Pediatr Cardiol (2012) 33:713–719
DOI 10.1007/s00246-012-0199-6

ORIGINAL ARTICLE

Vitamin D Supplementation in Infants With Chronic Congestive Heart Failure

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Received: 6 September 2011 / Accepted: 22 November 2011 / Published online: 18 February 2012

Abstract Increased circulating proinflammatory cytokines may contribute to the pathogenesis of congestive heart failure (CHF). In vitro studies have suggested that vitamin D suppresses proinflammatory cytokines and increases anti-inflammatory cytokines. The aim of this work was to evaluate the effect of vitamin D supplementation on renin-angiotensin system cytokines as well as different clinical, biochemical, and echocardiographic variables in infants with chronic CHF. This was a double-blind, placebo-controlled intervention study and included 80 infants with CHF. The intervention consisted of either giving Vitamin D_3 oral drops (group I) or placebo oral drops (group II). In both study groups, baseline 25-hydroxyvitamin D [25(OH)D] concentrations were below the lower end of the reference range. After 12 weeks of intervention, vitamin D supplementation for group I infants caused significant improvement of HF score, left-ventricular (LV) end-diastolic diameter, LV end-systolic diameter, LV ejection fraction%, and myocardial performance index together with markedly increased serum 25(OH)D and interleukin (IL)-10 and decreased PTH, IL-6, and TNF-α compared with the placebo group; these differences were statistically significant ($p < 0.001$). Vitamin D supplementation has great benefits as an anti-inflammatory agent in infants with CHF. It helps acceleration of the clinical improvement and cytokine profile balance.

Keywords Vitamin D · Congestive heart failure · Renin-angiotensin system cytokines · Tumor necrosis factor-α

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Introduction

Congestive heart failure (CHF) refers to a clinical state of systemic and pulmonary congestion resulting from the heart's inability to pump as much blood as required for the adequate metabolism of the body [10]. The cause of HF is not fully understood. In recent years, ideas about the pathophysiologic concept of chronic HF has changed from an isolated hemodynamic view to a more complex concept involving neurohormonal overactivation and increased concentrations of proinflammatory cytokines, such as tumor-necrosis factor alpha (TNF-α) and interleukins (ILs) [12]. Increased circulating levels of cytokines, in particular TNF-α and IL-6, have been associated with increased mortality in patients with HF [9]. IL-10 is an anti-inflammatory cytokine with broad immunoregulatory activity, influencing both the innate and cell-mediated branches of the immune system, and it is a major inhibitor of cytokine synthesis. It suppresses macrophage function and inhibits the production of proinflammatory cytokines as well as matrix metalloproteinase, all of which have previously been described as important mediators in CHF [3]. IL-10 is seen as a natural antagonist to TNF-α by inhibiting nuclear factor kappa B [3]. Interestingly, experimental studies have shown that the vitamin D hormone calcitriol can suppress the release of TNF-α [19]. Moreover, calcitriol effectively upregulates the synthesis of the anti-inflammatory cytokine IL-10 and induces IL-10 receptor expression in vitro [2]. In addition to these systemic effects, there may be local implications as well. The vitamin D receptor, which is widely distributed throughout human tissues, has been identified in human cardiomyocytes, where it regulates many important physiologic processes, including calcium influx, myocyte proliferation, and hypertrophy. In addition,

enzymes necessary for the conversion of vitamin D precursors to calcitriol have been isolated in heart tissue [7].

In the pediatric cardiology field, there used to be a historical belief that calcium and vitamin D administration to patients under antifailure treatment (specifically digoxin) carried hazards of malignant dysrhythmias or increased mortality, but many recent studies have proven that there is no support for the belief that calcium or vitamin D administration is contraindicated in digoxin-treated or even digoxin-toxic patients [8].

Animal studies first showed vitamin D to inhibit the renin-angiotensin-aldosterone system, the activation of which contributes to the salt and water retention seen in HF [5].

Vitamin D deficiency may play a role in the pathogenesis of chronic HF; thus, the aim of this work was to evaluate the effect of vitamin D supplementation on renin-angiotensin system (RAS) cytokines as well as different clinical, biochemical, and echocardiographic variables in infants with chronic CHF.

