Cardiology in the Young

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Clinical, biochemical, and echocardiographic evaluation of neonates with vitamin D deficiency due to maternal vitamin D deficiency

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Abstract

Objective: There are a few number of case reports and small-scale case series reporting dilated cardiomyopathy due to vitamin D-deficient rickets. The present study evaluates the clinical, biochemical, and echocardiographic features of neonates with vitamin D deficiency. *Patients and methods:* In this prospective single-arm observational study, echocardiographic evaluation was performed on all patients before vitamin D3 and calcium replacement. Following remission of biochemical features of vitamin D deficiency, control echocardiography was performed. Biochemical and echocardiographic characteristics of the present cohort were compared with those of 27 previously published cases with dilated cardiomyopathy due to vitamin D deficiency. *Results:* The study included 148 cases (95 males). In the echocardiographic evaluation, none of the patients had dilated cardiomyopathy. All of the mothers were also vitamin D deficient and treated accordingly. Comparison of patients with normocalcaemia and hypocalcaemia at presentation revealed no statistically significant difference between the ejection fraction and shortening fraction, while left ventricle end-diastolic diameter and left ventricle end-systolic diameter were higher in patients with hypocalcaemia. Previously published historical cases were older and had more severe biochemical features of vitamin D deficiency. *Conclusion:* To the best of our knowledge, in this first and largest cohort of neonates with vitamin D deficiency, we did not detect dilated cardiomyopathy. Early recognition and detection before developing actual rickets and preventing prolonged hypocalcaemia are critically important to alleviate cardiac complications.

Original Article

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Vitamin D deficiency is a public health problem affecting developed countries due to inadequate exposure to the sunlight and change in feeding habits, and developing countries due to malnutrition and limited access to health services.[1,2] Rickets, the typical manifestation of vitamin D deficiency in children before epiphyseal closure, is a metabolic bone disease characterised by hypocalcaemia, hypophosphatemia, elevated serum alkaline phosphatase, and defective bone mineralisation. Vitamin D deficiency primarily affects bone metabolism, while various extra-skeletal effects may also be observed in many organ systems, including the cardiovascular system.[3]

Vitamin D is reported to have anti-hypertrophic, anti-atherosclerotic, anti-inflammatory, and anti-oxidative effects on the cardiovascular system. In children, multiple case reports and some small case series have reported the relationship between calcium, vitamin D, and cardiac function, particularly dilated cardiomyopathy.[4–8] The majority noted that dilated cardiomyopathy recovered after vitamin D and calcium replacement.[9–14] In post-mortem examination of children with vitamin D-deficient rickets and cardiomyopathy, pericardial effusion, left ventricular dilatation, and increased interstitial fibrosis have been identified.[10] In a study evaluating cardiac function in patients with vitamin D-deficient rickets, although patients did not show any cardiac symptoms, echocardiographic parameters were shown to deteriorate compared to healthy controls.[15]

The underlying mechanism by which vitamin D deficiency and hypocalcaemia cause dilated cardiomyopathy has not been fully elucidated. There are a few case reports indicating the presence of dilated, usually reversible, cardiomyopathy due to rickets and/or hypocalcaemia. Nevertheless, to the best of our knowledge, there are no large-scale studies evaluating cardiac

function in neonates and infants with vitamin D deficiency. This study aims to assess the effects of vitamin D deficiency on cardiac function in a large series of neonates with hypovitaminosis D due to maternal vitamin D deficiency.

