Clinical Nutrition ESPEN xxx (2017) e1–e6

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

# Incidence of metabolic bone disease in preterm infants of birth weight <1250 g and in those suffering from bronchopulmonary dysplasia

Paola Gaio [a], Giovanna Verlato [a, *], Marco Daverio [a], Maria Elena Cavicchiolo [a], Daniel Nardo [a], Alessandra Pasinato [a], Francesca de Terlizzi [b], Eugenio Baraldi [a]

[a] Neonatal Intensive Care Unit, Department of Woman and Child's Health, University of Padova, Via Giustiniani 3, 35127, Padova, Italy
[b] Laboratory of Clinical Biophysics, IGEA, Modena, Italy

ARTICLE INFO

*Article history:*
Received 2 February 2017
Accepted 26 September 2017

*Keywords:*
Preterm newborns
Quantitative ultrasound
Bone development
Nutrition
Metabolic bone disease
Bronchopulmonary dysplasia

SUMMARY

*Background & aims:* Preterm infants are exposed to a higher risk of developing Metabolic Bone Disease (MBD) with an increased bone fragility, a higher fracture risk and a long-term reduced linear growth and childhood height. Monitoring bone growth has become mandatory in neonatology. Several risk factors have been identified among the population of extremely low birth weight infants, but we still do not know which is the real incidence of MBD since its evaluation is not routinely performed worldwide. The aim of this study was to evaluate the incidence of MBD in preterm infants and in those suffering from bronchopulmonary dysplasia (BPD).

*Methods:* Prospective evaluation of patients who developed BPD (BPD group) versus infants who did not develop it (no-BPD group). We examined, in preterms <1.250 g, the metacarpus bone transmission time (mc-BTT) at birth, 21 days and 36 weeks of gestational age (GA) together with biochemical markers of bone status.

*Results:* We included 135 patients, 55 with BPD. BPD patients received less total proteins in the first two weeks and less energy in the first month of life ($p = 0.007$ and $p < 0.001$ respectively). BPD patients had a worse growth velocity at two weeks of age ($12.36 \pm 7.86$ vs $16.59 \pm 7.05$ g/kg/day, $p = 0.001$). At 21 days, BPD patients had lower phosphatemia ($1.65 \pm 0.031$ mmol/L vs $1.85 \pm 0.034$ mmol/L, $p = 0.007$) and higher alkaline phosphatase levels ($411.62 \pm 135.31$ IU/l vs $338.98 \pm 102.20$ IU/l, $p = 0.005$). BPD patients had significantly worse mc-BTT at 36 weeks GA ($0.45 \pm 0.06$ vs $0.50 \pm 0.08$ μsec, $p < 0.001$) and a higher incidence of MBD (60% vs 34%; $p = 0.012$).

*Conclusions:* BPD infants are a special subset of patients among preterms who receive, in the first month of life, a lower energy intake than patients without BPD. BPD patients have a suboptimal bone growth and a higher incidence of MBD. Monitoring growth, bone status and optimizing nutritional intakes need to be further improved in preterm infants with BPD.



## Introduction

Preterm infants are at risk for developing Metabolic Bone Disease (MBD) which is characterized by low bone mass (osteopenia) and demineralization (osteomalacia) of bone tissue with a consequent increase in bone fragility and long-term reduced linear growth and childhood height [1,2].

It is estimated that MBD occurs in up to 55% of extremely low birth weight infants (ELBWI) but this data could be underestimated [3] due to the lack of an universal marker to be applied in preterms

* Corresponding author. Neonatal Intensive Care Unit, Department of Woman and Child's Health, Azienda Ospedaliera University of Padova, Via Giustiniani 3, 35128 Padova, Italy. Fax: +39 049 8213001.
*E-mail addresses:* paola.gaio@gmail.com (P. Gaio), verlatogiovanna@gmail.com, giovanna.verlato@aopd.veneto.it, giovanna.verlato@sanita.padova.it (G. Verlato), marco.daverio.va@gmail.com (M. Daverio), mecavicchiolo@gmail.com (M.E. Cavicchiolo), drnardo@gmail.com (D. Nardo), alepasinato80@gmail.com (A. Pasinato), f.deterlizzi@igeamedical.com (F. de Terlizzi), eugenio.baraldi@unipd.it (E. Baraldi).

https://doi.org/10.1016/j.clnesp.2017.09.008
2405-4577/

**Nomenclature**

| | |
|---|---|
| ALP | alkaline phosphatase |
| ANOVA | analysis of variance |
| BPD | bronchopulmonary dysplasia |
| BW | birth weight |
| ELBWI | extremely low birth weight infant |
| GA | gestational age |
| IVH | intracranial ventricular hemorrhage |
| MBD | metabolic bone disease |
| Mc-BTT | metacarpal bone transmission time |
| NEC | necrotizing enterocolitis |
| NICU | neonatal intensive care unit |
| PDA | patent ductus arteriosus |
| QUS | quantitative ultrasound |
| ROP | retinopathy of prematurity |
| SD | standard deviation |
| SGA | small for gestational age |
| TPN | total parenteral nutrition |
| VLBWI | very low birth weight infant |
| Z-mc BTT | Z score mc-BTT |

to detect MBD. More important we still do not know the long-term consequences in childhood and adulthood of patients with MBD since suboptimal bone growth early in life could limit the achievement of peak bone mass [4,5] and consequently increase the risk of developing later "early life programmed disease and in particular osteoporosis" [6,7].