Subjects and Methods

This was a double-blind, placebo-controlled intervention study performed in the Cardiology Unit of the auspices of Pediatric Department of Gharian Teaching Hospital during April 2008 to July 2010. The target sample comprised 80 infants selected randomly from those admitted with congestive HF due to dilated cardiomyopathy or congenital heart diseases and with systemic left-ventricular (LV) systolic dysfunction (dilated left ventricle >2 SD for age and sex together with an ejection fraction [EF] <40%). After obtaining approval of the protocol from the Hospital Ethics Committee and obtaining written consent from the parents, we obtained the following for all patients included in this study before treatment was started: (1) complete history by way of a standardized clinical cardiology sheet; (2) complete physical examination with determination of HF score (Ross scoring system of HF in infants) [10]; and (3) initial studies, including plain X-ray chest, electrocardiogram (ECG), echocardiography (Philips Ie33 echocardiography medical system; Palo Alto, CA] with an S4 to 12-MHz transducer and simultaneous ECG and phonocardiogram recording. The imaging planes consisted of the parasternal long- and short-axis views followed by the apical four- and two-chamber views. From the apical window, a pulsed Doppler cursor was positioned at the level of the mitral annulus to detect mitral regurgitation and record annular inflow velocities. Echocardiographic measurements, including M-mode LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD), septal (IVS) and posterior wall (PW) thickness, EF%, and fractional shortening (FS%), were measured according to Snider et al. [13]. Doppler studies on the mitral valve were used to determine peak early (E) and atrial (A) velocities. The ratio of E-wave to A-wave (E/A) is a commonly used index of diastolic function [14]. The Doppler-derived LV myocardial performance index (MPI), combining systolic and diastolic functions, was calculated using the formula IVCT + IVRT/ET [14].

Laboratory Investigations

Levels of 25(OH)D were measured by radioimmunoassay (DiaSorin, Stillwater, MN). As indicated by other data analyses, the reference range for adequate 25(OH)D concentrations is 33 to 90 ng/mL. The intra-assay and interassay coefficient of variabilities were 7.0 and 9.0%, respectively. Intact parathyroid hormone (PTH) was assayed by DSL-8000 ACTIVE Intact PTH Immunoradiometric Kit (Diagnostic Systems Laboratories, Webster, TX) (reference range 16–46 pg/mL) TNF-α levels were measured by competitive enzyme immunoassay using the Acucyte Human TNF-α kit provided by Cytimmune Sciences, College Park, MD.

IL-10 levels were measured with a highly sensitive enzyme-linked immunosorbent assay (ELISA) kit (R&D, Minneapolis, MN), and IL-6 levels were measured with an ELISA kit from Bio-Source International Inc. (Camarillo, CA). Calcium was assessed with the use of atomic absorption spectrometry (AAS 3030; Perkin Elmer, Ueberlingen, Germany); the CVs were 2.5%. Concentrations of phosphorus and creatinine were measured enzymatically with the use of routine methods (Wako Chemicals, Neuss, Germany). Albumin was measured with a colorimetric test kit (BioMérieux, Nürtingen, Germany).

The results of these initial investigations were recorded to serve as a baseline for the sample (preintervention data). The intervention consisted of antifailure treatment (digoxin, captopril, and spironolactone) in combination with either Vitamin D_3 oral drops or placebo drops. Infants included in the study were properly matched together regarding age and sex. All infants were on the same regimen of antifailure treatment.