Patients and methods

This prospective single-arm observational study was conducted in 148 neonates with vitamin D deficiency. Serum calcium, magnesium, albumin, phosphorus, and alkaline phosphatase levels were measured via the "bromocresol green succinate buffer method" (Abbott Architect c16000 system; Abbott Diagnostics, Wiesbaden-Delkenheim, Germany). Serum calcium was corrected for the level of serum albumin using the formula: serum calcium + 0.8 × [4−serum albumin]. As some patients referred from other centres had received calcium before admission, their calcium was normal at admission. We, therefore, created two groups according to presenting calcium levels; hypocalcemic and normocalcemic groups. Hypocalcaemia was defined as a total calcium level below 8 mg/dl (2 mmol/L) for babies born at term (≥36 weeks of gestation) and total calcium below 7 mg/dl (1.75 mmol/L) for babies born preterm (<36 weeks of gestation). Serum 25-hydroxyvitamin D and parathormone levels were measured by chemiluminescent microparticle immunoassay (Architect i2000sr; Abbott, Wiesbaden-Delkenheim, Germany). A serum 25-hydroxy vitamin D level of ≤12 ng/mL was considered as vitamin D deficiency.[16] Low calcium, low phosphorous, elevated parathormone, and elevated alkaline phosphatase were considered as biochemical features of vitamin D deficiency.

Electrocardiogram was performed after adjustment of the device to 10 mm/mV with a recording speed of 25 mm/s, using NIHON KOHDEN ECG-1250K Cardiofax S Electrocardiograph. QT interval measurements were calculated and adjusted according to the Bazett formula.

Echocardiographic examinations were performed using a Vivid S5 echocardiography device (GE Healthcare, Wisconsin, USA) using sector probes suitable for the age and weight of patients by the same experienced paediatric cardiologist. Echocardiographic measurements were assessed according to the American Echocardiography Association Pediatric Echocardiography Guideline.[16]

We commenced vitamin D3 (2000 IU/d, per oral) and calcium (calcium lactate: 500 mg/day, per oral) in all cases.[16,17] In case of severe symptomatic hypocalcaemia, an intravenous infusion of calcium gluconate (75 mg/kg/d) was given initially.

One month following appropriate treatment, we repeated all biochemical and cardiological evaluations. Once a diagnosis of vitamin D deficiency was considered, 25-hydroxy vitamin D levels of the mothers were also measured, and vitamin D3 replacement was introduced to those with vitamin D deficiency.

We compared the biochemical and echocardiographic parameters of the present cohort with those of previously published 27 patients with confirmed dilated cardiomyopathy due to vitamin D-deficient rickets (historical group).[12–14,18–29]

Statistical analyses

Statistical analyses were carried out by the SPSS Statistics for Windows software version 22.0 (SPSS IBM Statistics, Armonk, New York, USA). Levene test was used for equality of variances, and Shapiro–Wilk's test was used for normality distribution of the data. Descriptive data were expressed as number and percentage for categorical variables and as mean, standard deviation, median, minimum, and maximum for numerical variables. For normally distributed data, means were compared using Student's t-test, and Mann–Whitney U-test was performed for comparison of medians where the data were not normally distributed. Correlation analysis was performed using Pearson correlation analysis in normally distributed data, and the Spearman's rank test was performed for non-normally distributed data. A multivariate linear regression analysis was performed to evaluate the factors affecting the development of dilated cardiomyopathy. We performed receiver operating characteristic analysis for determining the best cut-off value for a calcium level associated with dilated cardiomyopathy. Statistical significance was set at the p-value < 0.05.

The study was performed with the ethical approval of the institutional review board of Erzurum Training and Research Hospital (Document Number: 2017/08–54) and in accordance with the principles of the Declaration of Helsinki with written informed consent obtained from the parents.

Table 1. The presenting clinical characteristics of neonates with vitamin D deficiency

	n	%
Age of presentation		
0–3 days	119	80.4
3–30 days	29	19.6
Mode of delivery		
SVD	62	41.8
C/S	86	58.2
Gestation week		
<36 weeks	82	55.4
≥36 weeks	66	44.6
Gender		
Male	95	64.2
Female	53	35.8
Birthweight status		
SGA	4	2.7
AGA	137	92.6
LGA	7	4.7
Feeding plan		
Breastfeed	5	3.3
Formula	24	16.2
Breastfeed +formula	119	80.5
Presenting symptoms		
Respiratory distress	98	66.2
Prematurity	47	31.8
Convulsion	3	2.0

AGA = Appropriate for gestational age; C/S = Caesarean section, LGA = Large for gestational age; SGA = Small for gestational age; SVD = Spontaneous vaginal delivery.

