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Investigating Vitamin D Serum Levels in Children with Congenital Heart Disease Compared with the Healthy Control Group

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Abstract

Background
Vitamin D is a fat-soluble vitamin that has an important function in bone metabolism, muscle activity, nervous system, and immunity. In this study, we compared the vitamin D level of children with congenital heart disease (CHD) with healthy control.

Materials and Methods
This case-control study was conducted on 56 children with CHD diagnosed with echocardiography and 56 healthy children with no sign of CHD matched for age, sex, and use of vitamin D supplementation. Participants were gathered from those who referred to the cardiac clinic of Vali-e-Asr hospital, Birjand, Iran, in 2017. Two ml of the blood sample was taken from all participants and serum vitamin D was assessed using Roche Diagnostic kit (Germany). The data analysis was achieved using SPSS software version 16 with descriptive statistics and Chi-square test.

Results
The median age of participants was 7 months (ranged1-24). The mean vitamin D serum level of all participants was 32.19 ng/ml (SD=28.79) (normal > 20). The level of vitamin D in the case and control group was 16.82 ng/ml (29.85-9.38), and 34.95 ng/ml (46.60-26.52), respectively; and this difference was significant (P<0.05). In the CHD patients group, 15 patients had vitamin D deficiency and 5 patients had high vitamin D levels. In the healthy patients' group, these numbers were 2 and 21, respectively.

Conclusion
Based on the results, children with CHD had significantly lower levels of vitamin D; therefore, we suggest more vitamin D supplement be used for patients with CHD than healthy children.

Key Words: Children, Congenital heart disease, Vitamin D.

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1- INTRODUCTION

Cardiovascular diseases are life-threatening disorders. They are responsible for 17.7 million deaths per year (1), of which 64% are coronary artery disease, 29.4% are valvar diseases, and 5.8% are congenital heart disease (CHD) (2). CHD is the most common congenital disorder in children, accounting for approximately 25% of all congenital malformations (3, 4), and is one of the leading causes of mortality in the first year of life (5, 6). Congenital heart abnormalities are classified into cyanotic and non-cyanotic groups, of which half of the cases are detected in the first month after birth. Congenital anomalies of the heart vary in severity. Some are very loud and discovered at an early age, but on the other side of the spectrum, there are people with mild defects that may not be marked until adulthood and hence, are discovered at a later age (7-10). A total of 130 million babies are born every year around the world, with 4 million deaths during infancy, while 7% of these deaths are due to congenital heart disease (11, 12).

The overall incidence of congenital heart disease is approximately 6-8 per 1,000 live births (13). Congenital anomalies of the heart have been considered in many communities due to its many complications and mortality and the high costs imposed on the health system. The results of various studies suggest CHD as a multifactorial disorder (14). Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism, which applies its genomic effect through vitamin D nuclear receptors (15, 16). Vitamin D is considered as a steroid hormone with a variety of effects and has important roles in the optimal function of many organs and may be a modifying factor for many chronic diseases including osteomalacia and rickets. Guidelines suggest vitamin D dose between 400 and 2000 IU/day based on age, body weight, disease-status, and ethnicity status (17). Vitamin D deficiency is a global health concern affecting both developed and developing countries and it is found in all age groups and in both genders (18, 19). Although the principal reason for the increased prevalence of vitamin D deficiency is not well known, lifestyle changes are likely the most important cause of this issue (2, 18). Lack of vitamin D levels in the infants can cause complications such as hypocalcemic seizures, hypotension, bone loss, loss of height and birth weight, enamel defects, and low Apgar score in the first minute (20). Although an association have been shown between Vitamin D deficiency and common chronic disorders such as type 1 diabetes mellitus, and autoimmune diseases like MS and psoriasis, and malignancies such as breast cancer (21-24), its role in the development of the heart during the embryonic period is not decisive. Vitamin D is involved in muscle growth and development and it regulates muscle contractility. Vitamin D deficiency results in decreased muscle size and strength (25). There are few studies comparing the level of serum vitamin D in CHD patients with healthy controls. Therefore, in this study we aimed to evaluate the vitamin D serum level in children with CHD compared to the healthy control group.

