l-879 IU/l, median 350 IU/l) with respect to those reported during the last two follow-up visits (101-969 IU/l, median 393 IU/l) but without a significant difference (Wilcoxon tests $p = 0.09$) (Table 6). On performing the Friedman test, a significant difference in the levels of serum Ca were seen but not with the serum P or AP level ($p > 0.05$).

Radiological changes suggestive of osteopenia were reported in 83.3% of the patients during the first 2 weeks of the study. During the third and the fourth weeks changes were observed in 76.7% as they were the patients who achieved improvement with Ca, P and vitamin D intake. However, during the fifth and sixth weeks, once again 83.3% of the patients ($n = 25$) reported osteopenia. At the end of the study, 86.7% of the patients had osteopenia ($n = 26$) and only four patients did not (13.3%). In that population, rickets predominated ($n = 18$) and, less frequently, osteomalacia ($n = 8$).

Table 1. Characteristics of the study population

Study characteristics	Values obtained ($n = 30$)
Gestational age (weeks)	
Median	29
Minimum-maximum	25-34
25-75th percentile	28.7-30.2
Birthweight (g)	
Median	1,055
Minimum-maximum	750-1,910
25-75th percentile	963.7-1,200
Apgar 5 min	
Median	8
Minimum-maximum	5-9
25-75th percentile	7-8
Age at admission (days)	
Median	4
Minimum-maximum	1-14
25-75th percentile	2-12
Length of hospital stay (days)	
Median	78
Minimum-maximum	55-180
25-75th percentile	65-90

In 33.3% (n = 10), clinical data such as costal rosary and widening of the wrist were detected. Diagnosis of osteopenia presented itself on day 16 (as a minimum) and on day 57 (as a maximum) of extrauterine life, with a median of 19 days (25-75th percentile of 16-25.7 days). Pathological fractures were seen on day 48 (minimum) and on day 85 (maximum), with a median of 69 days only in four patients.

With regard to the use of diuretics, the most utilized were furosemide and spironolactone, both in 23 patients (77%). Xanthines and steroids were also both used in 26 patients and each one was used in 86.7% of patients. Transfontanellar ultrasound was performed in all patients. Ten patients (33.3%) were reported with intraperiventricular hemorrhage (four with grade I and six with grade III according to Papille et al.[25]) An additional ten patients (33.3%) were diagnosed with periventricular leukomalacia. No alterations were reported in the other patients.

Length of hospital stay was 55-180 days (median 78 days). Five patients died. The most frequent cause was septic shock. Pathologies present at the end of the study were BPD reported in 26 (86.7%) patients. Age at time of detection was between 30 and 48 days (median 33 days). Neonatal sepsis occurred in 25 patients (83.3%), intrauterine growth retardation in nine patients (30%), persistence of ductus arteriosus in five patients (16.7%) and pathological fractures in four patients (13.3%). Some patients presented a combination of pathologies.

Table 2. Management with mechanical ventilation

Study characteristics	Values obtained (n = 29)
Time on mechanical ventilation (days)	
Median	30.5
Minimum-maximum	1-105
25-75th percentile	10.5-40
PIP maximum (cm H_20)	
Median	15
Minimum-maximum	14-40
25-75th percentile	14-39
Maximum cycles (cycles/minute)	
Median	50
Minimum-maximum	25-80
25-75th percentile	35-55
MAP maximum (cm H_2O)	
Median	10
Minimum-maximum	5-13
25-75th percentile	8.7-11.2

PIP, peak inspiratory pressure; MAP, mean airway pressure.

DISCUSSION

This is the first study performed in the NICU of the UMAE HG Dr. GGG of the CMNR. Frequency of osteopenia was

Table 4. Time of calcium and phosphorus contributions by enteral, parenteral and both routes in 30 preterm infants

Type of feeding	Time (days)
Enteral	
Median	35
Minimum-maximum	14-60
25-75th percentile	30-42.7
Parenteral	
Median	70
Minimum-maximum	20-150
25-75th percentile	60-78.7
Both routes	
Median	25.5
Minimum-maximum	7-60
25-75th percentile	20-30

Table 3. Comparison of the contributions of calcium and phosphorus during the 8-week study of 30 preterm infants

Average contribution	1st and 2nd weeks	3rd and 4th weeks	5th and 6th weeks	7th and 8th weeks	p*
Calcium gluconate (mg/kg/day)					
Average ± SD	178.6 ± 35.7	196 ± 49.1	225 ± 65.3	295 ± 97.6	<0.001
Minimum-maximum	100-250	100-300	150-400	150-400	
Potassium phosphate (mg/kg/day)					
Average ± SD	41.6 ± 7.4	42.5 ± 7.5	43.5 ± 7.3	44.6 ± 8	0.43 (NS)
Minimum-maximum	30-50	30-50	30-50	40-70	

*Repeated measures analysis; SD, standard deviation; NS, not significant.