Results

Presenting clinical and laboratory characteristics

The study included 148 neonates (95 males). Presenting clinical features of the patients are shown in Table 1.

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Table 2. Biochemical, electrocardiographic, and echocardiographic findings of neonates with vitamin D deficiency

	Pretreatment (Mean ± SD)	Post-treatment first month (Mean ± SD)	p-value
Biochemical investigations			
Calcium (mg/dl)	7.1 ± 0.5	10.0 ± 0.7	<0.001
Phosphorous (mg/dl)	6.3 ± 1.2	6.1 ± 1.0	0.100
ALP (U/L)	224.0 ± 82.7	314.0 ± 134.5	<0.001
PTH (pg/ml)	133.6 ± 79.5	44.5 ± 41.9	<0.001
Magnesium (mg/dl)	1.8 ± 0.2	2.0 ± 0.3	0.070
25(OH)D3 (ng/ml)	5.5 ± 2.4	28.5 ± 14.9	<0.001
Maternal 25(OH)D3 (ng/ml)	7.1 ± 3.5	NA	NA
Electrocardiography			
Heart rate (bpm)	150.2 ± 14.3	148 ± 12.8	0.76
QTc (s)	0.40 ± 0.01	0.39 ± 0.02	0.59
Echocardiography			
EF (%)	69.3 ± 6.1	70.6 ± 5.9	0.12
SF (%)	37.82 ± 4.28	38.22 ± 3.96	0.11
LVEDd (cm)	2.02 ± 0.16	1.94 ± 0.24	0.22
LVESd (cm)	1.48 ± 0.12	1.49 ± 0.14	0.19

25(OH)D = 25-hydroxy vitamin D; ALP = Alkaline phosphatase; bpm = beats per minute; EF = Ejection fraction; LVEDd = Left ventricle end-diastolic diameter; LVESd = Left ventricle end-systolic diameter; PTH = Parathyroid hormone; QTc = Corrected QT interval; SF = Shortening fraction.

Table 3. Biochemical and echocardiographic findings of neonates from our cohort who were presented with normocalcaemia and hypocalcaemia

	Normocalcemic (n = 75) (Mean ± SD)	Hypocalcemic (n = 73) (Mean ± SD)	p-value
Biochemical investigations			
Calcium (mg/dl)	7.8 ± 0.4	7.2 ± 0.6	<0.001
Phosphorous (mg/dl)	7.3 ± 0.8	6.3 ± 1.1	0.314
ALP (U/L)	237 ± 91	210 ± 71	0.052
PTH (pg/ml)	133.6 ± 79.5	44.5 ± 41.9	0.150
Magnesium (mg/dl)	1.8 ± 0.2	1.8 ± 0.2	0.322
25(OH)D3 (ng/ml)	5.3 ± 2.1	5.8 ± 2.7	0.193
Maternal 25(OH)D (ng/ml)	6.5 ± 2.9	7.9 ± 4.1	0.052
Echocardiography			
EF (%)	72.5 ± 2.9	72.6 ± 2.5	0.809
SF (%)	38.7 ± 2.5	39.0 ± 2.3	0.385
LVEDd (mm)	19.0 ± 1.4	19.9 ± 1.5	0.001
LVESd (mm)	11.5 ± 1.0	11.9 ± 1.0	0.009

25(OH)D = 25-hydroxy vitamin D; ALP = Alkaline phosphatase; EF = Ejection fraction; LVEDd = Left ventricle end-diastolic diameter; LVESd = Left ventricle end-systolic diameter; PTH: Parathyroid hormone; SF = Shortening fraction.

Cardiological evaluation

The electrocardiographic evaluation revealed no abnormality in T wave and corrected QT interval, as well as no prominent U waves, was detected (Table 2). In the echocardiographic evaluation performed at diagnosis and after the replacement of vitamin D and calcium, we did not detect dilated cardiomyopathy or any other cardiac dysfunction (Table 2).