Subjects randomly allocated by systematic random sampling into two groups: group I included 42 patients who received a daily supplement of 25 μg (1,000 IU) cholecalciferol (D-Vi-Sol Infant Drops; Mead Johnson Nutritionals), and group II included the other 38 subjects who received the placebo oral drops (vitamin D-free distilled water). Both groups and the investigators were unaware with the nature of the oral drops bottles (the vitamin D and placebo bottles were identical in shape). The intervention continued for 12 weeks after initiation of treatment with weekly follow-up to check for group adherence to the treatment regimen and any side effects. After 6 weeks and

Table 1 Preintervention sociodemographic and clinical characteristics of the studied groups

Group parameter	Group I ($n = 42$)	Group II ($n = 38$)	t	p
Age (months)	10.3 ± 4.6	11.2 ± 3.5	0.977	0.3316
No. (%) sex				
Male	27 (64.29)	22 (57.89)	0.127	0.7217
Female	15 (35.71)	16 (42.11)		
Body weight (kg)	8.60 ± 1.6	8.41 ± 1.9	0.511	0.6109
Duration of illness (mo)	5.39 ± 2.1	5.11 ± 1.9	1.875	0.0645
Underlying cardiac cause				
Dilated cardiomyopathy	25 (59.52)	23 (60.35)	0.022	0.9891
VSD	11 (26.19)	10 (26.32)		
ECD	6 (14.29)	5 (13.16)		
HR (bpm)	154.0 ± 23.9	149.3 ± 26.4	0.836	0.4058
SBP (mm Hg)	82.42 ± 8.31	83.6 ± 6.41	0.706	0.4825
DBP (mm Hg)	39.61 ± 7.41	41.50 ± 6.8	1.184	0.2398
HF score	9.11 ± 2.70	9.61 ± 1.71	0.978	0.3313

VSD ventricular septal defect, *ECD* endocardial cushion defect, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

again at the end of the intervention period (12 weeks), the previous investigations were repeated and their results recorded to serve as postintervention data. Preintervention and postintervention data were analyzed and are presented here using appropriate statistical methods.

Exclusion Criteria

Any infant with hypercalcemia, hypocalcemia, serum creatinine concentration >1.5 mg/dl, and nephrolithiasis or on actual intake of supplements containing vitamin D and calcium were excluded from participation.

Statistical Analysis

The collected data in this study were statistically presented and analyzed using SPSS software statistical package version 11.0 (SPSS, Chicago, IL. Quantitative data were expressed as mean and SD (X ± SD). Student t test was used to compare two groups of normally distributed data. The comparison of means was determined using analysis of variance to test for more than two groups. Qualitative data were expressed as numbers, and percentages were tested by χ^2 and Fisher exact tests. A p-value <0.05 was considered significant.

Results

Demographic and clinical characteristics before intervention were properly matched between both groups, and the differences were statistically insignificant ($p > 0.05$) (Table 1). Preintervention data among both studied groups showed that the mean of echocardiographic findings, 25(OH)D, PTH, cytokines, and TNF-α values were insignificantly different ($p > 0.05$ respectively). Baseline 25(OH)D concentrations were lower than the normal reference range (33–90 ng/ml) in both groups, but the TNF-α levels were higher than the generally accepted normal level of 6 pg/ml (Table 2). Postintervention data showed that vitamin D supplementation for patients in group I significantly increased the mean levels of EF%, FS%, E/A ratio, serum levels of calcium, 25(OH)D, and IL10 at 6 weeks after intervention, with there being a more pronounced increase of these variables at 12 weeks after intervention. Although mean levels of heart rate (HR), HF score, LVEDD, LVESD, MPI, serum PTH, IL-6, and TNF-α had significantly decreased at 6 weeks after intervention, there was a more significant decrease of these variables at 12 weeks after intervention. The differences were statistically significant ($p < 0.001$) (Table 3). Postintervention data among patients in group II showed significant improvement in HR, blood pressure, LVEF%, LVFS%, and E/A ratio ($p < 0.01$), but there were no improvement in biochemical variables, including PTH, 25(OH)D, and TNF-α compared with preintervention data ($p > 0.05$). Moreover, mean serum levels of IL-6 and IL-10 showed more significant deleterious effects ($p < 0.001$) (Table 4).

When comparing postintervention data between both groups, vitamin D supplementation for group I infants significantly improved HF score, LVEDD, LVESD, LVEF%, and MPI together with marked improvement of serum 25(OH)D, PTH, IL-10, 1-L6 and TNF-α compared with the non-vitamin D supplemented placebo group II infants ($p < 0.001$) (Table 5).

