ORIGINAL RESEARCH

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Evaluation of clinical and laboratory related factors of early-onset hypocalcemia in term neonates

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Abstract

Objective: Early-onset hypocalcemia (EOH) is a common metabolic disorder in neonates, which occurs during the first three days of life. The purpose of the study is to define the hypocalcemia characteristics, its clinical presentations, laboratory findings, and treatment for early-onset hypocalcemia in newborns.

Method: This is a cross sectional study obtaining the patient's data retrospectively from the Neonatal Intensive Care Unit at İzmir Buca Seyfi Demirsoy Training and Research Hospital. Fifty-one neonates born with ≥ 37 weeks of gestation who were diagnosed with hypocalcemia within the first three days of life between 2022-2024 were included in the study. The study analyzed demographic characteristics, laboratory values, timing and severity of hypocalcemia, treatment methods, and discharge details.

Results: The study found no significant association between 25-OH vitamin D levels and birth weight or gestational age in neonates with EOH. Neonatal hypocalcemia onset on the 2nd and 3rd days of life showed higher initial calcium levels, suggesting early calcium levels may play a role. No significant association was found between 25-OH vitamin D levels and serum calcium, ionized calcium, or albumin levels, and hospitalization length. The use of calcium or vitamin D supplements did not influence 25-OH vitamin D levels or hypocalcemia outcomes.

Conclusion: Gestational age and initial calcium levels are predictive of the timing and severity of EOH. However, 25-OH vitamin D levels were not significantly associated with birth weight, blood calcium, ionized calcium, or albumin levels in this population. These findings suggest that other factors influencing vitamin D metabolism in neonates with EOH require further investigation.

Keywords: Early-onset hypocalcemia, newborn, 25-OH vitamin D, blood calcium

INTRODUCTION

Early-onset hypocalcemia in neonates is characterized by low blood calcium levels within the first 72 hours of life. While it typically responds well to short-term treatment, failure to recognize and manage it promptly can lead to severe, potentially life-threatening complications (1,2). Neonatal hypocalcemia is characterized by a total blood calcium concentration below 8 mg/dL and/or an ionized calcium level below 4.4 mg/dL in term neonates. Neonates with birth weights over 1500 g and total serum calcium levels below 7 mg/dL, or ionized calcium levels below 3.6 mg/dL in preterm infants is characterized as hypocalcemia (2) which is an extreme reduction in the serum calcium that is present in the body during the first 72 hours of their birth (3). Since hypocalcemia is the most common abnormal calcium status of the newborn, preventing hypocalcemia abnormalities is an important component of neonatal care (4).

Evidently the most common factors involved in the onset of hypocalcemia in newborns are prematurity, maternal diabetes, and low birth weight, due to insufficient calcium reserves or impaired metabolism (5) resulting from the short fall of sufficient nutrient consumption from the majority of

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enteral sources, such as unfortified human milk, for optimal mineral retention (6). Roughly one-third of preterm babies and majority of the very low-birth-weight infants develop early neonatal hypocalcemia (7,8) because calcium is being actively moved to the placenta from mothers during the final trimester (3), but it can cause neonatal hypocalcemia due to the sudden stoppage of placental calcium transport that takes immediately after birth (9). As after the infant detaches from the placenta in the postpartum period, serum total and ionized calcium levels decrease a physiological lowest point in a healthy 2-day term infant resulting the increase of phosphate levels, leading to hypocalcemia or low calcium levels in the body (8). Early-onset hypocalcemia is typically without symptoms; thereby, it is recommended to conduct screening for hypocalcemia every 24 hours for two days for newborns identified as high risk for developing this condition. However, late-onset hypocalcemia, occurs with prominent symptoms after 72 hours of birth and approaches the conclusion at the first week of life. Common causes of late-onset hypocalcemia include excessive phosphate intake, hypomagnesemia, hypoparathyroidism, and vitamin D deficiency (3). Patients exhibiting hypocalcemia typically present with primary clinical manifestations including fatigue, vomiting, abdominal distension, diminished muscular tone, inadequate eating, irritability, myoclonic jerks, and both localized and generalized seizures (10). But addressing the patient with proactive therapy for early-onset hypocalcemia enhances infant care and patient outcomes. Although early-onset hypocalcemia is frequently temporary and effectively managed with short-term medication, its underlying etiology might differ significantly, requiring meticulous examination and management to avert complications (11). However untreated hypocalcemia in children can face developmental delays, behavioral and social inefficiencies, and other disabilities, suggested by association studies (12). Hypocalcemia therapeutic interventions often include calcium supplementation, correction of magnesium deficiencies, and addressing underlying causes such as vitamin D insufficiency or phosphorus imbalance. Early recognition and correction of these associated abnormalities can improve calcium stability and mitigate the risk of long-term complications (13).

