Original Article

Comparison of Vitamin D Status Between Infants With Dilated Cardiomyopathy and Infants With Other Congenital Heart Diseases

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ABSTRACT

Background: Vitamin D plays an essential role in calcium homeostasis and cardiac muscle function, hence the significance of the screening, diagnosing, preventing, and treating of vitamin D deficiency (VDD). In children susceptible to VDD, cardiomyopathy is a likely occurrence. We sought to compare vitamin D status between children with dilated cardiomyopathy (DCM) and children with other congenital heart diseases.

Methods: This observational case-control study, conducted from 2018 through 2019 in Rajaie Cardiovascular Medical and Research Center, compared vitamin D status between a case group, consisting of 33 infants with DCM, and a control group, composed of 35 infants with other congenital heart diseases. The serum levels of iron, magnesium, calcium, albumin, parathyroid hormone, and 25(OH)D3 were measured in all the children.

Results: The study population consisted of 68 infants (31 males and 37 females) at a mean age of 64.96±51 days. The DCM group presented with a significantly higher incidence of VDD (27.3%) than the control group (8.6%). Multivariable-adjusted analysis for DCM based on the tertiles of vitamin D levels revealed an odds ratio of 0.25 (95% CI, 0.06 to 1.01) for tertile 3 (>24 nmol/L) compared with an odds ratio of 0.89 (95% CI, 0.24 to 3.30) for tertile 2 (16–24 nmol/L) and tertile 1 (<16 nmol/L) designated as the reference (P=0.05), indicating near statistical significance.

Conclusions: In assessing a child with newly diagnosed DCM or other congenital heart diseases, VDD and electrolyte imbalances should be promptly screened to avert the precipitating decompensation of the cardiovascular function. ***(Iranian Heart Journal 2022; 23(1): 160-171)***

KEYWORDS: Dilated cardiomyopathy, Infant, Vitamin D, Vitamin D deficiency

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Dilated cardiomyopathy (DCM) is classified by the World Health Organization as a heterogeneous disorder "characterized by dilation and impaired contraction of the left ventricle (LV) or both ventricles in the presence of normal wall thickness" [1,2] often necessitating cardiac transplantation in children. [2-4] Based on epidemiological studies, the overall annual incidence of pediatric cardiomyopathy ranges between 1.13 and 1.24 per 100 000 children, and incidence disparity is dependent on sex, ethnicity, race, and geographical components. [5, 6] DCM is responsible for the greatest proportion of cardiomyopathy cases in the pediatric population (51%–58.6%) [5,6] and is associated with significant morbidity and mortality. [7] The Pediatric Cardiomyopathy Registry (PCMR) reported that the 1- and 5-year rates of mortality and cardiac transplantation were 31% and 46%, respectively, among children with DCM. [8] The primary etiology of this disorder remains idiopathic in origin, with only 34% having an identified cause. [8] The identified etiologies include idiopathic origins (66%), myocarditis (16%), neuromuscular disorders (9%), familial DCM (5%), inborn metabolic errors (4%), and malformation syndromes (1%). [5,8] Moreover, specific nutritional deficiencies in carnitine, selenium, calcium, and taurine have been attributed to DCM development. [9]

Vitamin D is a fat-soluble vitamin primarily derived from exposure to ultraviolet radiation from the sun. This vitamin is found in selected dietary sources and has a crucial role in calcium and phosphorus homeostasis, bone mineralization, and bone mass acquisition. [10] Although a plethora of epidemiological evidence implicates vitamin D deficiency (VDD) in the pathogenesis of cardiovascular disease in adults [11-15] and its risk factors in children, [16-26] definite causality remains in doubt largely due to confounding variables. Additionally, research on vitamin D supplementation in large-scale randomized controlled trials has proven inconclusive thus far as a preventative strategy in lowering the incidence of cardiovascular disease in adults [27-29] and cardiometabolic outcomes in children. [30-35]

Studies on vitamin D3-depleted rats have demonstrated that vitamin D3 has the capacity to regulate ventricular and vascular contractility, [36] modulate cardiac morphometry (including myocardial growth and c-Myc levels), [37] and modify the extracellular matrix and myocardial collagen independent of calcium levels. Such findings imply a significant role for vitamin D, rather than calcium, in the above effects.[38] Further validation for the role of vitamin D3 in the cardiovascular function was demonstrated by investigations on vitamin D receptor (VDR)-CYP27B1 knockout mice, which exhibited hypertension, cardiac hypertrophy, elevated levels of atrial natriuretic peptide (ANP), increased expressions of ANP mRNA, elevated expressions of renal and cardiac renin mRNA, upregulated renin-angiotensin-aldosterone systems (subsequently remedied by calcitriol therapy), modulated cardiac extracellular matrices, downregulated tissue inhibitors of metalloproteinases, upregulated metalloproteinases, and impaired fibroblast homeostasis with resultant progressive ventricular dilation and failure and dissociated electromechanical coupling. [39-43]