86.7%, higher than reported in the literature.[2] This study was an initial overview to determine the number of patients who have the disease and the number is high.

It is important to mention that, in this study, average intake of Ca and P by enteral, parenteral, or both routes on admission was low compared with what is recommended by the American Academy of Pediatrics. At the end of the study, Ca intake in the majority of patients was adequate, although not for P. The latter continued to be low; therefore, an adequate relationship between Ca and P was not achieved (1.7:1) to maintain an optimal extrauterine growth similar to intrauterine growth, thereby conditioning bone demineralization.[5]

Steichen et al. carried out a study on premature children with intakes of Ca that were 220-250 mg/kg/day, P from 110-125 mg/kg/day and vitamin D from 260-400 IU a day. Two groups were compared, one fed with formula for premature infants and the other fed exclusively with breast milk. The authors concluded that the newborns who received only breast milk had a greater risk of presenting bone demineralization.[16] In our study, Ca intake was similar to the ideal in the majority of the patients; however, intake of P was lower.

The majority of the patients presented BPD and required management with diuretics such as furosemide, methylxanthines and steroids. These drugs increase mineral loss in the urine. Shrivastava et al. demonstrated that patients with BPD who received steroids for more than 3 weeks showed growth delay, absorption of Ca and retention of Ca and P, thereby favoring alterations in bone mineralization.[7] BPD was present in a large part of the population studied. The frequency of the use of diuretics

Table 5. Comparison of weight, length and head circumference during the study

Measurements carried out	1st and 2nd weeks	3rd and 4th weeks	5th and 6th weeks	7th and 8th weeks	*p**
Weight (g)					
Median	1,200	1,400	1,700	2,000	<0.001
Mínimum-maximum	785-2,225	980-2,310	1,090 ± 2,420	1,220 ± 2,560	
25-75th percentile	975-1,300	1,182.5-1,500	1,500-1,762.5	1,550-2,225	
Length (cm)					
Median	38	40	43	44	<0.001
Minimum-maximum	32-47	33.8-44.8	35-49.8	36.4-52.1	
25-75th percentile	36.7-40	39.7-42	40-44	42.7-45	
HC (cm)					
Median	29	30	32	34	<0.001
Minimum-maximum	24-33	24-34	24.6-36	26.1-37.4	
25-75th percentile	25.7-30	28-31	31-33	32.7-35	

HC, head circumference. *Friedman test.

Table 6. Serum calcium, phosphorus and alkaline phosphatase of preterm infants

Serum values	1st and 2nd weeks	3rd and 4th weeks	5th and 6th weeks	7th and 8th weeks	*p**
Calcium (mg/dl)					
Median	10	9	9	9	<0.001
Minimum-maximum	6.5-11.6	6.5-11	6.5-9.7	6-10	
25-75th percentile	9-10	9-9.85	8.77-9	8.5-9	
Phosphorus (mg/dl)					
Median	3.75	4.35	4.45	5	0.32 (NS)
Minimum-maximum	0.9-7.5	2-7.5	1.5-7.5	2.1-7.4	
25-75th percentile	3-4	3.37-5	1.97-7	4-6	
AP (IU/l)					
Median	350	423	462	393	0.17 (NS)
Minimum-maximum	95-879	135-1,542	112-1,513	101-969	
25-75th percentile	150-462.5	282.5-450	375-562.5	315-525	

*Friedman test. NS, not significant; AP, alkaline phosphatase.

was 77% and of methylxanthines and steroids was 86.7%. It is known that these drugs are factors that may favor the presence of osteopenia.

The lack of mechanical stimulation and movement in the extremities as well as prolonged rest favors the increase of bone demineralization.[8-11] Moyer et al. showed that performing passive movements in the four extremities for 5 to 10 min promotes weight gain and increases bone mass.[8] All patients remained with prolonged rest and did not receive rehabilitation.

Neonatal sepsis has been linked with an increase in catabolism, causing an increase of bone depletion in the PTNB.[12] This diagnosis was revealed in 30% of the PTNB on admission and in 83.3% at the end of the study.

The amount of vitamin D did not have an influence on the presence of osteopenia. The main cause is the inadequate supply of minerals.[1,2,13,16,26] Only 33.3% of preterm infants were not able to receive 400 IU of vitamin D per day, making an unimportant factor for the presentation of osteopenia.

