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Trace elements, oxidative status and antioxidant capacity as biomarkers in very low birth weight infants

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ABSTRACT

Reference data on trace elements, oxidative status and antioxidants in very low birth weight infants (VLBW) are limited and need to be updated for use in clinical settings. Serum and urine of 30 VLBW infants (mean weight, 1167 g) at mean age of 23.8 (t0) and 37.8 (t1) days were analyzed. Cadmium (Cd), copper (Cu), iron (Fe), mercury (Hg), manganese (Mn), selenium (Se) and zinc (Zn), nitrate/nitrite (NOx), catalase (CAT), CuZnFeMn-superoxide dismutases (CuZnFeMn-SODs), total antioxidant capacity (SAC: sum of thiols, proteins, bilirubin, uric acid, β-beta-carotene, ascorbic acid, vitamin E) and total oxidative status (SOS: sum of lipo- and hydroperoxides) were determined. A higher urinary excretion of Cu and Zn was observed at t0 than at t1; while an increase in urine Cd was found at t1 respect to t0. A deficiency in serum levels of Cu and Zn was also found. A lower CAT activity, a higher total oxidants level (SOS) and a reduction of total antioxidant barriers (SAC) were observed in some infants. No Fe and Mn deficiency or Hg overload was found; also CuZnFeMn-SODs and NOx levels did not change.

The findings showed that losses of trace elements and incomplete mineral body stores were more pronounced in the earlier life stage (at 23.8th day) than later on; moreover, antioxidant defenses were poor and lipo- and hydroperoxides were higher still at 5 weeks of infants' life.

1. Introduction

Many of the determinants of birth weight are related to maternal suboptimal nutrition and infants' deficiency of some essential trace elements such as copper (Cu), iron (Fe), manganese (Mn), selenium (Se) and zinc (Zn), and also to maternal environmental exposures to toxic pollutants such as cadmium (Cd) and mercury (Hg) (Trindade, 2005). Very low birth weight infants (VLBW, < 1500 g birth weight) are particularly susceptible to deficiencies or toxicity of trace elements, due to their rapid growth, relatively low mineral stores at birth, poor absorption, excess intestinal and renal losses and high vulnerability to oxidative stress. In addition, size at birth demands urgent attention not only because of the significantly increased risk it poses for infants and young children, but also for the risk of developing diseases in adulthood.

Many neonatal diseases and complications including respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), chronic lung disease (CLD), retinopathy of prematurity (ROP) and intraventricular hemorrhage (IVH) have been associated with increased production of reactive oxygen species (ROS) and altered nitric oxide status, and reduced activity of antioxidant enzymes - as superoxide dismutases (SODs) and catalase (CAT) - in preterm infants (Saugstad, 2005; and Negi et al., 2012).

The urinary nitrite/nitrate (NOx) excretion is an index of endogenous nitric oxide formation and has been used for identifying preterm infants with abnormal nitric oxide production (Tsukahara et al., 1997); a possible role of NOx in the development of neuronal injury in small for gestational age infants (SGA) was recently reported (Huseynova et al., 2015).

Among trace elements, Cu is a cofactor in many detoxifying enzymes and proteins as SOD, ceruloplasmine, Cu-thioneine, and in the myelination and metabolism of several steroid hormones (Marriott et al., 2007). A decrement in SOD activity was associated to a low Cu status in VLBW infants (Nassi et al., 2009). Copper deficiency has been described as the cause of anemia, neutropenia, bone disease (osteopenia and fractures) and growth retardation in pediatric patients (Hurwitz et al., 2004). Moreover, deficiency of this element in premature cholestatic infants has been linked to long-term parenteral nutrition lacking Cu (Blackmer and Bailey, 2013).

As concern Fe, the need for additional supplementation of this

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element because of uncompensated phlebotomy losses in preterm infants is quite established (Rao and Georgieff, 2009). Poor physical growth, gastrointestinal disturbances, thyroid dysfunction, altered immunity and temperature instability has been attributed to Fe deficiency in VLBW and anemia is typically a late sign and suggests significant depletion of Fe stores (Aggett, 2000). It has been reported that antioxidant activities, such as that of CAT, decrease in children with Fe-deficiency anemia (IDA) (Altun et al., 2014). As the Fe deficiency, also the excessive Fe accumulation potentially affects multiple organs systems; there was an association between multiple transfusions and incidence and progression of ROP and bronchopulmonary dysplasia (BPD) through generation of ROS (Berger et al., 1995).

Manganese is a constituent of many enzymes involved in carbohydrate (pyruvate carboxylase) and protein (arginase) metabolism; it is utilized by various antioxidant enzymes such as Mn-SOD; it activates the glycosyltransferase necessary for the mucopolysaccharides used by cartilage, bone and other connective tissues (Erikson et al., 2007). Manganese deficiency may result in poor bone formation, birth defects, and increased susceptibility to seizures; on the contrary, an excess of Mn can produce ROS and toxic cathecolamines, laying the basis for neurodegeneration. In a birth cohort study in France, cord blood Mn was negatively associated with attention and non-verbal memory and boys' manual ability at 3 years, after adjusting for the mother's educational level (Takser et al., 2003).

Selenium influences the innate and the acquired immune system, mediated through its incorporation into glutathione peroxidase (GSH-Px) and thioredoxin reductase (TrxRs). So, resistance to viral and bacterial infections is likely to be modified by dietary Se intake, with important implications for dietary recommendations during pregnancy and lactation to ensure adequate Se transfer via placenta and mammary gland as well as during infancy when maternal milk is not fed (Dylewski et al., 2002). In a review article, Klein mentioned studies that relate Se deficiency to diseases of prematurity, like RDS and CLD (Klein, 2002).

