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Original article

Low phosphatemia in extremely low birth weight neonates: A risk factor for hyperglycemia?

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SUMMARY

Background & aims: Hyperglycemia occurs in more than half of the extremely low birth weight (ELBW) neonates during the first weeks of life, and is correlated with an increased risk of morbi-mortality. Hypophosphatemia is another frequent metabolic disorder in this population. Data from animal, adult studies and clinical observation suggest that hypophosphatemia could induce glucose intolerance. Our aim was to determine whether a low phosphatemia is associated with hyperglycemia in ELBW neonates.
Methods: This observational study included ELBW infants admitted in a tertiary neonatal care center (2010–2011). According to the center's policy, they received parenteral nutrition from birth and human milk from day 1. Phosphatemia and glycemia were measured routinely during parenteral nutrition. Hyperglycemia was defined by two consecutives values >8.3 mmol/L (150 mg/dL). Statistical analysis used a joint model combining a mixed-effects and a survival submodels to measure the association between phosphate and hyperglycemia.
Results: The study included 148 patients. Mean gestational (Standard Deviation) age was 27.3 (1.6) weeks; mean birth weight was 803 (124) grams; 57% presented hyperglycemia.
The multivariate joint model showed that the hazard of hyperglycemia at a given time was multiplied by 3 for each 0.41 mmol/L decrease of phosphate level at this time ($p = 0.002$) and by 3.85 for the same decreased of phosphate the day before ($p = 0.0015$).
Conclusion: To our knowledge, this is the first study suggesting that low phosphatemia can be associated with hyperglycemia in ELBW neonates. Further studies will have to demonstrate whether better control of phosphatemia could help in preventing hyperglycemia.

1. Introduction

Hyperglycemia is a frequent metabolic complication in critically ill neonates and was found to occur in more than a half of extremely low birth weight (ELBW) infants [1]. The frequency of this complication is inversely related to gestational age (GA) and birth weight (BW) [2]. Beside to induce an osmotic diuresis, dehydration, hyponatremia, hypokalemia and acidosis, studies suggest that hyperglycemia increases mortality [1–4] and several serious morbidities as sepsis, intraventricular hemorrhage [5] or retinopathy of prematurity [6,7]. Both insulin resistance and failure in pancreatic

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List of abbreviations

VLBW	Very Low Birth Weight
ELBW	Extremely Low Birth Weight
ATP	Adenosine Tri-Phosphate
NICU	Neonatal Intensive Care Unit
GA	Gestational Age
BW	Birth Weight
SGA	Small for Gestational Age

islet β-cell processing of pro-insulin could contribute to hyperglycemia in extremely preterm infants [8], but the pathogenesis remains to be elucidated. The identification of risk factors and mechanisms associated to glucose intolerance is thus especially important in the context of neonatal care [1–3,9]. There is so far no consensus on safe and efficient management of glucose intolerance, as both insulin treatment and reduction in glucose intakes can be deleterious [10–13].

Hypophosphatemia is another frequent metabolic disorder in premature newborns, especially in very low birth-weight infants (VLBW) and in small for gestational age (SGA) neonates, although normal values at this age remain uncertain [14–17]. In the critically ill children, it has been associated with a longer duration of mechanical ventilation and with a longer duration of stay in the pediatric intensive care unit [18]. In the preterm newborn, hypophosphatemia is frequently associated to postnatal growth deficiency and osteopenia of the preterm [19,20] and has been recently incriminated in susceptibility for septicaemia in VLBW [21]. Various mechanisms have been raised, like limited storage, insufficient intakes in the first days or a re-feeding like syndrome in VLBW undergoing enhanced nutrition [22].

Due to our common clinical observation of hypophosphatemia preceding severe and persistent hyperglycemia, we drafted the hypothesis that hypophosphatemia could play a role in glucose intolerance in the preterm neonate. This hypothesis was sustained by some experimental studies and adult data, where hypophosphatemia could be involved in insulin resistance found in metabolic syndrome [23,24]. Two mechanisms have been involved; first, hypophosphatemia leads to a low adenosine triphosphate (ATP) intracellular rates; in the beta cells of the pancreas, the consequent dysfunction in ATP-ase activity may lead to a reduction in the insulin production [8,25]. Secondly, phosphorus is involved in phosphorylation of the insulin cell-receptor, which could thus be less efficient in case of low phosphatemia [25]. Whether hypophosphatemia is a risk factor for hyperglycemia in preterm neonates remains to be elucidated [26].

