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# Osteopenic fractures in Preterm Infants <1500 Grams - A Retrospective Data Analysis Over 10 Years at the Medical University of Vienna

## Abstract

**Introduction:** Preterm infants, with a gestational age <29 weeks are at high risk to suffer from osteopenia of prematurity (39%) and may develop spontaneous fractures in 2%-10%. In addition to an insufficient prenatal bone mineralization, the inadequate supplementation with calcium/phosphorus and vitamin D3, immobility, prolonged parenteral nutrition and adverse effects of steroids or diuretics might be further risk factors. However, data on osteopenic fractures in preterm infants are limited and associated co-morbidities are not fully understood so far. Aim of the study was to report on preterm infants with osteopenic fractures and to analyzeco-morbidities.

**Materials and methods:** In this retrospective analysis all clinical reports of preterm infants with a birth weight <1500 gram, born between 2003-2012 at the Medical University of Vienna, were screened for the diagnosis "osteopenic fractures". Eligible patients were reviewed for serum parameters, duration of parenteral nutrition, concomitant medication and co-morbidities.

**Results:** The incidence of spontaneous osteopenic fractures in our cohort was 0.6% (10/1698). The mean gestational age of these patients was 26+3±2,3gestational weeks and the mean birth weight was 716±273 gram. 50% (5/10) of the patients with fractures underwent abdominal surgery previously and in 40% (4/10) parts of the bowel were resected. The mean duration of the parenteral nutrition was 123 ±44 days and 90% (9/10) developed a parenteral nutrition associated cholestasis. The meanionized calcium in serum was 1,29 ±0,09mmol/L and mean serum phosphate1,68 ±0,22 mmol/L. In 90% (9/10) of all patients serum- alkaline phosphatase was increased(mean 915 ±261 IU/L) and 80% suffered from vitamin D3 insufficiency (mean 52,9 ±18,1 mmol/L). Infants were on mechanical ventilation for 32,3±14,5 days (=mean) and 80% of them (8/10) developed bronchopulmonary dysplasia (BPD). 70% (7/10) of the patients received diuretics for more than 2 weeks and steroids (dexamethasone) for more than 5 days.

**Conclusion:** Spontaneous osteopenic fractures occurred primarily in the smallest and most immature, multimorbid preterm infants. We identified a variety of co-morbidities in our cohort such as abdominal surgery, parenteral nutrition associated cholestasis, BPD, vitamin D insufficiency, hypophosphatemia/ hypocalcemia and prolonged therapy with steroids and diuretics. To prevent osteopenic fractures diuretics and steroids should be applied only upon strict indication. A routinely screening for striking bone markers in serum and urine may be useful to prevent vitamin D insufficiency.

**Keywords:** Osteopenia; Spontaneous fractures; Metabolic bone disease; Preterm infant; Bone markers

Research Article

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**Abbreviations:** AP: Alkaline Phosphatase; BPD: Bronchopulmonary Dysplasia; Ca: Ionized Serum Calcium; IVH: Intraventricular Hemorrhage; NEC: Necrotizing Enterocolitis; Ph: Serum Phosphate; PVL: Periventricular Leukomalacia; ROP: Retinopathy of Prematurity

## Introduction

Osteopenia of prematurity is a complex and multifactorial disease characterized by a decreased bone mineral content and bone mass [1-4]. The fetal bone is mineralized up to 80% in the last trimester of pregnancy [5,6]. Therefore, preterm infants with a gestational age <29 weeks have less bone mineralization and are at high risk for developing osteopenia or osteoporosis (39%). In 2%-10% of these infants spontaneous fractures may occur [3,5,7]. In addition to an insufficient antenatal bone mineralization, the inadequate supplementation with calcium, phosphorus and Vitamin D3 [4,7,8] as well as immobility and prolonged parenteral nutrition [5,7,9,10] influence appropriate bone mineralization. Furthermore the adverse effects of drugs, like steroids and diuretics [11] are risk factors for osteopenia.

Only a few studies report on the relation of osteopenic fractures to outcome and morbidity in preterm infants [3,5,12]. Viswanathan et al. [2] described, that preterm infants with osteopenia or osteopenic fractures have higher mortality rates and a longer

hospital stay compared to controls without metabolic bone diseases [2]. There is also evidence for a persistent delay in linear growth and the development of osteoporosis later in life [1,13-15]. However, studies concerning fractures in preterm infants are limited and the characteristics of patients and associated co-morbidities are not fully understood so far [7,13,14]. Aim of this study was to report on preterm infants with osteopenic fractures and to analyze coherent co-morbidities.