Unfortunately, there is not an uniformly applied screening on MBD and its incidence could be underestimated though several studies suggested that the following conditions increase the risk of MBD: infants <28 weeks of gestational age (GA) [8], birth weight (BW) < 800 g [9], or very low birth weight infant (VLBWI) [10], prolonged total parenteral nutrition (TPN) > 3 weeks [8] or even TPN > 14 days [11]. Factors in intrauterine life can also expose preterms to the risk of developing MBD like altered placental function, environmental variables, maternal lifestyle and nutrition [12]. Nonetheless it is recognized that prematurity per se is the most important risk factor for developing MBD (reduced intrauterine accumulation of calcium and phosphorus, use of parenteral nutrition, medication use such as diuretics or steroids, immobilization) [8,13].

The American Academy of Pediatrics in a clinical report [14] indicates severe bronchopulmonary dysplasia (BPD) among risk factors for the development of rickets and also suggests to perform biochemical testing, such as alkaline phosphatase (ALP) and serum phosphorus after 4–5 weeks after birth in all VLBWI.

Recently it was investigated the percentage of MBD by retrospective radiography review in a group of severe BPD children [15]. According to x-ray findings, they found that 58% of patients had mild MBD and 31% had severe MBD. In a retrospective study in ELBWI the risk of rickets was reported to be 3 times higher in BPD patient [16] by means of radiological exams.

For the above-mentioned reasons monitoring bone growth is considered mandatory, but unfortunately radiological bone changes are a late sign as they appear only after a significant reduction of bone mineral content [17]. An alternative technique to analyze bone status in preterms is the quantitative ultrasound (QUS) method [18]. QUS has many advantages especially in the pediatric population: lack of radiation exposure (its measurements are based upon the velocity of transmission of an ultrasound beam through a specific body site emitted and received by two instrument probes), no need of sedation, portability and low cost. QUS allows not only measures at peripheral skeleton of mineral status but also of other bone properties such as cortical thickness, elasticity, geometry, and porosity [19]. Considering QUS methods, the presence of MBD is defined by metacarpus bone transmission time (mc-BTT) value < 2 standard deviations (SD) for age and length [20]. The aim of our study was to monitor the incidence of MBD in preterm infants with Birth Weight <1.250 g and in particular in those who developed BPD.

## Materials and methods

### *Study population and setting*

We prospectively enrolled preterm newborns weighing less than 1.250 g and in TPN since 48 h of life, hospitalized in the Neonatal Intensive Care Unit (NICU) of the Department of Woman's and Child's Health of the University of Padova (Italy). Infants admitted to our NICU from January 2012 to December 2013 were included in the analysis if they had no major malformation, congenital infections and metabolic disorders.

The study was approved by local Ethical Committee and informed consent was obtained from parents before the study start.

BPD was defined as treatment with oxygen >0.21 for at least 28 days and further defined as mild moderate or severe at 36 weeks of GA or discharge, whichever came first according to the definition of Jobe–Bancalari et al. [21].

We compared the population of patients who developed BPD (BPD group) versus the patients without BPD (no-BPD group).

### *Study procedures*

#### *Nutrition*

All patients received a progressive TPN regimen through a central umbilical or percutaneous catheter for at least 7 days according to our protocol [22] with the target to achieve a maximum of 4 g/kg/day of aminoacids and Non proteic Energy > 80 kcal/kg/day with calcium and phosphorus intakes between 0.8 and 2 mmol/kg/day to keep serum levels between 2 and 2.5 mmol/l and 1.8–2.6 mmol/l respectively. Parenteral vitamin D administration was 40 IU/kg per day.

During the first week of life patients received minimal enteral feeding (10–20 ml/kg/day of human milk or preterm formula); then, in the absence of contraindications enteral nutrition was advanced at the rate of 10–20 ml/kg/day. When feeding reached 100 ml/kg/day, infants were fed with their own mother's milk fortified (FM 85, Nestlé, Italian SPA, Milan, Italy) and 0.2 g of protein, 15 mg of calcium, 9 mg of phosphate and 3.53 Kcal were added to human milk for every g of fortifier (maximum 4–5 g/100 ml), or continued preterm formula (preterm formula had a protein content of 2.03 g, 100 mg of calcium, 55 mg of phosphate and 80 kcal/100 ml). PN was progressively decreased and stopped when full enteral feeding was reached (125 ml/kg/day). After PN stopped, oral vitamin D (800–1000 IU) supplementation was started.

We monitored patients from birth up to 36 weeks of GA, through anthropometric, clinical and biochemical parameters. Growth was assessed through anthropometric measurements: we registered daily weight, weekly total length and head circumference. Number of days to regain birth weight, number of days to reach 1800 g and weekly growth rate were also evaluated.

#### *Bone ultrasound assessment*

Assessment of bone status was performed through QUS with DBM Sonic BONE PROFILER (IGEA, Carpi, Modena) within 72 h from birth, at 21 days of life and at 36 weeks of GA and we tested the

Please cite this article in press as: Gaio P, et al., Incidence of metabolic bone disease in preterm infants of birth weight <1250 g and in those suffering from bronchopulmonary dysplasia, Clinical Nutrition ESPEN (2017), https://doi.org/10.1016/j.clnesp.2017.09.008