Diagnosis of osteopenia was made by taking into account high levels of AP (>280 IU/l) in rickets and osteomalacia, low or normal Ca, P levels and radiological changes such as decreased bone density, added or not to the increase in the width of the growth plate, bulging in the shape of a cup and signs of fraying. Some authors mention that the cut-off point to consider osteoclastic activity is when AP is >1000 IU/l.[27] Other authors[2] consider when it is >700 IU/l, and some other mention values ~400 IU/l.[28] Indeed, in this study an increase of AP was observed from the first 2 weeks of the study without statistical significance among the weeks the study continued. Clinical and radiological evidence of osteopenia was also present at about the third week of life, already with a more elevated median >400 IU/l. It remained as such until almost the completion of the study. This suggests that the problem of osteopenia presented itself earlier than average to what has been reported in the medical literature.[2,16-18] In many patients with biochemical disorders and radiological evidence of osteopenia, there are no clinical data such as wide anterior fontanel, craniotabes, widening of the wrists, and chondrocostal rosary until there are fractures of the ribs or long bones.[1] Miller reports that 10% of premature infants weighing <1000 g at the average age of 76 days have pathological fractures.[15] Brooke et al. found that 57% of premature infants weighing 1200 g had fractures.[3] We found the presence of fractures in ~13% of premature infants. Age of detection was 48-85 days. In only 33.3% of the patients, clinical data such as costal rosary and wrist widening were detected. Osteopenia with or without evidence of rickets was present between week 3 and week 12 of extrauterine life.[2,16-18] When evaluating the x-rays of this investigation, 83.3% of the patients presented data of osteopenia during the first 2 weeks of the study (at about the third week of extrauterine life) and 86.7% at the end of the study. In the study population, only rickets and osteomalacia were present. The extrauterine age of the premature infants at the time of diagnosis of osteopenia was 16-57 days (median 19 days). With these results it was demonstrated that osteopenia can be detected at about the third week of extrauterine life.

In this study we found an increase in the final serum AP with respect to the time of admission (although without statistical difference), despite greater Ca intake at the end of the study, with a similar P intake during the entire investigation and without changes reflected in the initial or final P serum. This may be related to the increase in the frequency of radiological changes reported during weeks seven and eight.

Complications of prematurity itself such as BPD lead to the use of the steroids, diuretics and methylxanthines, which cause excessive urinary mineral losses. Measurement of urinary Ca and P were not included in this study; therefore, it is suggested that this be done at a future date. Unfortunately, we were unable to have a control group because the majority of the patients had osteopenia.

Prolonged use of PN does not prevent that extra supply of minerals be provided using alternate means, with the goal of achieving ideal numbers, especially in premature children with history of mothers with preeclampsia, malnutrition or avitaminosis. At present, the additives of breast milk provide adequate amounts of Ca and P as well as an increase in caloric density, for which its use is suggested in order to decrease demineralization. It has been recommended that from 2 weeks of extrauterine life, Ca intake should be 200 mg/kg/day and for P should be 100 mg/kg/day. It is necessary to continue with this supply until at least 40 postmenstrual weeks and even for more time in premature infants who are fed exclusively breast milk.[29] In our study patients, the general average amount of recommended Ca was given. It was not so for P, which was below what is suggested and could have been a co-factor

for the presentation of the disease, in addition to those factors already mentioned. Serum AP and x-rays of the long bones were the best indictors of osteopenia in this study. Densitometry was not used because that resource was not available.

It is important to mention that during the neonatal period the total AP corresponds almost completely to the bone fraction; therefore, it can be used as an element for diagnosis of osteopenia.[28] It is also important to determine cut-off reference points (normal) for the PTNB in accordance with the techniques used in the different departments that care for ths type of patient. We conclude that osteopenia of prematurity can be detected at about the third week of extrauterine life with paraclinical exams available in the majority of the departments that care for this type of patient, and with greater reason when being treated with diuretics, methylxanthines and steroids. These results offer a different outlook from what is already known and reported in the literature. Taking these data into account, prevention of bone demineralization should be carried out earlier. This will be achieved by initiating the appropriate supply of minerals (Ca and P, among others) necessary in the PTNB in order to maintain normal Ca, P and AP levels from the time of admission to a NICU or a special care unit for premature infants.

