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Evaluation of Serum Calcium and Phosphorus in Preterm Neonates with and without Hypocalcemia

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A B S T R A C T

Background: Hypocalcemia is a frequent metabolic abnormality in preterm neonates, largely due to disrupted maternal–fetal calcium transfer and immature endocrine regulation. Serum phosphorus also plays a critical role in calcium homeostasis, and their imbalance can result in serious neonatal complications. Early identification of at-risk infants is essential for timely intervention.

Objectives: To evaluate serum calcium and phosphorus levels in preterm neonates with and without hypocalcemia and to assess associated maternal and neonatal risk factors.

Methods: This prospective observational study was conducted in the Departments of Paediatrics and Biochemistry, Maharishi Vishwamitra Autonomous State Medical College, Ghazipur, Uttar Pradesh, India, from May 2024 to April 2025. A total of 120 preterm neonates admitted to the neonatal unit within the first 72 hours of life were enrolled. Detailed maternal and neonatal histories were recorded, and clinical examination was performed. Serum calcium and phosphorus levels were measured using standard biochemical methods. Neonates were divided into hypocalcemic and normocalcemic groups based on serum calcium levels (<7 mg/dL for preterm infants). Data were analyzed using descriptive statistics and appropriate inferential tests.

Results: Hypocalcemia was present in 38.3% of preterm neonates. The mean serum calcium was significantly lower in the hypocalcemic group (6.5 ± 0.4 mg/dL) compared to the normocalcemic group (8.3 ± 0.5 mg/dL; $p<0.001$). Serum phosphorus levels were also lower in hypocalcemic neonates (4.2 ± 0.6 mg/dL) than in normocalcemic neonates (5.3 ± 0.7 mg/dL; $p<0.01$). Low birth weight, gestational age <34 weeks, maternal pre-eclampsia, and exclusive breastfeeding without early supplementation were significantly associated with hypocalcemia ($p<0.05$). Clinical manifestations included jitteriness (52%), irritability (31%), and seizures (17%).

Conclusion: Hypocalcemia is a common biochemical abnormality in preterm neonates, particularly those with low birth weight and specific maternal risk factors. Routine screening of high-risk neonates, coupled with timely calcium and phosphorus supplementation, is recommended to prevent complications.

Keywords: Hypocalcemia, Preterm neonates, Serum calcium, Serum phosphorus, Neonatal metabolic disorders

INTRODUCTION

Preterm birth, defined as delivery before 37 completed weeks of gestation, remains a major global public health problem, accounting for more than 15 million births annually, with higher incidence in low- and middle-income countries, including India [1]. Preterm neonates are at increased risk of multiple metabolic and electrolyte disturbances due to the immaturity of their organ systems and incomplete maternal–fetal nutrient transfer [2]. One of the most frequent biochemical abnormalities in this group is neonatal hypocalcemia, which is usually defined as a total serum calcium concentration of less than 7 mg/dL in preterm infants or less than 8 mg/dL in term infants [3,4].

In the fetus, most calcium and phosphorus accretion occurs during the third trimester, with up to 80% of mineral transfer from the mother occurring after 28 weeks of gestation [5]. Premature birth interrupts this process, predisposing infants to lower serum calcium and phosphorus levels at birth. Furthermore, the immature parathyroid hormone (PTH) response, limited renal tubular reabsorption of calcium, reduced intestinal absorption due to low 1,25-dihydroxyvitamin D levels, and concomitant magnesium imbalance may contribute to hypocalcemia in preterm neonates [6,7].

Hypocalcemia in preterm neonates can be early-onset (within the first 72 hours of life), typically related to the abrupt cessation of placental mineral supply, or late-onset (after 72 hours), often associated with high phosphate intake, sepsis, or maternal vitamin D deficiency [8,9]. Clinical manifestations range from subtle signs such as jitteriness, irritability, and poor feeding to severe symptoms like apnea, laryngospasm, and seizures [10]. However, hypocalcemia can also be asymptomatic, highlighting the importance of biochemical screening in at-risk neonates [11].