Comparison of patients with normocalcaemia and hypocalcaemia at presentation revealed no statistically significant difference between the ejection fraction and shortening fraction, while left ventricle end-diastolic diameter and left ventricle end-systolic diameter were higher in patients with hypocalcaemia (Table 3).

Comparison of the biochemical and echocardiographic features of our cohort with previously published historical cases revealed that patients who have been reported to have dilated cardiomyopathy were older and had more severe biochemical features of vitamin D deficiency, except for the vitamin D level (Table 4). Receiver operating characteristic analysis revealed the best cut-off value of calcium level for developing dilated cardiomyopathy was 6.83 mg/dl (1.71 mmol/L), with a sensitivity and specificity of 88.5% and 84.9% (Fig 1).

Correlation analysis showed a statistically significant correlation between calcium, phosphorus, alkaline phosphatase, parathormone, and magnesium levels with ejection fraction (Fig 2 (a and b) and Table 5). Multiple linear regression analysis revealed that age of presentation, serum calcium, magnesium, and alkaline phosphatase are independent factors affecting ejection fraction. 25-hydroxy vitamin D and parathormone were not found as independent factors affecting ejection fraction (Table 5).

Discussion

The current study is the largest prospective study evaluating cardiac function in neonates with vitamin D deficiency. In this population, electrocardiographic and echocardiographic measurements were normal, and specifically, we did not find evidence for dilated cardiomyopathy, with no change in the echocardiographic parameters after vitamin D3 and calcium replacement.

In adult studies, vitamin D deficiency has shown to cause myocardial fibrosis, cardiac hypertrophy, ventricular dilatation, apoptosis, and negative inotropic effects, which eventually lead to various cardiac problems such as left ventricular dysfunction, hypertension, arterial calcification, inflammation, and even congestive heart failure.[5,17,30] There are also case reports of dilated cardiomyopathy and cardiac failure in children, which recovered after vitamin D and calcium therapy.[10,13,14,18–22]).

Although the mechanism behind cardiac dysfunction in vitamin D deficiency has not been fully elucidated, a low vitamin D level, elevated parathormone, and hypocalcaemia are suggested as possible factors.[2,23]

Studies evaluating cardiac function in children with vitamin D deficiency are scarce. In small-scale studies and a limited number of case reports, dilated cardiomyopathy and electrocardiographic changes (T wave abnormalities, prominent U wave, and long

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Table 4. Comparison of biochemical and echocardiographic findings of present cohort versus historical cases with dilated cardiomyopathy.

	Present cohort (Mean ± SD)	Historical cases (Mean ± SD)	P-value
Age of presentation (days)	3.4 ± 5.0	205.0 ± 108.0	<0.001
Biochemical investigations			
Calcium (mg/dl)	7.1 ± 0.5	5.8 ± 1.1	<0.001
Phosphorous (mg/dl)	6.3 ± 1.2	4.0 ± 2.1	0.015
ALP (U/L)	224.0 ± 82.7	1310.1 ± 865.1	<0.001
PTH (pg/ml)	133.6 ± 79.5	308.6 ± 294.8	<0.001
Magnesium (mg/dl)	1.8 ± 0.2	1.5 ± 0.3	<0.001
25(OH)D3 (ng/ml)	5.5 ± 2.4	5.8 ± 4.3	0.610
Maternal 25(OH)D3 (ng/ml)	7.1 ± 3.5	10.3 ± 8.9	0.443
Echocardiography			
EF (%)	69.3 ± 6.1	31.2 ± 13.9	<0.001
SF (%)	37.8 ± 4.3	21.1 ± 3.2	<0.001
LVEDd (mm)	20.2 ± 1.6	36.6 ± 5.9	<0.001
LVESd (mm)	14.8 ± 1.2	29.9 ± 7.1	<0.001

25(OH)D = 25-hydroxy vitamin D; ALP = Alkaline phosphatase; DCM = Dilated cardiomyopathy; EF: Ejection fraction; LVEDd = Left ventricle end-diastolic diameter; LVESd = Left ventricle end-systolic diameter; PTH = Parathyroid hormone; SF = Shortening fraction.

