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# VITAMIN D STATUS IN PEDIATRIC PATIENTS WITH DILATED CARDIOMYOPATHY

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## ABSTRACT

**Child heart failure is frequently brought on by dilated cardiomyopathy and it is characterized by impaired contraction and left ventricular or biventricular dilation. Evidence from recent years has demonstrated that vitamin D is crucial in a number of cardiovascular illnesses that are now more well recognized. This study evaluated vitamin D status in pediatric patients with dilated cardiomyopathy and compared it with that of healthy controls.**

**This study is an observational case-control study, which included 23 patients with dilated cardiomyopathy aged less than 21 years of both genders, and a control group that included 45 healthy people who were matched for age, sex, and body mass index at the surgical specialty hospital-cardiac center in Erbil, Iraq. From each one, a blood sample was taken to evaluate the serum level of 25-hydroxyvitamin D3, parathyroid hormone, phosphorus, calcium, troponin I and creatin kinase-MB levels.**

**The study revealed that the mean serum vitamin D3 level and mean serum calcium were significantly lower in dilated cardiomyopathy patients than controls, and significantly higher mean serum PTH and serum creatin kinase-MB in patients than controls. The difference in serum troponin I levels was not significant between the two groups. Furthermore, the study's outcomes revealed a substantial, moderately significant negative correlation between hypovitaminosis D and the dimensions of the left ventricle's end diastole and end systole in children with dilated cardiomyopathy.**

***KEYWORDS:*** Dilated cardiomyopathy, Vitamin D, Heart failure

## INTRODUCTION

Dilated cardiomyopathy (DCM) is defined as an abnormality in the function and structure of the heart muscle by non-ischemic causes that can result in significant mortality and morbidity due to complications such as arrhythmia and heart failure. Among cardiomyopathies, DCM is the most prevalent kind among the pediatric age group (Hershberger et al., 2010). As stated by the American Heart Association, dilated cardiomyopathy is classified as genetic, acquired, or mixed (Maron, 2006).

Vitamin D (25-hydroxycholecalciferol) is a steroid hormone and a well-known important factor for maintaining adequate calcium and phosphate balance for musculoskeletal metabolism. However, there is increasingly apparent data pointing to a potential link between cardiovascular disorders and vitamin D deficiency. The entire cardiovascular system, including endothelium, cardiomyocytes, and vascular smooth muscle, contains vitamin D receptors (Wang et al., 2008; Judd & Tangpricha, 2009).

Numerous genes with vitamin D response elements in their promoters are regulated by the nuclear receptor known as the vitamin D receptor (VDR). These genes play regulatory roles in cellular processes that may be pertinent to cardiovascular disorders, such as cell differentiation and proliferation, cell death, membrane transport, tissue calcification, oxidative stress, and cell adhesion (Bouillon et al., 2008).

In the cardiomyocyte, 1,25 dihydroxycholecalciferol activates the voltage-dependent Ca2+ channels of the L type via activation of the system of adenylate cyclase, cAMP, and protein kinases through guanine nucleotide binding proteins. Consequently, vitamin D deficiency might lead to the pathogenesis of DCM, and vitamin D may have an impact on cardiac function (Zittermann et al., 2003).

Recent literatures noted that lack of vitamin D is linked with a bad prognosis in individuals with heart failure. It has been observed that the



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antihypertrophic effect on cardiomyocytes is achieved by the vitamin D-VDR signaling system. Furthermore, studies in the past hypothesized a relation between left ventricular geometry and vitamin D (Schierbeck et al., 2011; Chen et al., 2011).

Some DCM patients may have severe vitamin D deficiency as their underlying cause, in which case vitamin D therapy totally reverses heart failure and dilatation and improves survival and the NYHA functional class in these individuals. Since vitamin D deficiency is one of the few reversible causes of DCM, it must be taken into account as an underlying cause of cardiac dysfunction in individuals with DCM. The precise prevalence of DCM caused by vitamin D deficiency is unknown (Ameri et al., 2013).

Through excitation-contraction coupling, calcium has a direct impact on myocardial contractility. Hypocalcemia reduces the strength of myocardial contraction, but that the incidence of DCM due to hypocalcemia is very rare (Brown et al., 2009).