This study aims to evaluate the clinical, demographic, and laboratory characteristics of term neonates diagnosed with early-onset hypocalcemia and to investigate the potential statistical relationships between key biochemical and clinical parameters such as 25-OH vitamin D levels.

METHOD

This is a cross sectional retrospective study, utilizing hospital records to investigate early-onset neonatal hypocalcemia. An ethical approval for the study was obtained from the Non-Interventional Research Ethics Committee of Buca Seyfi Demirsoy Training and Research Hospital (Approval No and Date: 2024/356 and 27.11.2024). The data were collected from term neonates admitted to the neonatal intensive care unit at Buca Seyfi Demirsoy Training and Research Hospital between 2022 and 2024. The study included neonates, born at ≥37 weeks of gestation, who were diagnosed with hypocalcemia within the initial three days of life. Neonates excluded from the study were those who had significant deficiencies in medical records, were infants <37 weeks of gestation, infants with hypocalcemia first detected after the 3rd day. A total of 51 term neonates satisfying the criteria were incorporated into the study. Demographic data (patients' gender, gestational week, birth weight, length of stay in the neonatal intensive care unit, laboratory values related to blood calcium level, blood ionized calcium and blood calcium); hypocalcemia level and the first day it was detected; lowest calcium value and the day it was detected, the day calcium returned to normal, blood albumin level, blood magnesium level, blood 25-OH vitamin D level, diagnosis of admission to the neonatal intensive care unit; and parameters such as treatments received due to hypocalcemia were recorded.

Statistical analysis

The study used descriptive statistics (mean and standard deviation) to summarize continuous variables, providing an overview of central tendency and variability. For inferential statistics, the t-test was applied to compare means between two independent groups when the data followed a normal distribution. The assumption of normality was assessed using the Shapiro–Wilk test. For categorical variables, the Pearson's Chi-Square test was used to assess the association between two categorical variables. The significance level was set at $p < 0.05$, meaning that if the p-value is below this threshold, the observed differences or associations are considered statistically significant. The study employs IBM SPSS 27 for analysis, ensuring reliable statistical computation.

RESULTS

Retrospective data from 51 newborns with a gestational age of ≥37 weeks (term neonates) who were admitted to the hospital was collected. Among the 51 term infants, the majority were male (37, accounting for 72.5%), while the remaining 14 (27.5%) were female. Caesarean section accounted for 32 births (62.7%), whereas 19 (37.3%) were vaginal deliveries. Transient infant tachypnea was the most common primary diagnosis at hospitalization, detected in 38 instances (74.5%). The less common diagnoses were indirect hyperbilirubinemia (5; 9.8%), congenital pneumonia (3; 5.9%), and hypocalcemia-related disorders. Hypocalcemia was mostly identified on the second day of life (26; 51%),

followed by the third (18; 35.3%) and the first (7; 13.7%). Most newborns (35; 68.6%) received calcium carbonate and vitamin D3. A lesser fraction needed magnesium sulphate or calcium gluconate, calcium carbonate, and vitamin D3 in more complex regimens. Most babies were hospitalized for 8–14 days (31; 60.8%). Thirteen (25.5%) stayed 4–7 days, and 7 (13.7%) stayed 15+ days. The majority of newborns (25; 49%) were born at 37+0 to 37+6 weeks. Fewer were born at 38+0 to 38+6 weeks (15; 29.4%) and the smallest at 40+0 to 40+3 weeks (3; 5.9%). Demographic and clinical characteristics of newborns who developed early-onset and transient neonatal hypocalcemia are shown in detail in Table 1.