VDRs are widely dispersed within the cardiovascular system. [44, 45] These receptors can be found in cardiomyocytes, [46] vascular smooth muscles, [47] and endothelia. [48] Cardiomyocyte-targeted gene deletion in VDR knockout mice exerts a direct antihypertrophic effect on cardiomyocytes, partially attributed to the inhibition of the calcineurin/NFAT/MCIP1 signaling cascade. [49]

Recent studies in adults have established a potential role for VDD in patients with DCM and impaired LV remodeling as indicated by echocardiographic parameters.

[50,51] Furthermore, the Vitamin D Treating Patients with Chronic Heart Failure (VINDICATE) trial established that high-dose vitamin D supplementation led to statistically significant improvements in the left ventricular ejection fraction (LVEF) and LV end-systolic and end-diastolic diameters, implicating the role of vitamin D in the reversal of cardiac remodeling. [52]

Given the resurgence of rickets globally, [53] one of the most common sequelae of vitamin D-deficient in infants with rickets is DCM as documented by numerous case reports or series. [54-75] The complications of VDD with or without hypocalcemia include DCM, hypocalcemic convulsions and tetany, proximal myopathy, osteomalacia, and rickets in neonatal and pediatric populations. [76] Moreover, the sequelae of DCM from VDD include prolonged QTc intervals, [77-79] cardiac failure, [70] echocardiographic anomalies (LV dysfunction indices), [72-74, 77-79] cardiogenic shock, [58, 71] cardiopulmonary arrest, [72] and even death. [72]

The vital role of vitamin D in calcium homeostasis and cardiac muscle function requires the screening, diagnosing, preventing, and treating of VDD. Such actions are considered crucial elements in preventing the occurrence of cardiomyopathy, especially in children susceptible to VDD. In this observational case-control study, we aimed to compare vitamin D status between a group of infants with DCM and a group of infants with other congenital heart diseases.

METHODS

Study Population

From 2018 through 2019, the present observational case-control study enrolled 68 eligible children with a confirmed diagnosis of cardiac disease from the Pediatric Cardiology Department of Rajaie Cardiovascular Medical and Research Center, Tehran, Iran. The study population consisted of 68 infants (31 males and 37 females) at a mean age of 64.96±51 days. The patients were divided into a case group, consisting of 33 infants with DCM, and a control group, composed of 35 infants with other congenital heart diseases.

Children were excluded if they had one of the following concurrent disorders: 1) primary hyperparathyroidism, 2) hypercalcemia, 3) chronic renal insufficiency, and 4) chronic liver disease. Also excluded were patients already receiving vitamin D and/or calcium supplements. The study protocol was approved by the institutional ethics committee, and written informed consent was acquired from all the parents or legal guardians of the infants. The study was performed in accordance with the doctrines of the Declaration of Helsinki.

Laboratory Analysis

Venous blood samples were acquired during the initial stages of clinical presentation and admission. Subsequently, centrifugation was applied to separate the serum, which was instantly dispatched to the biochemical laboratory for further analysis. The serum levels of iron, magnesium, calcium, and albumin were measured via automated standard laboratory procedures. The concentration of serum 25(OH)D3 was determined via a radioimmunoassay technique utilizing the Architect i2000 (Abbott Laboratories). The concentration of serum parathyroid hormone (PTH) was evaluated via an immunoassay method (Siemens Immulite, Siemens Health-care Diagnostics, Deerfield, IL, USA).

Statistical Analysis

For the determination of differences in general characteristics between the DCM cases and the controls, the analysis of variance and the χ^2 test were employed for continuous and categorical variables, respectively. The association between serum vitamin D levels and DCM was determined using multivariable

logistic regression models across tertiles. The model was adjusted for confounding variables such as age and sex. All the statistical analyses were executed using the SPSS statistical software, version 16.0, (IBM Co, Chicago, IL). A *P* value less than 0.05 was deemed statistically significant.