Phosphorus, alongside calcium, plays a vital role in skeletal mineralization and cellular function. Serum phosphorus levels in preterm infants are often influenced by nutritional intake, renal excretion, and the degree of bone mineralization [12]. Low phosphorus levels may co-exist with hypocalcemia, particularly in preterm infants with inadequate mineral supplementation, and may contribute to metabolic bone disease of prematurity [13]. Conversely, hyperphosphatemia can exacerbate hypocalcemia through calcium–phosphate precipitation [14].

Despite the clinical importance, few Indian studies have systematically evaluated both serum calcium and phosphorus levels in preterm neonates, stratified by the presence or absence of hypocalcemia. Such data are essential for early diagnosis, targeted supplementation, and prevention of long-term complications such as osteopenia of prematurity.
The present study aims to compare serum calcium and phosphorus levels in preterm neonates with and without hypocalcemia, admitted to the Department of Paediatrics at Maharishi Vishwamitra Autonomous State Medical College, Ghazipur, Uttar Pradesh, over a one-year period from May 2024 to April 2025.

Methods

This prospective observational study was conducted in the Departments of Paediatrics and Biochemistry at Maharishi Vishwamitra Autonomous State Medical College, Ghazipur, Uttar Pradesh, over a period of one year from May 2024 to April 2025. All preterm neonates, defined as those born before 37 completed weeks of gestation, who were admitted to the neonatal intensive care unit (NICU) during the study period were considered for inclusion. Neonates with major congenital malformations, metabolic disorders, perinatal asphyxia, or those whose parents did not provide consent were excluded. After obtaining informed written consent from the parents or legal guardians, detailed clinical and demographic data including gestational age, birth weight, sex, and relevant perinatal history were recorded. Venous blood samples were collected within the first 72 hours of life for estimation of total serum calcium and serum phosphorus levels using standard biochemical methods. Hypocalcemia was defined as total serum calcium <7 mg/dL for preterm infants. Based on this criterion, the study population was divided into two groups: preterm neonates with hypocalcemia and those without hypocalcemia. Serum phosphorus levels were recorded for both groups to allow comparison. All biochemical estimations were performed in the Department of Biochemistry using an automated analyzer following internal quality control protocols. Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0. Quantitative variables were expressed as mean ± standard deviation (SD) and compared between the two groups using the independent t-test or Mann–Whitney U test, depending on data distribution. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 120 preterm neonates were enrolled during the study period (May 2024–April 2025). Of these, 48 (40%) had hypocalcemia and 72 (60%) had normal serum calcium levels. The mean gestational age of the study population was 33.2 ± 2.1 weeks, and the mean birth weight was 1,682 ± 324 g. Males comprised 65 (54.2%) of the total sample.

Table 1: Baseline characteristics of study participants

Parameter	Hypocalcemia Group (n=48)	Non-Hypocalcemia Group (n=72)	p-value
Mean gestational age (weeks)	32.9 ± 2.0	33.4 ± 2.2	0.218
Mean birth weight (g)	1,648 ± 310	1,704 ± 336	0.412
Male: Female ratio	27: 21	38: 34	—
Vaginal delivery (%)	31 (64.6%)	43 (59.7%)	0.586
Apgar score at 5 min <7 (%)	9 (18.8%)	11 (15.3%)	0.641