## Materials and Methods

In a retrospective analysis all clinical records of preterm infants with a birth weight <1500 gram, born at the Medical University Vienna between the years 2003-2012, were screened for the diagnosis of osteopenic fractures. Eligible patients were reviewed for patient characteristics, serum parameters, duration of parenteral nutrition, concomitant medication and co-morbidities. Spontaneous osteopenic fractures were defined as fractures, occurring without any obvious external injury, like birth trauma, resuscitation or any other external trauma during the hospital stay [16]. The diagnosis of spontaneous fractures was identified from the case record database of the division of neonatology, using the keyword "fractures", "osteopenia" and "osteoporosis". In all cases the diagnosis was verified by reviewing the X-rays from the radiological database. Data from the following serum laboratory parameters were collected: ionized calcium (Ca), phosphate (Ph), Vitamin D3 (25 OH-Cholecalciferol), alkaline phosphatase (AP) and conjugated Bilirubin. The levels of Vitamin D3 and AP were recorded at the date when fractures were first identified. The Vitamin D3 levels were classified as Vitamin D3 insufficiency (<75nmol/L) and Vitamin D3 deficiency (<50nmol/L) [17,18]. Hypophosphatemia and hypocalcemia were defined as <1,2mmol/L (Ca) and <1,6mmol/L (Ph) [5,19]. The cut off point for increased values of AP was >450 IU/L [20] and for conjugated Bilirubin>2mg/dl [21]. A prolonged treatment with diuretics or steroids was defined as daily single doses of furosemide >2 weeks and daily single dose of dexamethasone therapy >5 days.

Specific neonatal morbidities were defined as follows: bronchopulmonary dysplasia (BPD) as a need for supplement al oxygen at 36 weeks of gestational age, intraventricular hemorrhage IVH (>grade II), periventricular leukomalacia PVL (stage ≥II) and retinopathy of prematurity ROP (>stage II) [22-25].

All maternal records were reviewed for diseases or medication of the mother affecting the fetal bone metabolism. For descriptive data analysis the statistic program SPSS-version 21 was used. All numerous data were expressed as mean and standard deviation (SD±). To determine the prevalence of co-morbidities, variables were expressed as percentage.

## Results

### Patient's and mother's basic demographic data

In total 1698 patients with a birth weight <1500gram were born between the years 2003 and 2012and eligible for the analysis Of all infants with one or more bone fractures, one infant had to be excluded due to Lowe-Syndrome, a genetic disorder presenting with proximal renal tubular dysfunction, hypophosphatemia and renal rickets. The final incidence of spontaneous osteopenic bone fractures in our cohort was 0.6% (10/1698) with a mean gestational age at birth of 26+3 ±2,3weeks (+ days) and a mean birth weight of716±273 gram. 60% (6/10)of the patients were born small for gestational age (SGA) and in 40% (4/10) also an intrauterine growth restriction (IUGR) was present. In these 10 preterm infants (4 females, 6 males) a total of 37 fractures were detected indicating that 9/10 patients were suffering from multiple fractures. The following type of fractures occurred: serial rib fractures in 7 of 10 cases, long bone fractures in 5 of 10 cases (3 humerus fractures, 2 femur fractures, 1 tibia and 1 fibula fracture). The mean age of the infants at diagnosis of fractures was 42+4 ±5,0 weeks (+days) of gestation. Two out of ten preterm infants died at the age of 47+6 and 54+4 weeks (+ days) due to cardiac arrest.

None of the mothers received medication or suffered from a disease affecting fetal bone metabolism. Preterm labor and premature rupture of membranes were the main reasons (60%; 6/10) for preterm birth. In two of the four IUGR patients severe early onset preeclampsia was diagnosed. In all but one case lung maturation was completed.

### Co-morbidities

50% (5/10) of the patients with fractures underwent abdominal surgery previously to the diagnosis osteopenic fracture (three necrotizing enterocolitis, one gastroschisis with volvulus and one isolated intestinal perforation). In 40% (4/10) parts of the bowel were resected. Mean duration of parenteral nutrition was 123 ±44 days and 90% (9/10) developed parenteral nutrition associated cholestasis (mean conjugated bilirubin 15, 6±12,4 mg/dl.) 70% (7/10) of the preterm infants with osteopenic fractures received prolonged treatment with diuretics (furosemide >2 weeks) and steroids (dexamethasone >5 days). The mean duration of the mechanical ventilation was 32,3±14,5 days and 80% (8/10) of the infants developed BPD. Additionally all infants had at least one positive culture proven sepsis. During the hospital stay, three infants developed an IVH, one infant PVL and five infants ROP. All co-morbidities are given in Figure 1.