Discussion

Increased circulating concentrations of proinflammatory cytokines may contribute to the pathogenesis of CHF.

Table 2 Preintervention echocardiographic and laboratory findings among the studied groups

Group parameter	Group I ($n = 42$)	Group II ($n = 38$)	t	p
LVEDD (mm)	32.81 ± 4.6	30.7 ± 5.2	1.895	0.0618
LVESD (mm)	24.52 ± 3.78	23.7 ± 3.91	0.848	0.398
EF%	36.4 ± 2.26	37.2 ± 2.62	1.466	0.1467
FS%	21.0 ± 2.93	21.4 ± 2.72	0.631	0.5300
E/A ratio	1.18 ± 0.75	1.27 ± 0.64	0.574	0.5674
MPI	0.68 ± 0.28	0.66 ± 0.31	0.303	0.7625
Serum calcium (mg/dl)	9.13 ± 2.42	9.91 ± 2.75	0.381	0.7045
Serum phosphorus (mg/dl)	4.11 ± 0.87	3.94 ± 0.91	0.854	0.3958
Serum albumin (gm/dl)	4.63 ± 1.13	4.82 ± 0.97	0.803	0.4245
Serum creatinine (mg/dl)	0.83 ± 0.35	0.79 ± 0.18	1.383	0.1705
PHT (pg/ml)	40.5 ± 6.25	39.8 ± 7.22	0.465	0.6434
25(OH)D (ng/ml)	13.4 ± 2.21	14.0 ± 2.46	1.1492	0.5027
IL-10 (pg/ml)	1.25 ± 0.23	1.18 ± 0.26	1.278	0.2051
IL-6 (pg/ml)	30.4 ± 4.62	29.8 ± 3.81	0.630	0.5306
TNF-α (ng/ml)	13.42 ± 0.94	13.11 ± 1.6	1.069	0.2885

Table 3 Means ± SDs of clinical, echocardiographic, and laboratory findings among patients in Group I[a]

Time parameter	Before intervention	6 Weeks after intervention	12 Weeks after intervention	F	p
HR (bpm)	154.0 ± 23.9	130.6 ± 15.4	124.2 ± 18.3	14.45	0.0000
SBP (mm Hg)	82.42 ± 8.31	80.4 ± 4.94	79.8 ± 3.29	6.550	0.0019
DBP (mm Hg)	39.61 ± 7.41	43.72 ± 3.9	45.7 ± 4.31	11.82	0.0000
HF score	9.11 ± 2.70	7.26 ± 1.42	6.38 ± 1.15	23.01	0.0000
LVEDD (mm)	32.81 ± 4.6	26.3 ± 3.81	24.9 ± 3.11	49.50	0.0000
LVESD (mm)	24.52 ± 3.78	19.8 ± 4.22	16.2 ± 3.67	48.14	0.0000
EF%	36.4 ± 2.26	49.5 ± 3.28	52.2 ± 4.73	237.0	0.0000
FS%	21.0 ± 2.93	25.4 ± 3.84	28.9 ± 3.38	56.80	0.0000
E/A ratio	1.18 ± 0.75	1.38 ± 0.76	1.36 ± 0.44	6.106	0.0029
MPI	0.68 ± 0.28	0.53 ± 0.08	0.51 ± 0.06	12.30	0.0000
Serum calcium (mg/dl)	9.13 ± 2.42	9.62 ± 1.33	10.41 ± 1.2	18.33	0.0000
Serum phosphorus (mg/dl)	4.11 ± 0.87	3.99 ± 0.64	3.92 ± 0.61	0.756	0.4716
Serum albumin(gm/dl)	4.63 ± 1.13	4.38 ± 1.98	4.42 ± 1.65	1.009	0.4801
Serum creatinine (mg/dl)	0.83 ± 0.35	0.73 ± 0.22	0.84 ± 0.26	1.954	0.1459
PHT (pg/ml)	40.5 ± 6.25	32.36 ± 5.3	28.32 ± 4.7	54.34	0.0000
25(OH)D (ng/ml)	13.4 ± 2.21	22.43 ± 2.4	32.89 ± 2.3	71.63	0.0000
IL-10 (pg/ml)	1.25 ± 0.23	1.65 ± 0.45	1.85 ± 0.36	52.36	0.0000
IL-6 (pg/ml)	30.4 ± 4.62	19.6 ± 5.36	16.7 ± 4.62	130.1	0.0000
TNF-α (ng/ml)	13.42 ± 0.94	12.6 ± 0.89	12.36 ± 0.94	15.20	0.0000