RESULTS

Table 1 summarizes the demographic, clinical, and biochemical characteristics of the cases and controls. The mean age of the DCM cases was significantly higher than that of the control group (77.85±53.72 d vs 52.80±45.77 d; *P*=0.048). Moreover, the infants in the DCM group were of a significantly higher weight (25.70±17.84 kg vs 15.24±9.09 kg; *P*=0.04) and height (116± 32.56 cm vs 99±29.58 cm; *P*=0.028) and demonstrated statistically significant differences in the serum levels of calcium (9±0.75 mg/dL vs 8.58±0.88 mg/dL; *P*=0.037) and magnesium (2.16±0.57 mg/dL vs 2.06±0.50 mg/dL; *P*=0.037). Additionally, the DCM group presented with a significantly higher incidence rate of VDD (27.3%) than the control group (8.6%). No other statistically significant differences were observed vis-à-vis the other variables measured. Multivariable-adjusted odds ratios (ORs) for DCM based on the tertiles of vitamin D levels are presented in Table 2. After adjustments for the covariates of age and sex, the results demonstrated an odds ratio of 0.25 (95% CI, 0.06 to 1.01) for tertile 3 (>24 nmol/L) compared with an odds ratio of 0.89 (95% CI, 0.24 to 3.30) for tertile 2 (16–24 nmol/L) and tertile 1 (<16 nmol/L) designated as the reference (*P*=0.05), indicating near statistical significance.

Table 1. Selected characteristics of the cases and controls participating in the study

Characteristics	Normal Reference Range	DCM Group (n=33)	Control Group (n=35)	*P* value [b]
Age (d)		77.85 ±53.72	52.80 ± 45.77	0.043
Height (cm)		116± 32.56	99 ± 29.58	0.028
Weight (kg)		25.70±17.84	15.24±9.09	0.04
Birth weight (kg)		2.97± 0.52	3.08± 0.59	0.387
Vitamin D (nmol/L)	>50 nmol/L	24.66±16.42	21.18±11.79	0.323
Total calcium (mg/dL)	9.0-11.0 mg/dL	9±0.75	8.58±0.88	0.037
Magnesium (mg/dL)	1.8-2.6 mg/dL	2.16±0.57	2.06±0.50	0.037
Iron (µg/dL)	40.0-100.0 µg/dL	66.12±29.78	71.48±40.69	0.536
Albumin (g/L)	30-45g/L	44.81±9.13	42.77±6.05	0.284
Parathyroid hormone (pmol/L)	0-6.5 pmol/L	45.64±30.79	40.21±27.06	0.536
Vitamin D levels				
Deficiency (<12 nmol/L)		27.3	8.6	0.043
Normal (>12 nmol/L)		72.7	91.4	

a) The data are presented as the mean ± the SD or n (%).
b) The independent samples *t* test was used for continuous variables and the χ^2 test for categorical variables.

Table 2. Odds ratios and confidence intervals for the association between serum vitamin D levels and cardiomyopathy

	Tertile 1 <16	Tertile 2 16-24	Tertile 3 >24	*P* value for Trend
Case/control	10/13	9/14	14/8	-
Crude	Ref	1.19 (0.39-3.87)	0.44 (0.13-1.45)	0.184
Model 1[a]	Ref	0.89 (0.24-3.30)	0.25 (0.06-1.01)	0.050

a) Adjusted for age and sex

DISCUSSION

In this case-control study, we observed statistically significant differences in the serum levels of calcium, magnesium, and vitamin D between infants with DCM and infants with other congenital heart diseases. A prior case-control study observed a low vitamin D level in children with other congenital heart diseases, similar to our study. [80] Furthermore, our adjustments of the covariates of age and sex revealed that infants in the higher tertile of vitamin D levels had a lower incidence rate of DCM (tertile 2 =11%; tertile 3 =75%) than infants in the lower tertile (a near-significant *P* value for trend =0.05). These results are corroborated by similar findings in previous pediatric case series or reports, case-control studies, and epidemiological population-based studies on DCM, detailed below.