### Laboratory values

An overview of laboratory parameters representing bone markers is given in Table 1. In 50% of all patients a Vitamin D3 insufficiency and in 30% a Vitamin D3 deficiency was detected (in one case no data on Vitamin D3 levels were available) (Figure 1). The mean Ca was 1,29 ±0,09 m mol/L and mean Ph1,68 ±0,22 m mol/L (Table 1), respectively. In 20% (2/10) of our study cohort we detected hypophosphatemia and 20% (2/10) hypocalcemia (Figure 1).

**Table 1:** Bone metabolism markers (mean and SD±) in preterm infants with osteopenic fractures (n=10).

| | Values | Cut offs |
|---|---|---|
| Serum Alkaline Phosphate | 915 ±261 | >450 IU/L |
| Serum 25 OH-Cholecalciferol | 52,9 ±18,1 | <75mmol/L |
| Ionized Calcium | 1,29 ±0,09 | <1,2mmol/L |
| Serum Phosphate | 1,68 ±0,22 | <1,6mmol/L |

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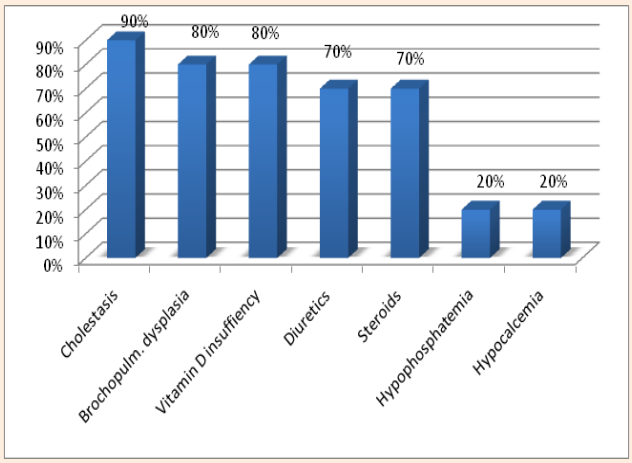


**Figure 1:** The following co-morbidities, expressed in percentage (%) could be observed in preterm infants <1500g with osteopenic fractures.

## Discharge and growth

The mean gestational age at discharge was 49 ±8,9 weeks (± days). The mean weight at discharge was 3806 ±1013 gram, the mean length 51,4±5,3 cm and the mean head circumference 34,4 ±3,5 cm. 60% (6/10) of these infants were below the 10$^{th}$ percentile for weight, height and head circumference at discharge, 30% (3/10) below the 10$^{th}$ percentile for height and head circumference. One patient (10%) was above the 10th percentile for weight, height and head circumference at discharge.

## Discussion

In this retrospective study preterm infants with a birth weight <1500g and osteopenic fractures were reviewed for co-morbidities associated with osteopenia of prematurity. Over a 9-year period the incidence of spontaneous osteopenic fractures in our cohort was 0.6% (10/1698). The mean gestational age of the infants was 26+3 weeks and the mean birth weight 716 gram, indicating that especially the smallest preterm infants were at highest risk for developing osteopenic fractures. Furthermore multimorbidity of the patients was an indicator for osteopenic fractures: 50% of the patients had abdominal surgery during their neonatal course before the fractures occurred and in 40% parts of the bowel had to be resected. As a consequence infants received prolonged parenteral nutrition for123 days. A variety of co-morbidities, such as parenteral nutrition associated cholestasis, BPD, vitamin D insufficiency, hypophosphatemia/hypocalcemia, and a prolonged therapy with steroids and diuretics were associated with osteopenic fractures.