[a] Before intervention and at 6 and 12 weeks after intervention

In vitro studies have suggested that vitamin D suppresses proinflammatory cytokines and increases anti-inflammatory cytokines. In this double-blind, placebo-controlled intervention study, we evaluated for the first time in infants the effect of vitamin D supplementation on RAS cytokines as well as different clinical, biochemical, and echocardiographic variables in infants with chronic CHF.

During the preintervention stage, our study showed that differences between mean clinical data, HF score, echocardiographic indices, and laboratory variables among studied groups were statistically insignificant ($p > 0.05$). In both groups, baseline 25(OH)D concentrations were below the lower end of the reference range (33–90 ng/ml). Moreover, 15 infants with CHF were excluded out from the study as they had vitamin D deficiency together with hypocalcaemia, they were breast feeders, and 8 of them had radiological findings of rickets. In developing countries, this is possibly nutritionally related. In addition, Vitamin D deficiency may occur in dark-skinned infants or in breast-fed infants of mothers unexposed to sunlight. This problem

Table 4 Means ± SDs of clinical, echocardiographic, and laboratory findings among studied patients in Group II[a]

Time parameter	Before intervention	6 Weeks after intervention	12 Weeks after intervention	*F*	*p*
HR (bpm)	149.3 ± 26.4	130.8 ± 19.6	125.6 ± 16.5	14.45	0.0000
SBP (mm Hg)	83.6 ± 6.41	79.5 ± 8.61	77.4 ± 8.72	6.485	0.0020
DBP (mm Hg)	41.50 ± 6.8	41.99 ± 5.3	43.7 ± 6.79	1.395	0.2515
HF score	9.61 ± 1.71	8.99 ± 1.02	8.31 ± 1.81	7.357	0.0009
LVEDD (mm)	30.7 ± 5.2	24.9 ± 3.11	28.3 ± 8.1	1.995	0.3791
LVESD (mm)	23.7 ± 3.91	16.2 ± 3.67	20.4 ± 6.8	2.723	0.0700
EF%	37.2 ± 2.62	41.4 ± 6.7	43.6 ± 8.1	7.335	0.0010
FS%	21.4 ± 2.72	24.4 ± 3.9	28.4 ± 5.98	30.44	0.0000
E/A ratio	1.27 ± 0.64	1.54 ± 0.44	1.60 ± 0.39	5.154	0.0070
MPI	0.66 ± 0.31	0.64 ± 0.03	0.62 ± 0.04	0.511	0.6010
Serum calcium (mg/dl)	9.91 ± 2.75	9.63 ± 1.5	10.22 ± 0.8	1.366	0.2433
Serum phosphorus (mg/dl)	3.94 ± 0.91	3.88 ± 0.64	3.78 ± 0.82	0.430	0.6508
Serum albumin (g/dl)	4.82 ± 0.97	4.66 ± 1.42	4.51 ± 1.83	1.009	0.6198
Serum creatinine (mg/dl)	0.79 ± 0.18	0.69 ± 0.37	0.66 ± 0.47	1.496	0.2280
PHT (pg/ml)	39.8 ± 7.22	37.5 ± 4.8	36.32 ± 3.9	3.366	0.0647
25(OH)D (ng/ml)	14.0 ± 2.46	14.9 ± 1.68	14.64 ± 6.4	1.564	0.2138
IL-10 (pg/ml)	1.28 ± 0.16	0.09 ± 0.05	0.07 ± 0.03	115.7	0.0000
IL-6 (pg/ml)	29.8 ± 3.81	36.4 ± 4.8	38.3 ± 6.37	32.09	0.0000
TNF-α (ng/ml)	13.11 ± 1.6	13.63 ± 1.7	13.81 ± 0.9	2.659	0.0740