In the pediatric population, vitamin D deficiency-induced hypocalcemia may be a reversible cause of DCM. Hypocalcemia-induced DCM is developed by the alteration of the amplitude or duration of Ca2+ transients. Dilated cardiomyopathy due to hypocalcemia responds exclusively to calcium and vitamin D supplementation with full recovery once serum calcium levels return to normal (Maiya et al., 2008; Sanyal & Raychaudhuri, 2013).

The justifications for the study are:

**1.** Recent research on vitamin D status in DCM has revealed that vitamin D serves more purposes than just regulating calcium metabolism. Cardiovascular disease and heart failure risk may rise if vitamin D deficiency is present because it probably confers physiologically significant pleiotropic activities, such as immunomodulatory and cardioprotective effects (Priya et al., 2016).

**2.** The function of the myocardium is influenced by the control of calcium and phosphorus concentration by parathyroid hormone. PTH secretion irregularities have been linked to diminished mechanical function of the heart muscle (Fattouh et al., 2010).

**3.** Chronic troponin (troponin I and troponin T) elevation in DCM indicates ongoing subclinical myocyte necrosis, apoptosis, or leakage. Troponin I has been chosen for this purpose as elevations in troponin I are more strongly associated with some cardiovascular disease outcomes (Welsh et al., 2019).

**4.** CK-MB level has been chosen as an indication of poor prognosis among DCM patients that might be helpful in determining if these individuals have any permanent myocardial injury. (Li et al., 2014).

## PATIENTS AND METHODS

This observational case-control research was conducted at Surgical Specialty Hospital-Cardiac Center, Erbil, Iraq, between May 2021 and May 2022, and it included 23 patients diagnosed to have DCM aged less than 21 years of both sexes, and 45 age, gender and BMI matched apparently healthy controls with absence of recent and/or chronic disease, and normal echocardiographic findings. The exclusion criteria for the DCM patients' group included: Age > 21 years; ischemic DCM; toxin induced DCM; patients with congenital heart disease; coronary artery diseases; hypertension; valvular heart diseases; patients having endocrine, metabolic, infectious, and autoimmune diseases. Also, any child received vitamin D, calcium and phosphorus supplementation, any patient who underwent surgical operation like gastric or bowel resection, and any patient who had taken drugs which interfering with level of vitamin D, like anticonvulsants or thiazide diuretic.

Two-dimensional transthoracic guided M-mode echocardiography was carried out for each participant using the apparatus (Vivid E9 by GE Healthcare Company, 2013 USA), using a three-megahertz (MHz) probe for adults and adolescents, five MHz probe for younger children, and a 12 MHz probe for neonates. The projections of the apical four and two chambers together with the parasternal long and short were used to get images. Depending on their functional condition, DCM patients have been categorized into several classes by the New York Heart Association (NYHA) various grades (Bennett et al., 2002).

From each subject, a total of 5 mL of blood was withdrawn by venipuncture for the determination of 25(OH) Vit D3, serum calcium, serum phosphorus, serum PTH, serum CK-MB, and serum troponin I. In terms of serum 25 hydroxyvitamin D3 levels, subjects were divided into three groups: vitamin D-deficient (25 OH vitamin D3 $\leq$ 20 ng/mL), insufficient (25 OH

vitamin D3 >20-<30 ng/mL), and normal (25 OH vitamin D3 ≥ 30 ng/mL) (Holick, 2007).

The assay analytic sensitivity of serum troponin I was 0.1 ng/mL; any results less than that are referred to as 0.1 ng/mL by the analyzer. (Antonio & Werther, 2008). Serum 25 (OH) vitamin D3, serum troponin I, serum CK-MB, and serum PTH levels were measured by the cobas e 411 analyzer (Roche company/Germany; serial number: 741-0050), which is a completely automated analyzer that performs immunoassay analysis using a unique ElectroChemiLuminescence (ECL) technology. Its sensitivity and specificity are high. Measurements of serum phosphorus and calcium were made by the cobas c 501 analyzer (Roche Company/ Germany; serial number: 0896-18).

A statistical analysis was carried out using the SPSS application for Windows, version 26. Descriptive results were expressed as mean ± standard deviation, proportions, and frequency for categorical variables. Data from categorical sources was analyzed using the Fisher Exact test and student t-test to compare numerical variables. The Pearson correlation coefficient (r) was used to estimate the strength of the correlation between variables. A p-value < 0.05 was regarded significant. The research was approved by the scientific and ethical committees of Hawler Medical College. The meeting code is 8 and the paper code is 17.