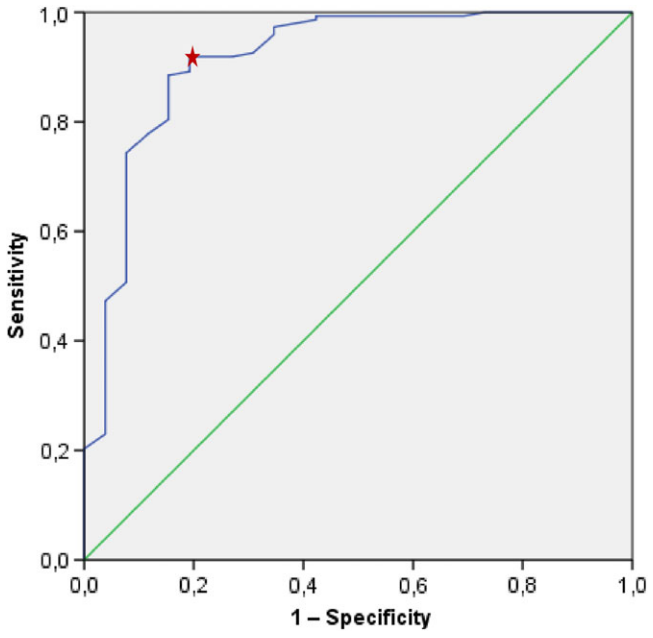

Figure 1. Receiver operating characteristic analysis has shown the calcium level of 6.83 mg/dl as the best cut-off for developing dilated cardiomyopathy, with a sensitivity of 88.5% and specificity of 84.9% [AUC: 0.914 (CI 0.843–0.984), p = 0.001].

Table 5. Correlation analysis between age and biochemical parameters versus ejection fraction (EF).

	Correlation analysis		Multivariate linear regression analysis		
	r	p	Beta	T	p
Age	−0.774	**<0.001**	−0.457	−7.679	**<0.001**
Calcium	0.600	**<0.001**	0.298	6.240	**<0.001**
Phosphorus	0.166	0.032	0.006	0.152	0.880
ALP	−0.663	**<0.001**	−0.196	−3.172	0.002
Magnesium	0.416	**<0.001**	0.087	2.069	0.040
PTH	−0.409	**<0.001**	−0.032	−0.684	0.495
25 (OH)D	−0.26	0.738	0.075	1.946	0.054

ALP = Alkaline phosphatase; 25(OH)D = 25-hydroxy vitamin D; PTH = Parathyroid hormone.

QT interval) have been reported, and which completely recovered after supportive therapy of heart failure along with treatment of vitamin D deficiency.[10–12,15,22,24,25] In the majority of the cases, the diagnosis was delayed for up to 1 year. Therefore, a diagnosis of rickets as an underlying aetiology has been made after excluding other etiologies and observing improvement of cardiac function in response to treatment for cardiac failure, dilated cardiomyopathy, and rickets. For instance, in two infants (at the age of 4 and 8 months) who were presented with acute respiratory distress and cardiac failure, a diagnosis of dilated cardiomyopathy due to vitamin D-deficient rickets was considered. While biochemical recovery was achieved 1 month following rickets treatment, complete recovery of the echocardiographic findings of dilated cardiomyopathy was not observed until after 1 year of follow-up.[22] In our study, none of the patients had clinical signs, electrocardiographic, or echocardiographic findings of dilated cardiomyopathy. There was no statistically significant change in the cardiac parameters in the second echocardiography performed after recovery of biochemical parameters. However, when compared to the historical cases with dilated cardiomyopathy, the age of diagnosis was earlier in our cases and the biochemical features of vitamin D deficiency were milder. We, therefore, suggest that the early recognition of vitamin D deficiency in neonates and infants would prevent the development of profound biochemical features of vitamin D deficiency and cardiological complications, such as dilated cardiomyopathy.