The aim of our study was to further investigate the association of low phosphate and the risk of glucose intolerance, defined as persistent hyperglycemia >8.3 mmol/L (>150 mg/dL) during the two first weeks of life in an ELBW cohort.

2. Methods

2.1. Patients

This study was conducted in a tertiary level Neonatal Intensive Care Unit (NICU) between January 2010 and December 2011 at the University Hospital “Femme Mère Enfant”, Lyon, France. The study population was a subset of a retrospective cohort study that was implemented in the NICU in order to monitor and assess several nutritional and growth issues in extremely low birth-weight infants [27]. It was approved by the Institutional Review Boards.

We included neonates without major congenital malformations, weighing <1000 g at birth and admitted at their first day of life in our NICU. Patients who did not have phosphate measurement between day 1 and day 14 were excluded.

2.2. Data collection

Clinical data, nutritional intakes and laboratory measurements were extracted from computerized medical charts of the patients: ICCA® Philips (IntelliSpace Critical Care and Anesthesia).

All available phosphate, calcium and glucose blood measurements from day 1 to 14 were recorded. Hyperglycemia was defined by at least two consecutives values >8.3 mmol/L (>150 mg/dL). Perinatal characteristics: Gestational age (GA), Birth weight (BW), multiple birth, delivery mode, antenatal steroids, small for gestational age (SGA), gender, Apgar score and main complications in the first two weeks of life as respiratory distress syndrome, intraventricular hemorrhage (≥grade 2), sepsis or death, were also collected. Exact daily parenteral and enteral intakes in glucose, amino acids, lipids, energy, phosphate and calcium were registered from day 1 to 14.

2.3. Nutritional regimens of the NICU

According to the nutritional policy of the centre, all the ELBW received individualized preparations of parenteral nutrition. Based on the ESPGHAN recommendations [28], our nutritional protocol recommended providing 1–1.5 mmol/kg/d of phosphate from day 2. Inorganic phosphate solutions were used (glucose-1-phosphate disodium (Phocytan®, Aguettant, France) or monobasic potassium phosphate 6.59%. Phosphorus intakes were thereafter adjusted to reach a serum phosphatemia between 1.5 and 2 mmol/L (4.7 and 6.2 mg/dL). Between 1 and 1.5 mmol/kg/d of calcium (solution of glucoheptonate calcium 10%) was provided from day 1 and was than adjusted from day 2 to target calcium serum level between 2.2 and 2.5 mmol/L.

A daily dose of 55–110 UI per day of parenteral vitamin D was introduced from day 2 to 3 in a mixed vitamin solution (Cernevit®, Baxter, Maurepas, France). Parenteral glucose and amino acids were provided from birth. Lipids were introduced from day 2. Glucose was initiated at 6–8 g/kg/d and increased until 14–16 g/kg/d, with a progression rate of 1–2 g/kg/d; amino acids were initiated at 2 g/kg/d and increased until 3.5 g/kg/d with a progression rate of 0.5 g/kg/d; lipids were initiated at 0.5–1 g/kg/d and increased until 3–3.5 g/kg/d with a progression rate of 0.5–1 g/kg/d.

Enteral nutrition was initiated in the first hours of following birth with 5–10 ml/kg/d of human milk (Mother's own milk or donor's milk) that was increased by 5–10 ml/kg/d depending on the enteral tolerance until the full ration of 160 ml/kg/d. Fortifiers (Eoprotine® and Liquigen®, Nutricia, Rueil Malmaison, France) were introduced when at least 100 ml/kg/d of human milk were tolerated. Enteral supplementation of 1000 units per day of vitamin D (Uvestérol ADEC®) was started when parenteral nutrition was discontinued.

2.4. Management of glucose intolerance

In case of glycemia ≥11 mmol/L (>200 mg/dL) confirmed on at least two blood checks in the same day, the nutritional protocol of the NICU was first to introduce insulin infusion. In case of refractory hyperglycemia despite progressive increase of insulin infusion rates from 0.01 U/kg/h to 0.03 UI/kg/h, the glucose infusion was reduced by 1–2 g/kg/d. Insulin was stopped when glycemia values were <4 mmol/L (<72 mg/dL).

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