Table 1. Evaluation of demographic and clinical data

		n = 51	%
Gender	Female	14	27.45
	Male	37	72.55
Type of birth	Caesarean section	32	62.75
	Normal vaginal	19	37.25
First primary diagnosis at the time of hospitalization	Congenital pneumonia	3	5.88
	Hypocalcemia	1	1.96
	Hypocalcemia and Seizure	2	3.92
	Hypoglycemia	1	1.96
	Indirect hyperbilirubinemia	5	9.80
	Neonatal abstinence syndrome	1	1.96
	Transient tachypnea of the newborn	38	74.51
Postnatal day when hypocalcemia first occurs	1. day	7	13.73
	2. day	26	50.98
	3. day	18	35.29
Treatment given during hospitalization	Calcium carbonate, Calcium gluconate, Vitamin D3	4	7.84
	Calcium carbonate, Calcium gluconate, Vitamin D3, Magnesium sulphate	6	11.76
	Calcium carbonate, Vitamin D3	35	68.63
	Calcium carbonate, Vitamin D3, Magnesium sulphate	5	9.80
	Calcium gluconate, Vitamin D3	1	1.96
Length of hospital stay	4-7 Days	13	25.49
	8-14 Days	31	60.78
	15 and above days	7	13.73
Gestational age (Week+Day)	37+0 to 37+6	25	49.02
	38+0 to 38+6	15	29.41
	39+0 to 39+6	8	15.69
	40+0 to 40+3	3	5.88

Statistical analysis was conducted on early-onset hypocalcemia neonates, categorized by postnatal day of start. Birth weight was the highest in the first-day group and the lowest in the third-day group. Blood calcium levels were the lowest on day 1, increasing in the subsequent days. Blood magnesium levels varied significantly, with the lowest in the first-day group and the highest in the second-day group. Blood 25-OH vitamin D levels varied significantly, with the highest in the second-day group and the lowest in the third-day group (Table 2).

Table 2. Analysis of laboratory data associated with neonatal hypocalcemia

Parameters	Postnatal day when hypocalcemia first occurs	n	Mean	Standard Deviation	p
Birth weight (gram)	1. day	7	3313.57	367.908	0.577
	2. day	26	3280.96	637.978	
	3. day	18	3108.61	565.693	
	Total	51	3224.61	579.790	
Initial blood calcium level at the time of admission (mg/dL)	1. day	7	7.971	1.3175	**0.003**
	2. day	26	9.235	0.8782	
	3. day	18	9.361	0.6972	
	Total	51	9.106	0.9856	
Lowest blood calcium level during hospitalization (mg/dL)	1. day	7	6.686	0.9990	0.416
	2. day	26	6.981	0.5261	
	3. day	18	6.761	0.6723	
	Total	51	6.863	0.6536	
Lowest Ionized blood calcium level (mmol/L)	1. day	7	0.8643	0.19527	0.573
	2. day	26	0.9315	0.13511	
	3. day	18	0.9272	0.15840	
	Total	51	0.9208	0.15085	
At the time of hypocalcemia-Blood albumin level (g/dL)	1. day	7	3.3429	0.40999	0.980
	2. day	26	3.3200	0.33228	
	3. day	18	3.3117	0.34109	
	Total	51	3.3202	0.33916	
At the time of hypocalcemia-blood magnesium level (mg/dL)	1. day	7	1.4914	0.21091	**0.018**
	2. day	26	1.7315	0.17988	
	3. day	18	1.6600	0.20416	
	Total	51	1.6733	0.20530	
At the time of hypocalcemia-blood phosphorus level (mg/dL)	1. day	7	8.0614	1.15668	0.679
	2. day	26	7.7938	1.41145	
	3. day	18	7.5700	1.15918	
	Total	51	7.7516	1.28053	
At the time of hypocalcemia-blood 25-OH vitamin D level (ng/mL)	1. day	7	11.3186	5.36596	**0.039**
	2. day	26	14.0169	6.14550	
	3. day	18	9.5244	4.84930	
	Total	51	12.0610	5.89211	

The study found that the primary diagnosis at hospitalization significantly influenced the day of hypocalcemia onset in newborns. Factors such as sex, birth type, hospital stay

length, and gestational week did not significantly vary with the onset of hypocalcemia. However, conditions like transient tachypnea of the newborn (TTN) were more common in neonates who developed hypocalcemia on the second day, while congenital pneumonia and seizures were primarily observed in the first day group. The types of treatments given also varied, suggesting that there may be differences in management strategies between the groups. No effect of treatment differences on outcomes was observed, as all cases of hypocalcemia became normocalcemic with treatments (Table 3).