## RESULTS

In this study, the age of DCM patients ranged from 4.8 months to 17 years. Twenty-three patients (14 males and 9 females, mean age: 8.74 ± 5.08 years) and 45 healthy controls (26 males and 19 females, mean age: 8.84 ± 4.64 years) were recruited. According to the New York Heart Association (NYHA), we categorized the DCM patients into several classes; 10 patients were in Grades I and II, 8 were in Grade III, and 5 were in Grade IV. Table 1 displays the basic features of the two groups.

**Table (1):-** Basic features of the patients and the controls.

| variables | DCM patients (n=23) | Controls (n=45) |
|---|---|---|
| Age (years) | 8.74 ± 5.08 | 8.84 ± 4.64 |
| Sex: Male/female | 14 (60.9%) / 9 (39.1%) | 26 (57.8%) /19 (42.2%) |
| BMI (kg/m$^2$) | 15.20 ± 4.86 | 17.30 ± 2.75 |

Data was expressed in mean±SD.

Regarding echocardiographic parameters, LV ejection fraction (LVEF) was significantly lower in patients with DCM, while LV end diastolic dimensions and LV end systolic dimensions were significantly higher in DCM individuals compared to the healthy controls, p <0.001, as shown in Table 2.

**Table( 2):-** Comparison between echocardiographic parameters of patients with DCM and control group.

| Variables | DCM patients (n=23) | Controls (n=45) | P-value |
|---|---|---|---|
| LVEDd (mm) | 54.69 ± 15.95 | 36.69 ± 5.04 | < 0.001 |
| LVESd (mm) | 48.13 ± 15.66 | 24.18 ± 3.77 | < 0.001 |
| EF ( %) | 29.04 ± 9.54 | 64.78 ± 2.97 | < 0.001 |

Data was expressed in mean±SD by T-test.

The mean serum 25(OH) D3 levels were (14.82 4.90 ng/mL) and (22.61 6.90 ng/mL) in both patients and controls, respectively, and this outcome was highly significant statistically (p-value = <0.001).

As shown in Table 3, the differences were found to be statistically significant in the mean serum calcium level between patients and control groups and in the mean PTH level between the two groups, while the difference between the mean serum phosphorus in DCM patients and that of the control group was not significant statistically.

The control group had normal serum levels of CK-MB and troponin I. The study showed that the serum CK-MB level in DCM patients was significantly higher than that in the control group (5.34 ± 5.68 ng/mL vs. 2.61 ± 1.56 ng/mL, p=0.004), while the level of serum troponin I between patient and control groups revealed no significant variation, as in Table 3.

**Table (3):** -Comparison of the biochemical parameters between patients with DCM and control group.

| Variables | DCM patients (n=23) | Controls (n=45) | P-value |
|---|---|---|---|
| 25(OH)D3(ng/mL) | 14.82 ± 4.90 | 22.61 ± 6.90 | < 0.001 |
| Calcium (mg/dl) | 8.68 ± 0.92 | 9.27 ± 0.50 | 0.001 |
| Phosphorus (mg/dl) | 4.54 ± 0.72 | 4.76 ± 0.67 | 0.22 |
| PTH (pg/mL) | 45.16 ± 22.7 | 33.09 ± 11.24 | 0.005 |
| Troponin I (ng/mL) | 1.197 ± 5.188 | 0.100 ±0.002 | 0.15 |
| CK-MB (ng/mL) | 5.34 ± 5.68 | 2.61 ± 1.56 | 0.004 |

Data was expressed in mean±SD by T-test.

In the current study, 18 of 23 patients had 25(OH) D3 deficiency (≤ 20 ng/mL), whereas 18 of 45 healthy controls had vitamin D deficiency. The difference in 25(OH)D3 categorical levels (vitamin D deficiency, insufficiency, and sufficiency) between DCM patients and the control group exhibited statistical significance (p = 0.008), as demonstrated in Table 4.

**Table (4):-** Vitamin 25(OH)D3 status in patient and control groups.

| Variables | DCM patients | controls | total | P value |
|---|---|---|---|---|
| 25(OH)D3 deficient group (≤ 20 ng/mL) | 18 (78.3 %) | 18 (40%) | 36 (52.9%) | 0.008 |
| 25(OH)D3 insufficient group (> 20 ng/mL- < 30 ng/mL) | 5 (21.7 %) | 24 (53.3%) | 29 (42.6%) | |
| 25(OH)D3 sufficient group (≥30 ng/mL) | 0(0 %) | 3 (6.7 %) | 3 (4.4%) | |
| Total | 23 (100%) | 45 (100%) | 68 (100%) | |

P-value is measured by Fisher's Exact Test.

