



Vitamin D Deficiency in Premature Infants and Its Effects on Neonatal Prognosis

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ABSTRACT

Aim: In the present study, the relationship between neonatal morbidity and cord vitamin D levels is investigated.

Materials and Methods: Premature infants who were born before 32 weeks of gestation and admitted to our neonatal intensive care unit between January 2014 and January 2015 were included in the study. Vitamin D levels in the cord blood of infants were measured. Serum calcium, phosphorus and alkaline phosphatase levels were recorded in the first 24 hours. All neonates were followed up for neonatal morbidities until discharge.

Results: The mean gestational age of the study subjects was 29.2±2.6 (23-32). The mean vitamin D level was 27.4±19.3 ng/mL (4-76). Fourteen (46.7%) infants had normal vitamin D levels; 2 infants (6.7%) had vitamin D insufficiency (20-30 ng/mL), 14 infants (46.7%) had vitamin D deficiency (<20 ng/mL), and 7 infants had severe vitamin D deficiency (23.3%). In 60% of infants with intrauterine growth restriction had vitamin D deficiency of $p<0.05$. Serum phosphorus levels on the first day of life were significantly lower in infants with vitamin D deficiency ($p<0.001$).

Conclusion: In more than half of the study population vitamin D deficiency was determined. Infants with intrauterine growth restriction had vitamin D deficiency in more than half of the cases. Low levels of phosphorus may be a marker of vitamin D deficiency in the first days of life.

Keywords: Preterm birth, vitamin D, intrauterine growth restriction

Introduction

The importance of vitamin D as a modulator of calcium and bone metabolism is well known (1), and it is also involved in the innate immune system, cell proliferation and neuromuscular functions (2-4). Vitamin D is reported to inhibit the nuclear factor-kappa beta pathway and reduce inflammation in decidua (5). Recently, vitamin D has been suggested to be involved in the pathogenesis of many diseases such as cancer, multiple sclerosis, diabetes and cardiovascular disease via cell proliferation and immune function (6). Vitamin D deficiency in newborns is related to neonatal sepsis and respiratory system infections. Maternal vitamin D deficiency increases the risk of premature delivery, preeclampsia, gestational diabetes mellitus and intrauterine

growth restriction (7-9). These perinatal complications trigger preterm delivery and these premature infants have a greater risk of vitamin D deficiency. Studies have shown that vitamin D deficiency is more prominent in the second and third trimesters. The rate of premature delivery is 8-12% in the world and results in fetal morbidity and mortality (10). Considering the wide distribution of vitamin D receptors and its newly suggested roles in many adult diseases, particularly those associated with inflammatory pathways, it may also be involved in neonatal morbidities related to immature immune system and inflammation. Furthermore, early recognition of vitamin D deficiency makes early and appropriate supplementation possible to prevent the increased risk of possible vitamin D related morbidities. Thus, in this study cord blood vitamin D levels were measured

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so as to determine the rate of Vitamin D deficiency in very preterm newborns (<32 weeks) and to illuminate its relation with neonatal morbidities.

Materials and Methods

Premature infants with gestational ages below 32 weeks who were born in the University Hospital and admitted to the neonatal intensive care unit NICU between January 2014 and January 2015 were enrolled in the study. Patients with cyanotic heart disease, chromosomal anomalies, and congenital anomalies were excluded from the study. This study was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 11-12.2/4). The parents provided informed consent for the study.

Assessment of Blood Vitamin D Levels

Vitamin D levels were measured in the cord blood of the infants. Serum calcium, phosphorus and alkaline phosphatase (ALP) levels were measured in the first 24 hours. Serum 25-hydroxyvitamin D3 [25(OH)D3] level lower than 20 ng/mL is defined as vitamin D deficiency. Serum 25(OH)D3 level lower than 10 ng/mL is defined as severe vitamin D deficiency. Serum 25(OH)D3 level between 20-30 ng/mL is defined as insufficient vitamin D (10).