Table 3. Comparison of demographic and clinical data with hypocalcemia

		Postnatal day when hypocalcemia first occurs			p
		Day 1	Day 2	Day 3	
Gender	Female	2	10	2	0.135
	Male	5	16	16	
Type of birth	Caesarean section	4	17	11	0.908
	Normal vaginal	3	9	7	
First primary diagnosis at the time of hospitalization	Congenital pneumonia	2	0	1	**0.003**
	Hypocalcemia	0	1	0	
	Hypocalcemia and Seizure	2	0	0	
	Hypoglycemia	0	0	1	
	Indirect hyperbilirubinemia	1	1	3	
	Neonatal abstinence syndrome	0	0	1	
	Transient tachypnea of the newborn	2	24	12	
Treatment given during hospitalization	Calcium carbonate, Calcium gluconate, Vitamin D	0	1	3	0.050
	Calcium carbonate, Calcium gluconate, Vitamin D, Magnesium sulphate	3	1	2	
	Calcium carbonate, Vitamin D	4	22	9	
	Calcium carbonate, Vitamin D, Magnesium sulphate	0	2	3	
	Calcium gluconate, Vitamin D	0	0	1	
Length of hospital stay	4-7 Days	2	9	2	0.388
	8-14 Days	4	15	12	
	15 and above days	1	2	4	
Gestational age (Week+ Day)	37+0 to 37+6	3	12	10	0.939
	38+0 to 38+6	3	7	5	
	39+0 to 39+6	1	5	2	
	40+0 to 40+3	0	2	1	

The results showed no significant correlation between birth weight and 25-OH vitamin D levels, suggesting that birth weight does not significantly influence vitamin D levels in neonates. Gestational age was also not strongly linked to 25-OH vitamin D levels. Lower 25-OH vitamin D levels were not found to be associated with lower blood calcium levels during hypocalcemia. Neonates with higher 25-OH vitamin D levels normalized blood calcium levels faster after hypocalcemia, but this hypothesis could not be directly tested due to the lack of a specific variable measuring the speed of normalization. Blood ionized calcium levels and blood albumin levels were also not significantly associated with 25-OH vitamin D levels. Finally, prolonged hospitalization was not found to be associated with lower 25-OH vitamin D levels, suggesting no significant relationship between these variables (Table 4).

DISCUSSION

This study provides important insights into the clinical, demographic, and laboratory factors associated with early-onset hypocalcemia in term neonates, with a particular emphasis on the role of 25-OH vitamin D. Although previous studies have highlighted the significance of vitamin D in calcium homeostasis and neonatal health in hypocalcemia, the findings of the current study reveal nuanced relationships that challenge certain existing hypotheses. Vitamin D deficiency has been significantly associated with early neonatal hypocalcemia in preterm infants (10,14). Although it is a treatable condition, it remains a significant health concern. Common causes include maternal vitamin D deficiency, malabsorption, renal failure, and hepatobiliary diseases in the newborn (3). The study results revealed that there is no significant connection between gestational age, birth weight, and 25-OH vitamin D levels in neonates with EOH. This aligns with previous research suggesting that maternal vitamin D levels have a greater impact on the neonate's vitamin D status than gestational age or birth weight (15). This highlights the importance of optimizing maternal vitamin D levels during pregnancy to support neonatal calcium metabolism (16). Calcium levels should be measured at 12, 24, and 48 hours in extremely low birth weight infants and monitored until normalization, especially in newborns of diabetic mothers or those with acute illnesses (3). Dynamic fluctuations in serum calcium during the first 48–72 hours may contribute significantly to the development of hypocalcemia (17).

Contrary to previous assumptions, the study did not find a meaningful connection between 25-OH vitamin D levels and calcium levels in neonates with EOH. This challenges the idea that vitamin D deficiency is a primary cause of neonatal hypocalcemia (18), indicating that other factors like transient hypoparathyroidism or magnesium disturbances may be involved (19). Hypocalcemia is a frequently observed clinical and laboratory abnormality in neonates. Ionic calcium is crucial for many biochemical processes including blood coagulation, neuromuscular excitability, cell membrane integrity,

Table 4. Relationship between 25-OH vitamin D levels and clinical and demographic parameters