There was a moderate negative significant correlation between 25(OH) D3 concentrations and LV end diastolic and end systolic dimensions (r = −0.40; P = 0.016, r = −0.42; P = 0.010, respectively, as shown in Figures 1 and Figure 2). On the contrary, there was moderate positive significant correlation between 25(OH) D3 levels and LVEF (r = 0.51; P = 0.010, as shown in Figure 3).

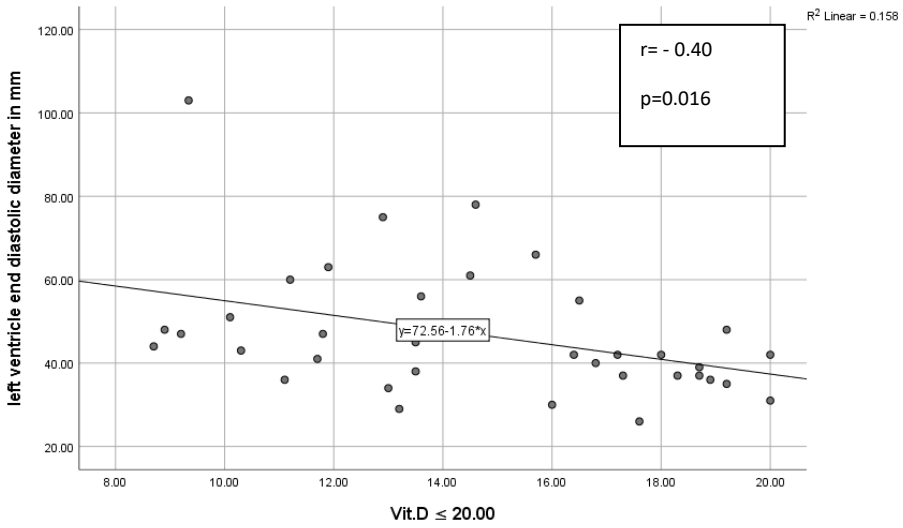


**Fig.(1):-** Correlation of hypovitaminosis D with LVEDD.

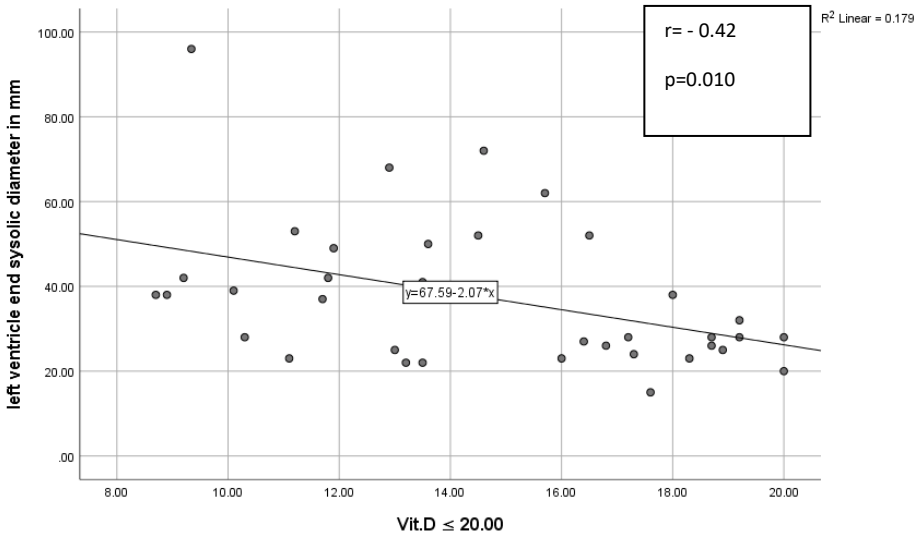


**Fig.( 2):-** Correlation of hypovitaminosis D with LVESD.

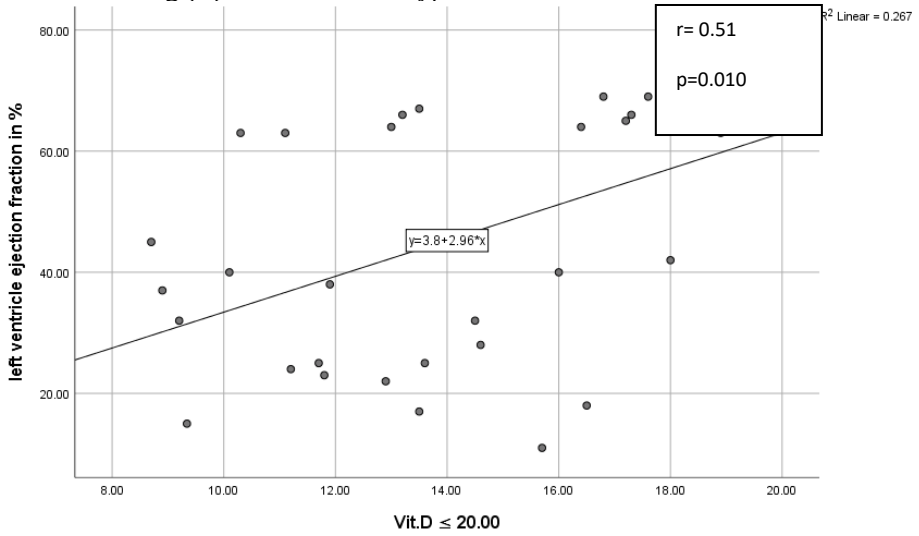


**Fig.( 3):-** Correlation of hypovitaminosis D with LVEF.

## DISCUSSION

Despite the Middle East receiving lots of sunshine, research evaluating vitamin D status found a significant rate of vitamin D deficiency. In children with DCM, it can be attributed to inadequate sunlight exposure, restricted outdoor play, and lying down position, as well as to poor vitamin D absorption because of edema of the intestinal wall in DCM patients. (Green et al., 2015; Abu Shady et al., 2016).

The mean serum 25(OH)D3 level was significantly lower in DCM patients compared to control groups in this study, which was consistent with (Ameri et al., 2013) and (Laguardia et al., 2006).

Similarly, a significantly lower mean serum calcium level was observed in the DCM patient group compared to that of the control group, and the patient group had considerably greater serum PTH levels than controls. These findings were consistent with studies that were carried out in other areas, which observed significant hypocalcemia and an elevated mean PTH level in DCM patients with heart failure (Laguardia et al., 2006; Tomar et al., 2010), and also agreed with a study that assumed that PTH might provide a stand-alone contribution to myocardial dysfunction in patients with DCM (Van Ballegooijen et al., 2013).