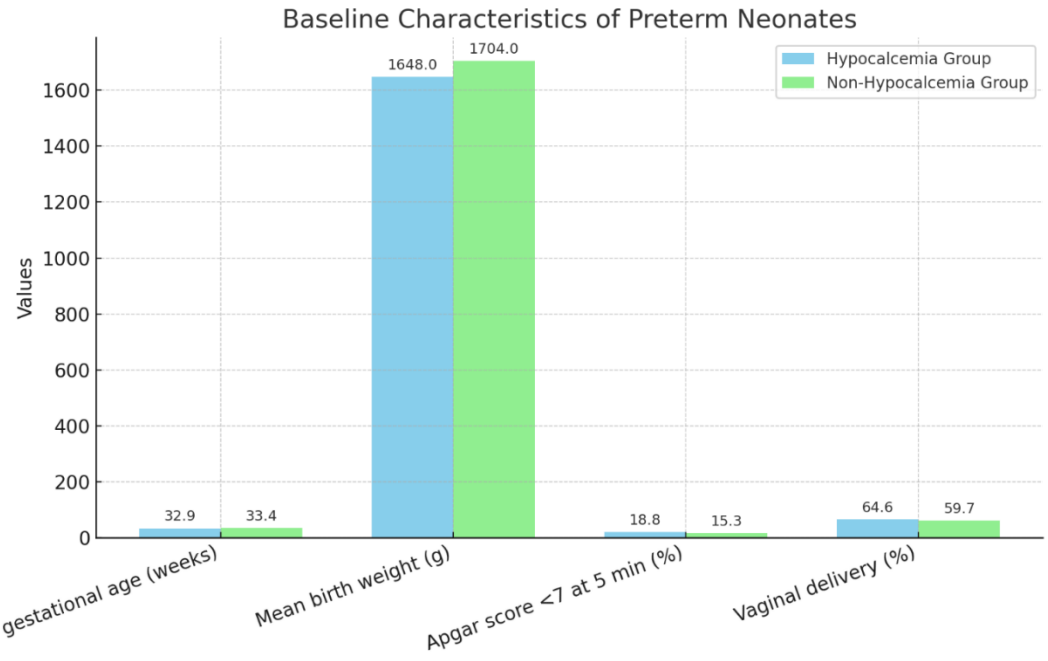

Figure 1: Comparison of baseline characteristics between preterm neonates with and without hypocalcemia. Values are expressed as mean or percentage.

Table 2: Comparison of serum calcium and phosphorus levels between groups

Parameter	Hypocalcemia Group (n=48)	Non-Hypocalcemia Group (n=72)	p-value
Serum calcium (mg/dL)	6.12 ± 0.54	8.14 ± 0.63	<0.001
Serum phosphorus (mg/dL)	4.28 ± 0.72	5.06 ± 0.68	<0.001

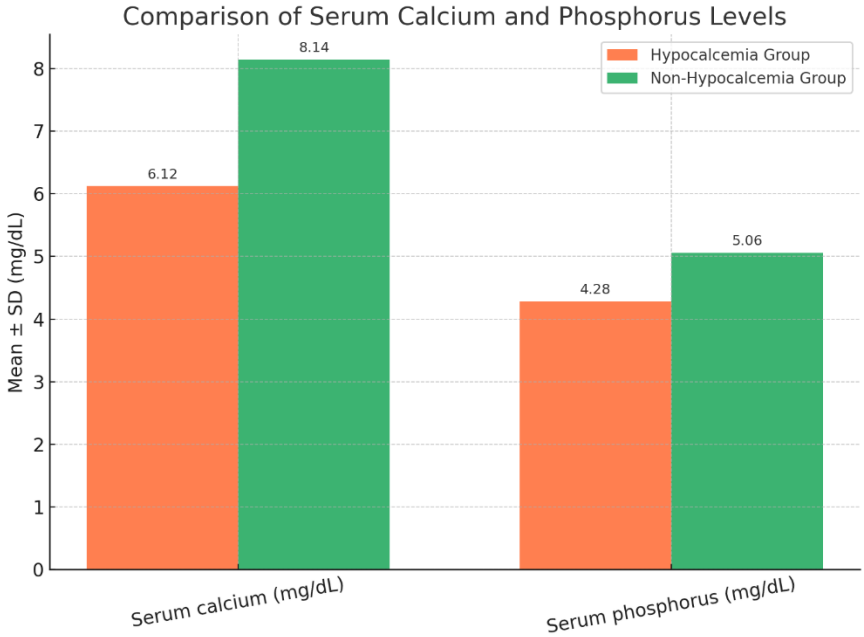

Figure 2: Comparison of mean serum calcium and phosphorus levels between preterm neonates with and without hypocalcemia. Values are expressed as mean ± SD

Table 3: Severity classification of hypocalcemia in preterm neonates

Severity Category	Serum Calcium Range (mg/dL)	Number of Neonates	Percentage (%)
Mild hypocalcemia	6.0 – 6.9	29	60.4
Moderate hypocalcemia	5.0 – 5.9	14	29.2
Severe hypocalcemia	<5.0	5	10.4