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REFERENCES

1. Rubin LP. Trastornos del metabolismo del calcio y del fósforo. In: Taeusch HW, Ballard RAS, eds. Tratado de Neonatología de Avery. Madrid: Ediciones Harcourt SA; 2000. pp. 1189-1206.
2. Hospital Británico. Departamento de Pediatría. Unidad Neonatal. Osteopenia del prematuro. Arch Pediatr Urug 2006;77:290-292.
3. Brooke OG, Lucas A. Metabolic bone disease in preterm infants. Arch Dis Child 1985;60:682-685.
4. McIntosh N, Livesey A, Brooke OG. Plasma 25-hydroxyvitamin D and rickets in infants of extremely low birthweight. Arch Dis Child 1982;57:848-850.
5. Rigo J, De Curtis M, Pieltain C, Picaud JC, Salle BL, Senterre J. Bone mineral metabolism in the micropremie. Clin Perinatol 2000;27:147-170.
6. Prestidge LL, Schanler RJ, Shulman RJ, Burns PA, Laine LL. Effect of parenteral calcium and phosphorus therapy on mineral retention and bone mineral content in very low birth weight infants. J Pediatr 1993;122(5 Pt 1):761-768.
7. Shrivastava A, Lyon A, McIntosh N. The effect of dexamethasone on growth, mineral balance and bone mineralization in preterm infants with chronic lung disease. Eur J Pediatr 2000;159:380-384.
8. Moyer-Mileur L, Luetkemeier M, Boomer L, Chan GM. Effect of physical activity on bone mineralization in premature infants. J Pediatr 1995;127:620-625.
9. Litmanovitz I, Dolfin T, Friedland O, Arnon S, Regev R, Shainkin-Kestenbaum R, et al. Early physical activity intervention prevents decrease of bone strength in very low birth weight infants. Pediatrics 2003;112(1 Pt 1):15-19.
10. Moyer-Mileur LJ, Brunstetter V, McNaught TP, Gill G, Chang GM. Daily physical activity program increases bone mineralization and growth in preterm very low birth weight infants. Pediatrics 2000;106:1088-1092.
11. Eliakim A, Nemet D. Osteopenia of prematurity—the role of exercise in prevention and treatment. Pediatr Endocrinol Rev 2005;2:675-682.
12. Eliakim A, Shiff Y, Nemet D, Dolfin T. The effect of neonatal sepsis on bone turnover in very-low birth weight premature infants. J Pediatr Endocrinol Metab 2003;16:413-418.
13. Chan GM. Growth and bone mineral status of discharged very low birth weight infants fed different formulas or human milk. J Pediatr 1993;123:439-443.
14. Rowe J, Rowe D, Horak E, Spackman T, Saltzman R, Robinson S, et al. Hypophosphatemia and hypercalciuria in small premature infants fed human milk: evidence for inadequate dietary phosphorus. J Pediatr 1984;104:112-117.
15. Miller ME. The bone disease of preterm birth: a biomechanical perspective. Pediatr Res 2003;53:10-15.
16. Steichen JJ, Gratton TL, Tsan RC. Osteopenia of prematurity: the cause and possible treatment. J Pediatr 1980;96(3 Pt 2):528-534.
17. Kulkarni PB, Hall RT, Rhodes PG, Sheehan MB, Callenbach JC, Germann DR, et al. Rickets in very low-birth-weight infants. J Pediatr 1980;96:249-252.
18. Campbell D, Fleischman AR. Rickets of prematurity: controversies in causation and prevention. Clin Perinatol 1988;15:879-890.
19. James JA, Mayne PD, Barnes IC, Kovar IZ. Growth velocity and plasma alkaline phosphatase activity in the preterm infant. Early Hum Dev 1985;11:27-32.
20. Kovar I, Mayne P, Barltrop D. Plasma alkaline phosphatase activity: a screening test for rickets in preterm neonates. Lancet 1982;1:308-310.
21. Lucas A, Brooke OG, Baker BA, Bishop N, Morley R. High alkaline phosphatase activity and growth in preterm neonates. Arch Dis Child 1989;64:902-909.
22. Glass EJ, Hume R, Hendry GM, Strange RC, Forfar JO. Plasma alkaline phosphatase activity in rickets of prematurity. Arch Dis Child 1982;57:373-376.
23. Faerk J, Peitersen B, Petersen S, Michaelsen KF. Bone mineralisation in premature infants cannot be predicted from serum alkaline phosphatase or serum phosphate. Arch Dis Child Fetal Neonatal Ed 2002;87:F133-F136.
24. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr 1991;119:417-423.
25. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-534.

26. Chang GM, Mileur L, Hansen JW. Effects of increased calcium and phosphorus formulas and human milk on bone mineralization in preterm infants. J Pediatr Gastroenterol Nutr 1986;5:444-449.
27. Gandy GM, Roberton NC. Neonatología. México D.F.: El Manual Moderno; 1989. p. 324.
28. Román NA, Wilson SJ, Beca IJP, Cortés EJM, Polette BV, Espíndola AAM. Fosfatasas alcalinas en el estudio de osteopenia del prematuro. Rev Chil Pediatr 1993;64:359-363.
29. Ceriani-Cernadas JM, Fustiñana CA, Mariani G, Jenik A, Lupo EA. Neonatología Práctica. 4th ed. Buenos Aires: Editorial Médica Panamericana; 2009. p. 260.