Maternal and Neonatal Demographic and Clinical Data

Detailed antenatal history including maternal age, gestational week, mode of delivery, number of live births, history of preeclampsia, diabetes mellitus, and premature rupture of membranes, was recorded. All the premature infants were prospectively followed for neonatal morbidities (Respiratory Distress syndrome [RDS]), sepsis, pneumonia, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage, mortality and the duration of mechanical ventilation. Clinical sepsis is defined as documentation of infection with a serious systemic illness in which non-infectious explanations for the abnormal pathophysiological state are excluded or unlikely. By definition, in early clinical sepsis clinical signs appear in the first 5 days and in late sepsis >5 days (11). RDS is diagnosed clinically with early respiratory distress manifested with cyanosis, grunting, retractions and tachypnea. The diagnosis is confirmed with blood gas analysis and chest X-ray with a classical "ground glass" appearance and air bronchograms (12). BPD is defined according to universal guidelines in infants with prolonged oxygen requirement and accompanying radiological changes (13). NEC is the mucosal ischemic necrosis of the intestines. Staging defined by Schanler et al. (14) is used. Intraventricular bleeding is classified according to Papile classification (15).

Statistical Analysis

SPSS 16.0 (SPSS, Chicago, IL) was used for statistical analysis. The statistical analyses were performed in Ege University Biostatistics Unit. Data were expressed as mean

and standard deviation. Differences between the two groups were analyzed by Student t-test or Mann-Whitney U test, where appropriate. Pearson test was used to analyze the correlation between variables. p value of <0.05 was accepted as significant.

Results

The mean gestational week of the study population was 29.2±2.6 (23-32), the mean birth weight was 1331±414 (620-2815) grams (Table I). In antenatal history preeclampsia rate was 20% (n=6) and intrauterine growth restriction rate was 16.7% (n=5) (Table I). In clinical follow-up, the rate of RDS was 46.3% (n=14), sepsis 50% (n=15), pneumonia 16.7% (n=5), BPD 25% (n=7), NEC 10% (n=3), intraventricular bleeding 36% (n=11) and mortality was 16.7% (n=5). The mean vitamin D level was 27.4±19.3 ng/mL (4-76). Vitamin D level was normal in 14 cases (46.7%). Vitamin D insufficiency was present in two cases (6.7%) while 14 cases (46.7%) had vitamin D deficiency. Severe vitamin D deficiency was seen in 7 cases (23.3%) (Table II). Gestational age and birth weights of infants with or without vitamin D deficiency were similar. However, intrauterine growth restriction was present in 42% of cases with 25(OH)D level lower than 10 ng/mL. Intrauterine growth restriction was present in 8.7% of cases with 25(OH)D level greater than 10 ng/mL. In 60% of cases with intrauterine growth restriction vitamin D level was ≤20 ng/mL (p<0.05). There was no correlation between vitamin D deficiency and premature rupture of membranes, neonatal sepsis, respiratory distress, NEC, BPD, intraventricular bleeding and mortality. On the first day of life, the mean calcium level was 8.3±0.8 mg/dL. and the mean phosphorus level was 4.6±1.46 mg/dL. In cases with vitamin D deficiency, the mean phosphorus level was significantly lower (p<0.001) (Table III).

Parameter	Value
Mean gestational age	30±2.9
Mean birth weight	1335±414
Female/male ratio	12/18
Rate of preeclampsia	6/30 (20%)
Rate of gestational diabetes mellitus	2/30 (6.7%)
Rate of premature rupture of membranes	5/30 (16.6%)
Delivery mode	C section 23/30 vaginal 7/30

25(OH)D level	Distribution of cases (n/%)
>30 (ng/mL)	14 (46.7)
20-30 (ng/mL)	2 (6.7)
≤20 (ng/mL)	14 (46.7)
≤10 (ng/mL)	7 (23.3)

25(OH)D: 25-hydroxyvitamin D

Table III. Serum calcium, phosphorus and alkaline phosphatase levels in the first 24 hours of life

	Vitamin D >20 ng/mL	Vitamin D ≤20 ng/mL	p value
Mean calcium	8.5±0.7 mg/dL	8.2±0.8 mg/dL	0.44
Mean phosphorus	5.1±0.8 mg/dL	3.3±0.8 mg/dL	0.001
Mean ALP	168±70 IU/L	164±50 IU/L	0.80