In the present study the incidence of 0.6% (10/1298) preterm infants with spontaneous fractures was lower than in previous studies by Dabezies and Warren [3] 10.5% and Amir et al. [26] of 1.2%. Lucas et al. [5] reported an incidence of 0.5%, 0.4% and 2.6% of bone fractures in three different study sites. Furthermore in the recent study by Wei et al. [7] the incidence was1.6%; however fractures resulting of a traumatic cause were not excluded in this study. In summary, the incidence of spontaneous bone fractures shows a wide variation and might be influenced by several factors: one cause for these conflicting data could be the different nutritional management and supplementation of calcium, phosphate and Vitamin D3 in the different studies [3,26]. A further issue might be a different screening procedure for osteopenic fractures. In the study by Lucas-Herald et al. [5] and Dabezies and Warren [3] all X-rays were screened retrospectively for spontaneous fractures by a radiologist. 8 of 26 spontaneous fractures were only detected after the X-rays were reviewed for the study [3]. In contrast to these studies Amir et al. [26], Wei et al. [7] and in our study only clinical records were screened for the diagnosis "spontaneous osteopenic fractures". These different inclusion criteria might explain the various incidences in previous studies and have to be stated as limitation of our study. As a consequence of these data it may be useful to screen X-rays in extreme preterm infants with a special focus on spontaneous fractures.

In 1919, Yippo A [27] first described osteopenic fractures in preterm infants. He examined 700 preterm infants with spontaneous fractures and hypothesized, that the low content of bone-building minerals, like calcium and phosphate in human milk causes rachitic changes. In further studies, the insufficient supply of calcium and phosphate in preterm infants fed with human milk and formulas could be detected as a risk factor for the development of osteopenia and osteopenic fractures [28-32]. However in our study we detected hypophosphatemia and hypocalcaemia in only 20% of all cases. These results are consistent with the study by Lucas-Herald et al. [5] (hypophosphatemia 19.2% and hypocalcemia 30.7%.) The reason for the relatively low incidence of calcium and phosphate deficiency in our cohort may be the individual supplementation of our patients adapted to serum and urine values, by measuring serum and urinary calcium and phosphate concentrations once a week [30]. Hypophosphatemia and hypocalcemia are potential risk factors for developing osteopenic fractures and an individual supplementation may be useful to minimize this co-morbidity. Recent studies go along with this finding and recommend this approach [30,33].

Sufficient Vitamin D3 supplementation is a key factor for the mineralization of the bone. The recommendations for Vitamin D3 supplementation in preterm infants are 800-1000 IU per day to reach 25(OH) Vitamin D3 levels above 75nmol/L [33]. However, studies showed that preterm infants did not meet the recommended levels [20,34,35]. In our cohort Vitamin D3 insufficiency could be detect in 80%, although all infants received the recommended Vitamin D3 supplementation. Therefore, routinely determination of Vitamin D3-status in multimorbid patients with a long duration of parenteral nutrition might be reasonable to prevent Vitamin D deficiency.

Additionally we evaluated concomitant medication: In 7 of 10 infants prolonged treatment with diuretics (furosemide) and steroids (dexamethasone) was observed. This finding goes along with the studies by Amir et al. [26] and Lucas-Herald et al. [5]. Treatment with diuretics (furosemide, spironolactone and hydrochlorothiazide) causes an abnormal renal loss of calcium and phosphate leading to demineralization of the bone [36]. Furthermore dexamethasone may increase the excretion of phosphate in the urine and decreases the phosphate concentration in serum [11]. The treatment with diuretics and dexamethasone in preterm infants is often mandatory, but should be applied only upon strict indication. In conclusion diuretics and steroids influence bone metabolism and therefore may increase the risk for spontaneous fractures.

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50% (5/10) of the osteopenic preterm infants in the present study underwent abdominal surgery and in 40% (4/10) parts of the bowel were resected, leading to long-term parenteral nutrition, enteral malabsorption of nutrients and poor growth. Prolonged parenteral nutrition (mean 123 days) was also observed in our study cohort and 90% (9/10) of all infants developed parenteral nutrition associated cholestasis. In addition 90% of all infants were below the 10th percentile for height at discharge. This data are consistent with previous studies [5,7,26] and are a consequence of postnatal growth restriction caused by diseases associated with extreme prematurity like BPD and NEC. Clinically relevant consequences are the impact on linear growth as well as the risk for the development of osteoporosis later in life.

## Conclusion

Over a nine year period (2003-2012) the incidence of osteopenic fractures was 0,6% (10 /1698) in a cohort of preterm infants, born with a birth weight<1500 gram. Spontaneous osteopenic fractures occurred primarily in the smallest and most immature, multimorbid preterm infants. We identified a variety of co-morbidities in our cohort such as: abdominal surgeries, parenteral nutrition associated cholestasis, BPD, vitamin D insufficiency, hypophosphatemia/hypocalcemia and prolonged therapy with steroids. To prevent osteopenic fractures diuretics and steroids should be applied only upon strict indication. A routine screening for striking bone markers in serum and urine may be useful to prevent vitamin D insufficiency.

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