In a rat model, vitamin D has been shown to affect cardiac morphology and function through its effects on cardiomyocytes and vascular smooth muscle cells. Vitamin D deficiency causes an increase in collagen in the extracellular and myofibrillary area, which results in cardiac hypertrophy characterised by interstitial fibrosis.[26,27] In vitamin D receptor knock-out mice, elevated renin, myofibrillar hypertrophy, and dysfunction have been reported.[26,27] Physiological and morphological changes in myocardial tissue have been reported and occurred after prolonged vitamin D deficiency.[8,26-29] However, the duration of exposure to vitamin D deficiency, which leads to such changes, has not been reported. Also, the absence of difference between 25-hydroxy vitamin D in our cohort and historical cases with dilated cardiomyopathy due to vitamin D deficiency suggested that there is no clinically relevant role of short-term isolated vitamin D deficiency on developing dilated cardiomyopathy.

Hypocalcaemia negatively affects myocardial contraction, which results in ventricular dysfunction, followed by reversible dilated

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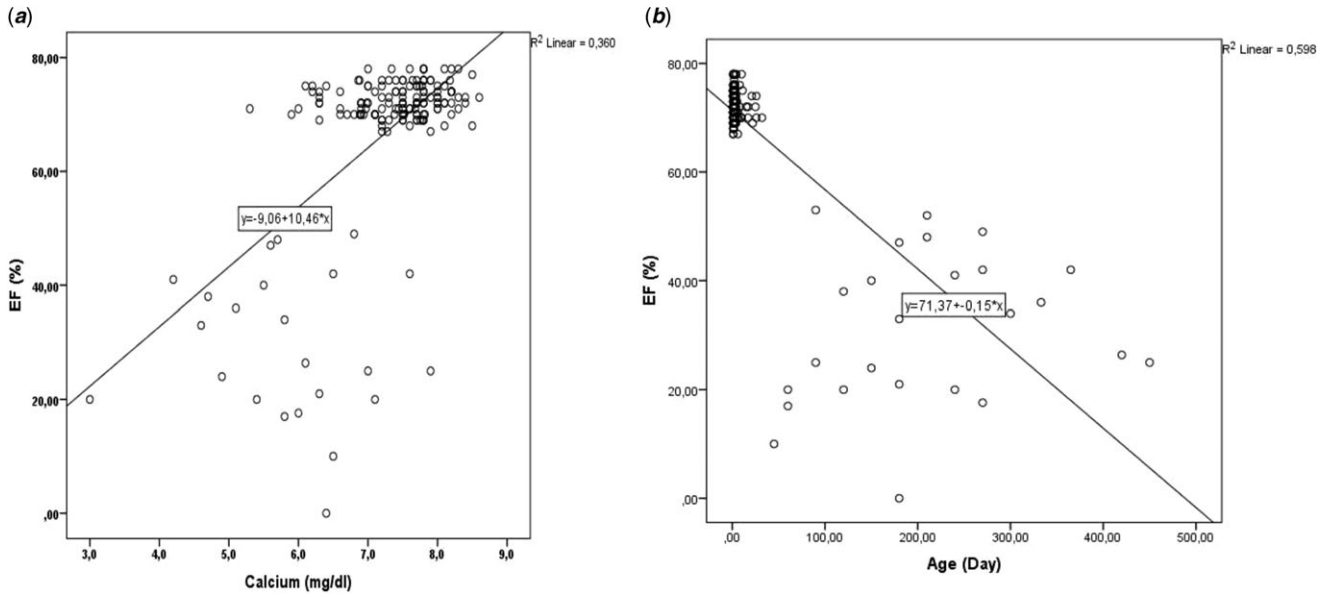

Figure 2. (***a*** and ***b***) Ejection fraction was positively correlated with calcium level and negatively with the age of presentation.