ALP: Alkaline phosphatase

Discussion

Vitamin D deficiency is a worldwide problem and yet it is a preventable disease. Umbilical cord vitamin D level is correlated with maternal serum vitamin D level. Also, in fetal and neonatal period vitamin D level correlates with maternal serum level of vitamin D. During pregnancy if the mother has a vitamin D deficiency, fetuses carry a significant risk of vitamin D deficiency. The rate of vitamin D deficiency in premature infants is reported to be 64% in the United States of America, 83% in India, 63.7% in France. In a study from Australia, vitamin D levels in cord blood was <20 ng/mL in 40% of infants (16). There are limited studies on neonatal vitamin D levels in our country; and most data are obtained from studies in children. Ataseven et al. (17) from Middle Black Sea, examined 152 preterms with gestational ages 29-35 weeks. They found severe vitamin D deficiency in 64%. Serum 25(OH)D3 is a very good marker of vitamin D level in the blood. In our study the mean 25(OH)D level was 27.4±19.3 ng/mL (4-76). Vitamin D level was normal in 14 cases (46.7%). Vitamin D insufficiency was present in two cases (6.7%), and vitamin D deficiency was seen in 14 cases (46.7%). Severe vitamin D deficiency was present in 7 cases (23.3%). Burris et al. (18) reported umbilical cord 25(OH)D level of 34 ng/mL in their study including term and preterm infants. In their study 40% of the newborns had vitamin D levels lower than 30 ng/mL and 14.4% had vitamin D levels lower than 20 ng/mL. In the same study population 25% of the newborns born before 32 weeks of gestation had vitamin D levels lower than 20 ng/mL. In our study the mean vitamin D level was lower and vitamin D deficiency rates were higher when compared to Burris study.

In another study the mean vitamin D level in premature infants was 16.3 ng/mL (19). Park et al. (20) found vitamin D level as 10.7±6.4 ng/mL in a study of 278 cases with a mean gestational age of 33±2 weeks. In the cohort of Park et al. (20) 91% of newborn babies have vitamin D deficiency and there is severe vitamin D deficiency in 51%. In our study the mean vitamin D level was higher and vitamin D deficiency rates were lower when compared to the above studies (19,20). In our study, vitamin D levels were not related to gestational age and birth weight. Burris et al. (18) did not see any linear correlation between vitamin D level and gestational week. Park et al. (20) reported insignificant correlation of vitamin D levels with gestational age and birth weight.

We did not observe any correlation of vitamin D levels and the presence of premature rupture of membrane. In our cases with intrauterine growth restriction vitamin D level was ≤20 ng/mL in 60% of cases (p<0.05). Low maternal vitamin D levels during pregnancy also have been shown to be associated with increased risk of specific conditions including gestational diabetes, preeclampsia and poor fetal growth (20). Park et al. (20) reported insignificant correlation of vitamin D levels with premature rupture of membranes and preeclampsia, and a small correlation with gestational age. Wei et al. (8,9) reported a higher risk of preterm delivery, preeclampsia, gestational diabetes mellitus in maternal vitamin D deficiency. In our study the striking finding is the lower vitamin D level in the newborns with intrauterine growth restriction. We found no correlation between vitamin D deficiency and neonatal sepsis, respiratory distress, NEC, intraventricular bleeding and mortality. Onwuneme et al. (21) reported no significant statistical correlation between vitamin D level and respiratory distress, NEC, intraventricular bleeding, sepsis and mortality in 94 preterm infants under the gestational age of 32 weeks. But Fettah et al. (22) found significantly increased respiratory distress risk in infants with vitamin D levels lower than 15 ng/mL. In our study, on the first day of life, the mean calcium level was 8.3±0.8 mg/dL and the mean phosphorus level was 4.6±1.46 mg/dL. In cases with vitamin D deficiency, the mean phosphorus level was significantly lower. In similar studies in the literature, serum calcium and phosphorus levels do not change significantly; however, there is prominent increase in ALP levels (20).

Study Limitation

There is not enough number of cases.

Conclusion

Vitamin D deficiency was present in more than half of the study population. Vitamin D deficiency was encountered more often in intrauterine growth restricted fetuses. The low phosphorus level on the first day of life may be a marker of vitamin D deficiency. More studies are needed with larger populations of premature infants to clarify the complex interactions of vitamin D.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 11-12.2/4).

Informed Consent: The parents provided informed consent for the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Medical Practices: N.K., M.Y., Concept: Ö.A.K., M.A., Design: Ö.K., D.T., M.Y., Data Collection or Processing: D.T., G.Ö., Analysis or Interpretation: D.T., M.Y., Literature Search: D.T., F.E., Writing: N.K., Ö.K., D.T.

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