Zinc is an important micronutrient that supports normal growth, cell differentiation, metabolism, antioxidant protective enzyme activities as Zn-SOD and Zn-thioneine, hormone structure, and brain development (Trindade, 2005; and Marriott et al., 2007). Preterm infants have lower Zn reserves than term infants because are less efficient at absorbing and retaining Zn for their immature gastrointestinal tract. Main characteristics following a Zn deficiency include weight loss, failure to thrive, and enhanced susceptibility to infections (Aggett, 2000). Studies demonstrated that Zn supplementation has a positive effect on linear growth in premature infants (Díaz-Gómez et al., 2003).

Cadmium is well known for its potential toxicity in humans and exposure to Cd has been linked to several risks to health. The association of maternal smoking on birth weight and fetal development was found through the probable accumulation of Cd in the placenta during gestation (Menai et al., 2012 and Johnston et al., 2014). It is hypothesized that the higher Cd levels can lead to insufficient transfer of Zn to the fetus, which can retard intrauterine growth (Kippler et al., 2010). Another possible mechanism is through the detrimental effect of Cd on 11beta-hydroxysteroid dehydrogenase type 2 activity, which is directly linked to fetal growth (Yang et al., 2006).

Mercury exists in three forms and each form has its specific toxicological profile: inorganic Hg salts can cause kidney damage; organic Hg compounds (as methylmercury) can cross the blood-brain barrier and produce neurological damage; elemental Hg can harm both renal and nervous system (Park and Zheng, 2012). With respect to pregnant women and their foetuses, the exposure to methylmercury occurs primarily through the consumption of contaminated seafood and rice grown in contaminated waters, and an impaired neurodevelopment as a result of prenatal exposure is widely considered to be the most sensitive endpoint (Bose-O'Reilly et al., 2010 and Bellinger, 2014).

Basing on the above reported data, the concentration of trace elements in preterm infants and their implication as major modulators of oxidative stress and antioxidant defence aroused much interest, also considering the difficulty to obtain data for such a vulnerable population group. In this study, the concentrations of Cd, Cu, Hg, Fe, Mn, Se and Zn were determined in serum and urine of VLBW infants in two different early postnatal periods (t0: mean age of 23.8 days; t1: mean age of 37.8 days). Moreover the serum total oxidative status (SOS), the serum total antioxidant capacity (SAC) and the urinary nitrate/nitrite (NOx) levels were evaluated in the two time periods. Also the activity of specific antioxidant enzymes, namely the CAT and CuZnFeMn-SODs, were determined. The data emerging in this paper offer a contribution for a better knowledge of the role of trace elements, oxidative stress and antioxidants as biomarkers for VLBW status of infants.

2. Methods

2.1. Study Population

The cohort consists of 30 VLBW inborn infants, consecutively admitted to the neonatal intensive care unit at the S. Giovanni Calibita Fatebenefratelli Hospital in Rome (Italy). Parental consent was obtained and the study protocol was approved by the Hospital Ethics Committee. At birth, infants had mean gestational age (GA) 33.2 weeks (min-max, 30–35 weeks), mean birth weight 1167 g (min-max, 800–1400 g), mean body length 38.3 cm (min-max, 35–42 cm) and mean head circumference 27.3 cm (min-max, 24–29 cm). The male/female ratio was 1.5, and all the babies were Caucasian. The average length of hospital stay was 50.1 days, ranged between 32 and 77 days.

Before enrolling, the 27% of newborns required invasive mechanical ventilation (mean, 3.5 days; min-max, 1–17 days), the 70% received non-invasive mechanical assistance (nasal CPAP) with an average of 4.76 days (min-max, 1–16 days) and the 86% required oxygen therapy (mean, 6.2 days; min-max, 1–30 days).

At t0 infants had a mean age of 23.8 days and at t1 infants had a mean age of 37.8 days. Exclusion criteria to enrol eligible patients were the following: perinatal asphyxia (Apgar score < 5 at 5 min); CRIB (clinical risk index for babies) score > 5; PROM (prolonged rupture of membranes) > 18 h; congenital malformations; congenital infections or infections; congenital heart disease; need for endotracheal intubation; fraction of inspired oxygen (FIO_2) > 30% in the incubator or with nasal ventilation; surgical pathologies.

No cases of NEC were registered in the study cohort, while 3 infants had ROP, stage 1–2; 6 of them developed BPD; 3 babies had IVH, stage 1–2; 7 neonates had intrauterine growth retardation (IUGR). During the study period, 4 infants (13,3%) received 1 or more transfusions of packed red blood cells (RBC).

2.2. Nutritional protocol and maternal information

All infants received an intravenous nutrition from birth to t0. During this period, each infant received a minimal enteral feeding, equal to a volume of 10 mL/Kg/d of milk in 8 feeds, starting from the first or second day of life.

At t0, the 93% of babies were fed by fresh maternal milk and the 30% of them received also the preterm infant formula; only 2 babies (7%) received preterm formula exclusively. The 43% of infants fed with maternal milk received an integration with a breast milk fortifier (BMF) started when infants achieved an enteral intake of ca. 100 mL/Kg/d. The reconstituted BMF (Aptamil BMF®), added at a concentration of 4.4% in breast milk, contained, per 100 mL, 0.61 mg of Zn, 35 μg of Cu, 8.1 μg of Mn, 1.7 μg of Se, 66 mg Ca, and other minerals (as sodium, potassium, magnesium, iodine).

The progression of the enteral feeding was performed with amounts between 5 and 20 mL/Kg/d (mean, 10 mL/Kg/d). During the study period a variable part of infants received a mixture of maternal milk and preterm infant formula and reached full feeds within 2 weeks from t0. At t1, the 100% of infants received maternal milk and the 60% of