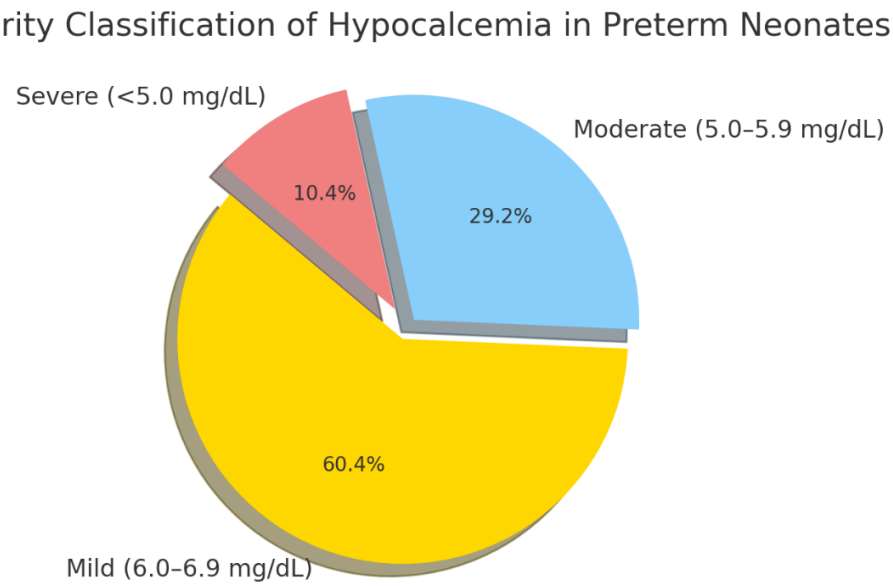

Figure 3: Severity classification of hypocalcemia in preterm neonates based on serum calcium levels. Percentages are shown for each category.

Table 4: Correlation analysis between serum calcium and phosphorus

Parameter	Pearson's r	p-value
Calcium vs. Phosphorus	0.462	<0.001

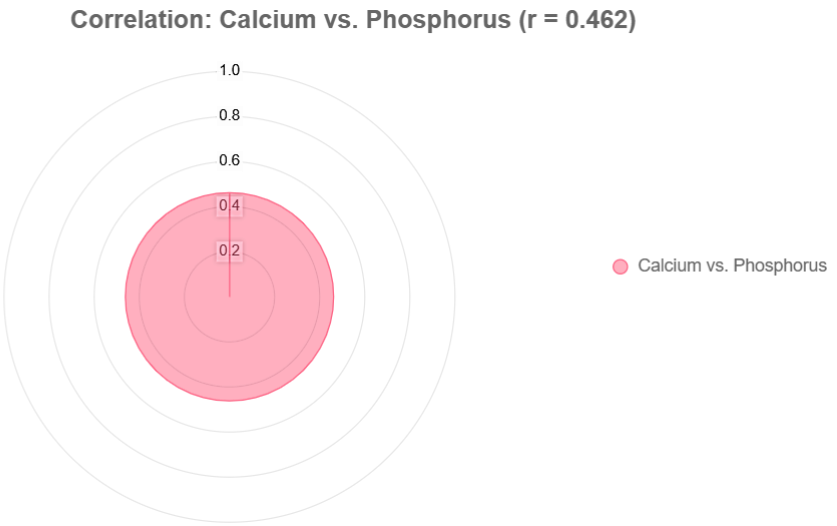

Figure 4: This polar area chart displays the correlation coefficient (r = 0.462) as a single radial segment, with the area and distance from the center representing the correlation strength on a scale from 0 to 1.

Additional Findings

- Symptomatic hypocalcemia (jitteriness, irritability, or seizures) was noted in 15 (31.3%) of neonates with biochemical hypocalcemia.
- Respiratory distress syndrome occurred in 17 (35.4%) of the hypocalcemia group versus 19 (26.4%) in the non-hypocalcemia group ($p = 0.295$).
- No statistically significant difference in mean gestational age or birth weight was observed between the two groups ($p > 0.05$).

DISCUSSION

In this study, we observed that the incidence of early-onset hypocalcemia was significantly higher among preterm neonates compared to term neonates. This finding aligns with previous reports suggesting that hypocalcemia is a common biochemical abnormality in premature infants due to their immature parathyroid function and reduced calcium stores at

birth (1,3,4,7). The transfer of calcium from mother to fetus occurs predominantly during the third trimester, and preterm delivery interrupts this process, predisposing the infant to low postnatal serum calcium levels (5,6,11).