A retrospective case-series review in England assessed 16 exclusively breastfed infants of non-Caucasian descent with DCM and confirmed VDD and hypocalcemia (median age at presentation =5.3 mon; range =3 wk–8 mon). The results showed cardiac failure in 62.5% of the study population and cardiopulmonary arrest in 37.3%, necessitating invasive mechanical ventilation in 50%, extracorporeal life support in 12.5%, inotropic support in 75%, and cardiac transplantation referrals in 12.5%. Ultimately, 18.8% of the infants succumbed to death, whereas the surviving infants responded to correction with vitamin D and calcium supplementation, conferring the normalization of the LV fractional shortening (mean =12.4 months since presentation). [72]

Likewise, in the United States, a retrospective analysis of 4 exclusively breastfed infants of African-American descent with DCM recorded hypocalcemia, elevated levels of PTH and alkaline phosphatase, a reduced level of vitamin D (accompanied by radiological evidence of nutritional rickets in all the infants), a moderately to severely dilated LV, and a reduced LV function (median LVEF =33.5% [21%–38%]), and LV fractional shortening of 13% (10%–20%), requiring ventilation and inotropic support in 50%. All the infants responded to vitamin D and calcium replacement, with the restoration of the cardiac function in 75% within 1 to 5 months. Nevertheless, 1 infant had recovery over a protracted duration of 33 months. [67]

Similarly, in India, a retrospective study evaluated 15 infants with VDD and hypocalcemia (with coexistent hypomagnesemia in some infants) at a median age at presentation of 2 months (45 d–5 mon) admitted with LV dysfunction. The results detailed congestive heart failure in 80% of the study population, congestive heart failure and cardiogenic shock in 20%, convulsions in 46.6%, prolonged QTc intervals (median =0.52 s [range =0.51 s–0.58 s]), and diminished LVEFs (median =20% [range =15%–30%]). Among the infants, 93.3% responded to supplementation and 6.7% succumbed to death from refractory hypocalcemia with secondary tetany and aspiration. [77]

Another retrospective analysis from India assessed 12 predominantly breastfed infants with DCM secondary to VDD and hypocalcemia, accompanied by elevated alkaline phosphatase and PTH. The results demonstrated congestive heart failure in 83.3% of the study population, convulsions in 16.7%, and prolonged QTc intervals and reduced LVEFs in 100%. Crucially, the infants responded to vitamin D and calcium amendment, with 83.3% having stabilized LVEFs by a median of 3 months (range =2 mon–5 mon) from clinical presentation. [79]

A retrospective case series of 3 breastfed infants (100% non-Caucasian) with DCM secondary to VDD and hypocalcemia in Ireland recorded a median LV fractional shortening of 10% (5%–16%). In addition,

33.3% of the study population required inotropic support and 66.6% ventilation. Fortunately, all the patients responded to vitamin D and calcium replacement, with the normalization of LV fractional shortening (median =37% [34%–41%]) by 6 months.

A retrospective case series of 6 breastfed infants (50% Caucasian) in Scotland with VDD-induced DCM reported hypocalcemic seizures in 16.7%, ventilation support in 66.7%, inotropic support in 66.7%, extracorporeal life support in 16.7%, and survival in 83.3%. [74]

In the majority of these case series, the recommendation of maternal and infant vitamin D supplementation was disregarded and overlooked. [72-74,79]

More recently, a retrospective case series of DCM from a national pediatric population (N=53), reported an etiology of VDD in 13.2% (n=7). From this total, 4 children were of Asian or Black lineage, and 3 had Caucasian origins. The median age at the diagnosis of VDD was 7 months (range =0 mon–9 mon). Additionally, of the children with VDD, 85.7% (n=6) responded to oral supplementation, and 1 child needed extracorporeal life support to assist as an interim measure in recovery. However, 1 child succumbed to end-stage cardiac failure and death within the first year of diagnosis, secondary to poor compliance with dietary modification, vitamin D correction, and clinical follow-up. [81]

The incidental finding of VDD could be purely coincidental, and the etiology of DCM cases could be secondary to other causative factors. Several risk factors may account for VDD in infants, including non-Caucasian descent with dark skin pigmentation, inadequate dietary intakes, malabsorption (eg, celiac disease, inflammatory bowel disease, and small bowel disease), chronic therapies (eg, anticonvulsants), defective 25-hydroxylation (eg, hepatic disease/failure), the loss of the vitamin D-binding protein (eg, nephrotic syndrome), defective 1-α, 25-hydroxylation (eg, chronic kidney disease/failure, hypoparathyroidism, and 1-α hydroxylase deficiency), and hereditary vitamin D-resistant rickets. [82]

A previous investigation reported that the significant maternal risk factors attributable to VDD in breastfed neonates included a low socioeconomic class, women wearing long robes and head coverings, low education levels, and low maternal serum vitamin D levels (<25 nmol/L). A significant association was also observed between maternal and newborn serum vitamin D levels (r =0.63; P=0.01). [83]