(Maiya et al., 2008) reported 16 cases of DCM due to hypocalcemia in children, associated with vitamin D deficiency. Also, one of many studies about hypocalcemia-associated reversible dilated cardiomyopathy that have been published in international journals was conducted in Turkey by (Yilmaz et al., 2015), who detected 8 pediatric patients who developed DCM with heart failure because of rickets-associated hypocalcemia in a period of 3 years.

Troponin is a useful marker in the prediction of prognosis of DCM. Higher levels have been associated with poorer clinical outcomes in patients with DCM and heart failure (Masson et al., 2012).

In this study, no statistically significant difference was found between mean serum troponin I levels of DCM patients and control groups, and these findings agreed with other studies who found no association between troponin I elevation and DCM morbidity and mortality (Baba et al., 2015; Miller et al., 2007), but were not in harmony with those of some researchers who detected a significant association (Miettinen et al., 2008; Vecchia et al., 2000; Jia et al., 2017; Nellessen et al., 2006). This could be explained by the fact that the selected DCM patients in this study were clinically stable (Latini et al., 2007).

There was a statistically significant difference in patients' levels of CK-MB, indicating that CK-MB level could be an indicator of myocardial damage and unfavorable prognosis in patients with DCM. This finding was consistent with studies carried out by other researchers who found that CK-MB levels were significantly greater in patients with DCM than in the control group (Miettinen et al., 2008; Soongswang et al., 2002), but those findings did not agree with results that have been reported in a study by (Jia et al., 2017).

This study revealed a moderate negative significant correlation between vitamin D deficiency and LEVDD and LVSDD, and a moderate positive significant correlation between hypovitaminosis D and LVEF. These results were in concordance with previous case-control studies conducted by (Priya et al., 2016), and (Ameri et al., 2013), but were inconsistent with results that have been reported in a study conducted in Egypt in 2021, which found no significant correlation between vitamin D level and LEVDD and LVSDD of DCM patients (Duaa et al., 2021).