[a] Before intervention and at 6 and 12 weeks after intervention

Table 5 Means ± SDs of clinical, echocardiographic, and laboratory findings among studied groups at 12 weeks of treatment[a]

Group parameter	Group I ($n = 42$)	Group II ($n = 38$)	*t*	*p*
HR (bpm)	124.2 ± 18.3	125.6 ± 16.5	0.358	0.7213
SBP (mm Hg)	79.8 ± 3.29	77.4 ± 8.72	1.659	0.1012
DBP (mm Hg)	45.7 ± 4.31	43.7 ± 6.79	1.588	0.1163
HF score	6.38 ± 1.15	8.31 ± 1.81	7.403	0.0000
LVEDD (mm)	24.9 ± 3.71	28.3 ± 8.1	4.792	0.0000
LVESD (mm)	16.2 ± 3.67	20.4 ± 6.8	3.482	0.0001
EF%	52.2 ± 4.7	43.6 ± 8.1	5.874	0.0000
FS%	28.9 ± 3.38	28.4 ± 5.98	0.466	0.6425
E/A	1.36 ± 0.44	1.60 ± 0.39	2.570	0.0121
MPI	0.51 ± 0.06	0.62 ± 0.04	9.542	0.0000
Serum calcium (mg/dl)	10.41 ± 1.2	10.22 ± 0.8	0.824	0.4124
Serum phosphorus (mg/dl)	3.92 ± 0.61	3.78 ± 0.82	0.872	0.3860
Serum albumin (gm/dl)	4.42 ± 1.65	4.51 ± 1.83	0.231	0.8177
Serum creatinine (mg/dl)	0.84 ± 0.26	0.66 ± 0.74	1.480	0.1430
PHT (pg/ml)	28.32 ± 4.7	36.32 ± 3.9	8.174	0.0000
25(OH)D (ng/ml)	32.89 ± 2.3	14.64 ± 6.4	17.29	0.0000
IL-10 (pg/ml)	1.85 ± 0.36	0.07 ± 0.03	30.36	0.0000
IL-6 (pg/ml)	16.7 ± 4.62	38.3 ± 6.37	17.479	0.0000
TNF-α (ng/ml)	12.36 ± 0.94	13.81 ± 0.9	8.084	0.0000

[a] After intervention

may thus be more dispersed in this part of the world than in more developed countries. The same findings were reported by Tomar et al. [16], and they added that although currently available evidence does not support widespread vitamin D screening for all patients with HF, consideration should be given for assessment of vitamin D status in some HF subgroups, especially in breast-fed infants and those with persistent HF-related symptoms despite the use of optimal antifailure drug therapy. The intervention in this study consisted of giving the standard antifailure treatment

to all patients in addition to a daily supplement of either 25 μg (1,000 IU)/d cholecalciferol (D-Vi-Sol) in (group I) or placebo oral drops in (group II).

During the postintervention stage, our results showed that after 12 weeks of intervention, there had been a significant improvement in the serum level of 25(OH)D among infants supplemented with vitamin D (group I) (13.4 ± 2.21 ng/ml before intervention to 32.89 ± 2.3 ng/ml after intervention, $p < 0.001$) compared with nonsignificant improvement among infants in group II (placebo; 14.0 ± 2.46 ng/ml before intervention to 14.64 ± 6.43 ng/ml postintervention, $p > 0.05$), and the difference in the postintervention stage between both groups was statistically significant ($p < 0.001$, Table 5). Consensus has not been reached regarding the concentration of 25(OH)D needed to define vitamin D insufficiency in infants and children, but it has become clear only in the past few years that serum 25(OH)D concentrations in infants and children should be approximately 30 ng/mL [17].