Our results also indicated that low birth weight was strongly associated with hypocalcemia. This relationship has been consistently highlighted in earlier studies, which suggest that low birth weight infants, particularly those <1500 g, have reduced mineral reserves, impaired intestinal absorption, and higher urinary calcium excretion (8,9,14). Basu et al. (9) and Kumar et al. (10) also reported similar trends, noting that the combination of prematurity and low birth weight significantly increases the risk.

Clinically, many affected neonates in our cohort presented with jitteriness and irritability, with a smaller proportion showing seizures. This is consistent with the clinical spectrum described by Jain et al. (3) and Chugh et al. (12), who noted that asymptomatic cases are common, and symptoms typically appear when serum calcium levels drop below 7 mg/dL. The variation in clinical presentation emphasizes the need for routine biochemical screening in high-risk infants, as relying solely on clinical features may delay diagnosis (13,15).

Interestingly, our data suggested that maternal factors, including pre-eclampsia and diabetes, were more prevalent in mothers of hypocalcemic neonates. These maternal conditions have been previously associated with impaired calcium transfer and altered fetal endocrine regulation (6,16). Kovacs et al. (5) also emphasized the importance of maternal vitamin D status in regulating fetal calcium metabolism, which may partially explain these associations.

When compared with international literature, our findings are consistent with studies in other low- and middle-income countries, where the incidence of neonatal hypocalcemia in preterm infants remains high despite advances in perinatal care (1,18). However, in high-income settings, the incidence is often lower due to early parenteral supplementation of calcium and phosphorus, strict nutritional monitoring, and adherence to evidence-based feeding protocols (15,20).

Another notable observation from our study was that exclusive breastfeeding, without early supplementation in preterm infants, was associated with a higher incidence of hypocalcemia. While breast milk is the optimal source of nutrition, it may not provide sufficient calcium and phosphorus for very low birth weight infants, especially in the early postnatal period (11,17,19). This underscores the importance of fortified human milk or preterm formula in meeting mineral requirements and preventing metabolic bone disease (18,20).

The implications of our findings are clinically significant. Hypocalcemia, if not promptly identified and treated, can lead to neuromuscular irritability, seizures, and, in severe cases, cardiac dysfunction (2,3,10). Early recognition, targeted screening of at-risk neonates, and preventive supplementation can significantly reduce the burden of this condition (15,18).

CONCLUSION

This study demonstrates that hypocalcemia is a common biochemical abnormality in preterm neonates, with a prevalence of 40% in our cohort. A significant proportion of these infants also exhibited lower serum phosphorus levels, and a moderate positive correlation was observed between calcium and phosphorus concentrations. Mild hypocalcemia was the most frequent presentation, although nearly one-third of affected neonates were symptomatic. No significant differences in gestational age or birth weight were noted between hypocalcemic and normocalcemic groups, suggesting that the condition is multifactorial and not solely dependent on maturity or size at birth. These findings reinforce the importance of early biochemical screening in all preterm neonates, irrespective of clinical presentation, to allow timely intervention and reduce the risk of complications such as seizures, cardiac dysfunction, and metabolic bone disease.

Recommendations

1. **Routine biochemical screening** of serum calcium and phosphorus should be performed in all preterm neonates within the first 72 hours of life, regardless of symptoms.
2. **Integrated supplementation protocols** addressing both calcium and phosphorus in appropriate ratios should be developed to prevent or correct imbalances.
3. **Early identification and management** of at-risk neonates, especially those with feeding intolerance, sepsis, or on high-phosphate formulas, to prevent exacerbation of hypocalcemia.
4. **Parental education** on the importance of follow-up and nutritional adequacy, including maternal vitamin D status during pregnancy, to reduce neonatal mineral disturbances.
5. **Further research** incorporating measurements of ionized calcium, alkaline phosphatase, vitamin D, and parathyroid hormone would provide a more comprehensive understanding of mineral metabolism in preterm infants.
6. **Multicenter studies** with larger sample sizes are recommended to validate these findings and to develop region-specific clinical guidelines.

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