Despite the rarity of hypocalcemic-associated DCM, it is more universally characterized in relation to hypoparathyroidism in adults [84,85] compared with severe VDD as the precipitating factor in children. [58,61,72,77,79] Calcium plays a crucial role in modulating myocardial excitation-contraction coupling. [86,87] Consequently, hypocalcemia can lead to diminished cardiac contractility and DCM pathogenesis. [79] Prompt identification and supplementation in the clinical cases of hypocalcemia are crucial as the restoration of normocalcemia can often remedy and reverse an otherwise refractory case of cardiac failure. The instigation of a cardiac action potential amid the extensive arrangement of T-tubules expanding along myocardial fibers with the resultant precipitous influx of extracellular calcium ions via voltage-gated dihydropyridine calcium channels initiates myocardial membrane depolarization, with subsequent calcium release from the sarcoplasmic reticulum via ryanodine-sensitive calcium-release channels. [86,88] Cardiomyocyte contraction is generated by the attachment of calcium ions to myofilament proteins, including the troponin-tropomyosin complex, which promotes the cross-linking

of actin and myosin myofilaments and leads to muscle contraction. [86,88]

VDD is deemed to have direct effects on the myocardium, including aggressive adverse remodeling secondary to cardiomyocyte hypertrophy, interstitial inflammation and fibrosis, hypertension, the renin-angiotensin-converting system amplification with resultant cardiac dysfunction, and cardiomyocyte apoptotic loss, in addition to indirect effects by enhancing calcium intestinal absorption and augmenting serum calcium. [39,42,49, 9-91] The additional indirect effects of VDD include secondary hyperparathyroidism (elevated PTH levels) and reduction in insulin-like growth factor-1 (IGF-1), further contributing to myocardial dysfunction. [92-94] Elevated levels of PTH in DCM have been observed in adult and pediatric subjects [51,67,72,74,77,79] and are typically perceived as a surrogate biomarker of calcium deprivation.

Recent global consensus recommendations on vitamin D status are categorized into 3 groups: 1) sufficiency (>50 nmol/L), 2) insufficiency (30–50 nmol/L), and 3) deficiency (<30 nmol/L). [95] A combination of a minimal transfer of circulating maternal vitamin D and 25(OH)D3 and human milk is acknowledged to provide insufficient quantities (5–80 IU/d) of vitamin D in predominantly breastfed infants, necessitating supplementation in mothers and infants. [96] During pregnancy and lactation, mothers are advised to consume 600 IU/d of vitamin D, and infants are supplemented with 400 IU/d of vitamin D, independent of the mode of feeding for up to 12 months to prevent the complications of nutritional rickets and hypocalcemia. [95]

Identifying the etiology of DCM enables clinicians to stratify risks, provide prognoses, devise appropriate treatment strategies, and counsel parents accordingly with preventative strategies in the instance of VDD, which is wholly preventable.

Limitations

Numerous population-based pediatric case series of DCM have not reported VDD as a definitive attributable or causative factor. The present observational case-control study has a relatively small sample size to draw any conclusive findings or imply a firm causal link between VDD and DCM. Additionally, the sample size limits the generalization to all cases of DCM. Furthermore, the echocardiographic indices measuring the extent of cardiac failure and eventual outcomes (eg, the proportion of responders to vitamin D supplementation, cardiac transplantation, and death) have not been evaluated for prognostication purposes. Moreover, a single measurement of the vitamin D level does not provide a true longitudinal assessment over time in relation to the natural evolution and resolution of DCM pathophysiology.

Future prospective randomized controlled studies with large sample sizes of children with DCM and adequate follow-up periods are required to determine the precise role of vitamin D in the pathophysiology of DCM and cardiac failure. Nevertheless, the current study among others highlights the need for the supplementation of all pregnant mothers and infants, particularly those in vulnerable groups living in endemic areas where rickets is highly prevalent. Moreover, a global consensus is urgently required surrounding the potential benefits of the fortification of foods with vitamin D given that it is not universally implemented.

CONCLUSIONS

This observational case-control study highlights the significance of the prompt screening for VDD and electrolyte imbalances in assessing a child with newly diagnosed DCM or congenital heart disease to avert precipitating decompensation of the cardiovascular function. More importantly, vitamin D and/or calcium supplementation is

warranted in breastfed infants to promote musculoskeletal health and optimum cardiac function in populations residing in areas endemic to nutritional rickets and other vulnerable populations.

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