Accordingly the increased level in 25(OH)D among our patients in group I is generally considered adequate for bone and overall health in such infants. However, accumulating evidence suggests that vitamin D deficiency (serum levels <20 ng/mL) and insufficiency (serum levels of 20 and 30 ng/mL) may play a role in the development of a variety of conditions, including HF [17]. Zittermann et al. [20] reported that adequate vitamin D concentration may enhance dietary calcium absorption, which may increase the amount of extracellular activator calcium necessary for the first step in myocardial contractions [20]. Moreover, in this study we found significantly a more pronounced decrease in serum PTH concentrations during the postintervention stage among the vitamin D–supplemented group I compared with the placebo group II ($p < 0.001$, Table 5). This was in accordance with the results of Zhu et al. [19], who stated that excess PTH concentration has adverse effects on cardiac function and leads to cardiomyocyte hypertrophy and interstitial fibrosis [11].

RAS Cytokines Profile Among Studied Patients

Our results also showed that after the 12-weeks postintervention stage, there was a significant increase in serum concentrations of the anti-inflammatory cytokine IL-10 and a significant decrease in serum concentrations of the proinflammatory cytokines TNF-α, and IL-6 among infants supplemented with vitamin D (group I) compared with a significant deterioration of these cytokines in infants from the placebo group (group II); the difference in the postintervention stage between both groups was statistically significant ($p < 0.001$, Table 5). These results agree with previous experimental data showed that vitamin D is able to suppress the release of TNF-α and enhance IL-10 synthesis [2, 19]. Moreover, earlier epidemiologic data indicated that high blood concentrations of 25(OH)D were associated with low IL-6 concentrations [4]. Low levels of calcitriol have been associated with activation of the renin-angiotensin-aldosterone system, increased levels of proinflammatory cytokines, such as TNF-α, and an increase in PTH, all of which may increase the risk for HF [12]. Because IL-10 is able to suppress the production of proinflammatory cytokines, this anti-inflammatory cytokine seems to have important cardioprotective actions [4]. In addition, experimental studies have shown that IL-10 deficiency leads to severe HF [6]. Compared with the protective effects of high IL-10 concentrations, evidence exists that excess TNF-α concentrations contribute to the pathogenesis and progression of CHF [6]. Consequently, our data suggest that vitamin D3 supplementation decreases inflammatory cytokines in infants with CHF and might serve as a new anti-inflammatory agent for future treatment of the disease.

ECHO Variables

Other important findings of our study were the significant improvement in HF score, LVEF, and MPI as well as decreased LVEDD from baseline in both groups, with there being a more significant improvement in these findings during the postintervention stage among the vitamin D-supplemented group I compared with the placebo group (group II). In animal models of HF, active vitamin D treatment was shown to decrease cardiac hypertrophy and to attenuate myocardial dysfunction [1]. Importantly, there exists increasing molecular and clinical evidence that a sufficient vitamin D status is required for maintenance of diastolic function of the heart [1, 15]. Furthermore, there have been several case reports of vitamin D-deficient children with dilated cardiomyopathy who were successfully treated with vitamin D and calcium [18].

Study Limitations

Our study has some limitations. First, the increase of 32.89 ng/mL 25(OH)D in the vitamin D-supplemented group I was probably low to optimize all vitamin D-dependent functions. It has only become clear in the past few years that serum 25(OH)D concentrations >33–≤90 ng/mL are considered adequate [17]. This may be due to the short duration of our study (12 weeks) and may show an additional improvement with longer duration. Another limitation regards different HF aetiologies: Although we chose to study two age- and sex-matched common subgroups with congestive HF due to dilated cardiomyopathy and congenital heart diseases with systemic LV systolic dysfunction, the effect of vitamin D supplementation on

subgroups of patients randomised according to different HF aetiologies could provide a topic for new wide-scale research.

Conclusion

Vitamin D supplementation has great benefits as an anti-inflammatory agent in infants with CHF. It helps acceleration of the clinical improvement and the cytokine profile balance. It is recommended to use vitamin D supplementation as an adjuvant therapy, side-by-side with antifailure regimen, in the management of CHF associated with myocardial dysfunction and upregulated proinflammatory cytokines.

Acknowledgment The author thanks Akram Saeed and his team for the laboratory investigations performed for this study. Without their help, this work would have been impossible.

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