cardiomyopathy and eventually congestive heart failure. Infants and children with vitamin D deficiency can develop dilated cardiomyopathy, which is usually reversible and is attributed to prolonged hypocalcaemia.[10,18,20,21] However, the exact mechanism of dilated cardiomyopathy has not been fully elucidated. In our cohort, echocardiographic parameters (ejection fraction, shortening fraction, left ventricle end-diastolic diameter, left ventricle end-systolic diameter) did not show evidence of dilated cardiomyopathy or ventricular dysfunction. Comparison of these parameters between patients who were presented with normocalcaemia and hypocalcaemia in our cohort revealed no statistically significant difference for ejection fraction and shortening fraction, although left ventricle end-diastolic diameter and left ventricle end-systolic diameter were increased in the hypocalcemic group. Furthermore, all of these parameters were better in our cohort compared to the historical cases. Therefore, the development of dilated cardiomyopathy and deterioration of the cardiac parameters might require a certain time of exposure to more severe and prolonged hypocalcaemia. We have shown this with regression analysis, where the calcium level and age of presentation were found to be the most strong independent factors affecting the development of dilated cardiomyopathy. Although a calcium level of 6.83 mg/dl (1.71 mmol/L) was found as the best cut-off value associated with dilated cardiomyopathy with a sensitivity of 88.5% and specificity of 84.9%, it does not eliminate the requirement for exposure to hypocalcaemia for a longer duration. Previously reported cases were older, with presumably a delayed diagnosis of vitamin D deficiency when compared to our cases. The lack of dilated cardiomyopathy and cardiac failure in our cases was therefore attributed to the short duration of hypocalcaemia, and vitamin D deficiency, as the majority of our cases presented in the early postnatal period. Hence, it is critically important to recognise and treat vitamin D deficiency due to maternal vitamin D deficiency to prevent the development of other complications, particularly dilated cardiomyopathy, a life-threatening disorder.

There are studies reporting the relationship between increased parathormone levels and cardiac diseases.[5,28,31] Hyperparathyroidism has been reported to cause myocardial hypertrophy and diastolic dysfunction. Parathormone is thought to cause cellular overgrowth by increasing protein kinase C activity. Indeed, in the rat model, increased protein kinase C activity has been shown to influence the development of left ventricle hypertrophy.[31] Hence, Vitamin D replacement may decrease parathormone activity, thereby inhibiting protein kinase C and contributing to the recovery of dilated cardiomyopathy in rickets.[5,28,31] Nevertheless, although we detected a negative correlation between the parathormone level and echocardiography parameters, regression analysis did not confirm the parathormone level as an independent factor for the development of dilated cardiomyopathy.

The strength of the present study is that it is the first study to evaluate cardiac function in a large number of neonates with vitamin D deficiency due to maternal vitamin D deficiency. Second, to evaluate the predictive factors affecting the development of dilated cardiomyopathy, we compared the data of our cohort with a subset of historically reported cases with dilated cardiomyopathy due to vitamin D deficiency. Third, all of the neonates who we recruited had a 25-hydroxy vitamin D level below the value suggested as vitamin deficiency, and additional biochemical features of vitamin D deficiency including hypocalcaemia and elevated parathormone. Limitations of the study were the absence of X-ray examination to evaluate possible skeletal manifestations of vitamin D deficiency, the lack of comparison with a healthy control group, and the absence of longitudinal follow-up of patients with vitamin D deficiency who had not been treated.

In conclusion, in a large series of neonates with vitamin D deficiency, we did not detect echocardiographic evidence of a dilated cardiomyopathy or electrocardiographic abnormalities. In contrast to infants and children, vitamin D deficiency seen in the early neonatal period seems unlikely to be a cause of dilated cardiomyopathy. Therefore, the underlying aetiology of neonatal dilated cardiomyopathy should be extensively investigated even in the presence of biochemical features of vitamin D deficiency.

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Conflicts of interest. The authors have no conflicts of interest to declare.

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Ethical standards. This study protocol was approved by the local ethic committee (Protocol Number: 2017/08-54). The written informed form was taken from all parents.

Author contributions. A.C.: main author, designed and drafted the article and approved the final version. H.D.: critically revised the content of the article and approved the final version.

A.A, U.U.G, H.K, D.Y, E.K, D.V, A.K, G.B: made a substantial contribution to the study, and critically revised the content of the article and approved the final version.

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