		Birth weight (gram)	At the time of hypocalcemia-Blood 25-OH vitamin D level (ng/mL)	Gestational week (week+day)	Postnatal day when hypocalcemia first occurs	Lowest blood calcium level during hospitalization (mg/dL)	Initial blood calcium level at the time of admission (mg/dL)	Lowest Ionized blood calcium level (mmol/L)	At the time of hypocalcemia-Blood albumin level (g/dL)
Birth weight (gram)	Pearson Correlations	--							
	N	51							
At the time of hypocalcemia-blood 25-OH vitamin D level (ng/mL)	Pearson Correlation	0.047	--						
	Sig. (2-tailed)	0.741							
	N	51	51						
Gestational age (week+day)	Pearson Correlation	0.460	0.083	--					
	Sig. (2-tailed)	0.001	0.564						
	N	51	51	51					
Postnatal day when hypocalcemia first occurs	Pearson Correlation	0.514	0.132	0.933	--				
	Sig. (2-tailed)	0.000	0.354	0.000					
	N	51	51	51	51				
Lowest blood calcium level during hospitalization (mg/dL)	Pearson Correlation	0.145	0.164	0.058	0.162	--			
	Sig. (2-tailed)	0.311	0.249	0.685	0.256				
	N	51	51	51	51	51			
Initial blood calcium level at the time of admission (mg/dL)	Pearson Correlation	0.095	0.325	0.051	0.175	0.318	--		
	Sig. (2-tailed)	0.509	0.020	0.721	0.219	0.023			
	N	51	51	51	51	51	51		
Lowest Ionized blood calcium level (mmol/L)	Pearson Correlation	-0.114	0.038	-0.048	0.036	0.624	0.271	--	
	Sig. (2-tailed)	0.426	0.789	0.739	0.804	0.000	0.055		
	N	51	51	51	51	51	51	51	
At the time of hypocalcemia-blood albumin level (g/dL)	Pearson Correlation	0.258	-0.098	-0.007	0.022	0.000	0.074	-0.052	--
	Sig. (2-tailed)	0.067	0.494	0.961	0.879	1.000	0.603	0.718	
	N	51	51	51	51	51	51	51	51

and many of the cellular enzymatic activities [1]. Early-onset hypocalcemia can result in a number of complications, which can affect organ systems within the body. can affect organ systems within the body. According to current neonatal care guidelines (20), there is no significant correlation between blood albumin levels and 25-OH vitamin D in neonates with early-onset hypocalcemia, suggesting that albumin-bound calcium fluctuations may not significantly contribute to its pathophysiology. As outlined by Goyal et al. (21) disturbances in phosphate, magnesium, albumin, and bicarbonate levels play a critical role in the pathophysiology of hypocalcemia. Changes in albumin concentration affect total calcium measurement (3). To have a better understanding of calcium homeostasis, one need to measure not just the total calcium but ionized calcium as well as serum albumin levels too (22).

A retrospective study involving 600 neonates born to mothers at high risk for vitamin D deficiency demonstrated that neither the length of hospitalization nor early postnatal supplementation with calcium or vitamin D significantly influenced neonatal 25-OH vitamin D concentrations or the

incidence of hypocalcemia, indicating that short-term supplementation may have limited impact on acute vitamin D status in this population (23). Serum calcium concentrations may be either elevated (hypercalcemia) or reduced (hypocalcemia) in clinical settings, often influenced by various underlying pathologies and potentially leading to life-threatening outcomes (24). The study will have significant clinical implications by focusing on the importance of early calcium monitoring and stabilization in newborns along with the identification of the lack of association between 25-OH vitamin D levels and hypocalcemia outcomes, which suggests that routine measurement of vitamin D may not be immediately informative in early onset hypocalcemia. Instead, efforts should prioritize maternal vitamin D optimization during pregnancy and proactive management of high-risk neonates with supplemental calcium during the transitional period (25,26). The study presents multiple opportunities for more investigation. It is essential to investigate additional factors affecting vitamin D metabolism in neonates, including genetic variations in vitamin D receptor. Longitudinal studies evaluating the effects of extended vitamin D treatment on hypocalcemia prophylaxis and overall newborn outcomes are essential.

Limitations of the Study

This study has a few limitations. Being a single-center study, the results may not be fully generalizable to all neonatal populations. Additionally, due to its retrospective design, some clinical or maternal data that could have contributed to a broader interpretation were not available. Despite these minor limitations, the findings provide useful insights into early-onset hypocalcemia in term neonates and may serve as a basis for future prospective studies.

CONCLUSION

While gestational age and initial calcium levels emerged as predictors of early onset hypocalcemia timing and severity, the findings of the present study challenge the presumed centrality of 25-OH vitamin D levels in this context (25-OH vitamin D levels were not significantly associated with birth weight, blood calcium, ionized calcium, or albumin levels in this population). These results underscore the complex and multifactorial nature of neonatal hypocalcemia, advocating for a broader perspective in its clinical evaluation and management.

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