Our research has a lot of possible limitations. First of all, the study's sample size was too small to be generalized to all young patients with DCM in our area. Second, as the current study is an observational one, it cannot establish the causal link between vitamin D deficiency and DCM or establish whether it is the cause or result of heart failure in DCM patients. It is also cannot demonstrate the involvement of vitamin D in the pathogenesis of DCM. Lastly, one measurement of vitamin D3 may not be enough to tell the exact long-term status of vitamin D levels in people with DCM.

## CONCLUSIONS

Pediatric DCM patients had significantly lower mean serum 25OH vitamin D3 levels compared with healthy controls. Cardiac function and parameters were significantly correlated with a lack of vitamin D. A significantly lower serum calcium level was seen in the patient group than that of the control group, and a significantly higher serum PTH level was observed in DCM patients compared to controls. A significant difference was found between the mean serum CK-MB levels of DCM patients and control groups, but the difference in serum troponin I levels was not significant between the two groups.

## RECOMMENDATIONS

Screening for Vitamin D deficiency is recommended in pediatric patients with DCM that could have an effect on cardiac function. Further studies are required to determine the precise role of vitamin D deficiency in the etiology of DCM. Multiple cardiac centers can be included in such a study. The DCM cases should be picked up at their first diagnosis, and some of them can be given vitamin D and others not by a double-blinded study method. Pediatric cardiologists should consider hypocalcemia as a cause of DCM in children.

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**الخلاصة**

**الخلفية: اعتلال عضلة القلب التوسعي هو سبب مهم لفشل القلب عند الأطفال ويتميز بضعف الانقباض وتمدد البطين الأيسر أو البطينين. في السنوات الأخيرة ، أصبح الدليل على أن فيتامين (د) يلعب دورًا مهمًا في مجموعة متنوعة من أمراض القلب والأوعية الدموية واضحًا بشكل متزايد.**

**الأهداف: لتقييم حالة فيتامين (د) بناءً على مستوى مصل ٢٥-هيدروكسي فيتامين د ٣ في مرضى الأطفال المصابين باعتلال عضلة القلب التوسعي ومقارنتها مع الأطفال الأصحاء.**

**الطريقة: تم تسجيل ثلاثة وعشرون مريضا يعانون من اعتلال عضلة القلب التوسعي الذين أعمارهم أقل من ٢١ عامًا من كلا الجنسين ، و٤٥ أطفال أصحاء مطابقين للعمر والجنس وأجريت هذه الدراسة في وحدة أمراض القلب للأطفال في المستشفى التخصصي الجراحي / مركز القلب في مدينة أربيل / العراق ، خلال الفترة من ١ مايو ٢٠٢١ إلى نهاية مايو ٢٠٢٢. تم الحصول على عينة دم من كل واحد لقياس مستويات مصل ٢٥-هيدروكسي فيتامين د ٣ والكالسيوم والفوسفور وهرمون الغدة الجار درقية والتروبونين ١ و الكرياتين كيناز- م ب.**

**النتائج: في هذه الدراسة كان متوسط مستوى مصل فيتامين د٣ أقل بشكل ملحوظ في مرضى اعتلال عضلة القلب التوسعي، مقارنة بالأطفال الأصحاء.كانت الفروق في متوسط مستوى الكالسيوم ومتوسط مستوى هرمون الغدة الجار درقية في الدم بين مجموعات المرضى والأطفال الأصحاء مهمة. لم تكن مقارنة متوسط مستوى تروبونين ١ بين المرضى و والأطفال الأصحاء مهمة ، بينما كان الاختلاف مهما في متوسط مستوى الكرياتين كيناز-م ب في مصل الدم بين المجموعتين، كان هناك ارتباط سلبي مهم بين نقص فيتامين د ٣ و ابعاد البطين الايسر في نهاية الانبساط و نهاية الانقباض ، وكانت هناك علاقة ارتباط موجبة معتدلة مهمة بين حالة نقص فيتامين د٣ والكسر القذفي للبطين الايسر.**

**الاستنتاج: كان لدى مرضى اعتلال عضلة القلب التوسعي للأطفال متوسط مستوى مصل فيتامين د ٣ أقل بشكل ملحوظ مقارنة بالأطفال الأصحاء. نقص فيتامين د٣ له علاقة مهمة مع وظيفة ومعامل القلب.الكلمات الدالة: اعتلال عضلة القلب التوسعي, فيتامين (د), عجزالقلب.**