2- MATERIALS AND METHODS

2-1. Study design and population

This analytical descriptive study was conducted in Vali-e-Asr hospital, Birjand, Iran, in 2017. Participants were chosen from those who referred to cardiac clinic of Vali-Asr hospital. Fifty-six children with congenital heart disease whose disorder was confirmed using echocardiography (EKO7, Samsung, Korea) were assigned to case group, and 56 children were matched for age, sex, and using vitamin D supplements without any sign of CHD based on

electrocardiography, physical examination, and chest X-ray were selected for the control group. Considering the following formulae, and needed parameters (where first type error (α) = 1.96, second type error (β) = 0.84, levels of 25(OH) vitamin D variance in case = 20.72, the level of 25(OH) vitamin D in the controls = 19.61, average level of 25(OH) vitamin D in case= 26.6, mean level of 25(OH) vitamin D in the controls= 37.78), 51 participants were calculated for each group. Taking into account a 10% drop, our study sample size was 56 in each group.

$$n = \frac{(s_1^2 + s_2^2)(z_{1-\alpha/2} + z_\beta)^2}{(\mu_1 - \mu_2)^2}$$

2-2. Methods

Baseline checklists were designed to gather patients' information including sex, age, family history of CHD, pregnancy age, complaints of referral time, and the type of disease and supplements used for the child.

2-3. Laboratory measurements

Two ml of participants' venous blood was obtained by a trained technician at the clinic or hospital ward and was carried in cold chain condition. The samples were centrifuged and serum samples were isolated and were used to assess Vitamin D level using Roche Diagnostic kit (Roche Diagnostics GmbH, Mannheim, Germany). After categorization of the levels of 25-hydroxyvitamin D in the groups, based on IOM criteria, the subjects in each group were divided into four subgroups: deficient (<12 ng/ml), insufficient (12-20 ng/ml), normal (20-50 ng/ml), and high (>50 ng/ml) (26).

2-4. Ethical consideration

This study was approved by Ethics Commitee of Birjand University of Medical Sciences (ID-code: IR.BUMS.REC.1397.117). Before the study, parents of the subjects were informed about the aim of the study and written consent was obtained from them.

2-5. Inclusion and exclusion criteria

Children with congenital heart disease whose disease had been confirmed after diagnostic and echo procedures, and who were recieving vitamin D supplementation according to national guidelines, were included in the case group. Loss of data from the initial assessment, withdrawal of the child's family from examination, child's death, constrictive pericarditis, cardiac tumors, patients with history of pericarditis, myocarditis, pulmonary embolism, obstructive sleep apnea, chronic liver or kidney diseases, endocrine disorders such as hyperparathyroidism, insulin use, use of anticonvulsants, stop receiving vitamin D prophylaxis, and recent high dosage of vitamin D injections, led to exclusion from the study.

2-6. Data Analyses

The data were analyzed using SPSS software package for Windows™, version 16.0 (SPSS Inc., Chicago, IL, USA) using descriptive statistics and Chi-square test. Kolmogorov-Smirnov test was used to assess normal distribution. Mann-Whitney U and Chi-square tests were used to analyze the data. A P-value < 0.05 was considered statistically significant.

3- RESULTS

In this study, 112 participants were studied, including 56 children with CHD and 56 healthy children. The median age was 7 months (ranged 1-24) and difference in participants' age in the two considered groups was not significant. 50% of the participants in each group were male. The family history of CHD was present in only 2 patients (3.5%) with CHD and was not present in the control group. 12.5% (n=7) of the patients in both groups were preterm. Of the 56 children with congenital heart disease, 38 patients had

been diagnosed with murmur, 5 patients with cyanosis complaints, 3 patients with tachycardia complaints and 2 patients with weight loss. In each of the complaints of nausea, pneumonia, cardiomegaly, diagnosis during pregnancy, fatigue, poor nutrition, dyspnea, and palpitation at the time of referral was one person. In the CHD group, 6 patients (10.7%) had cyanosis. Distribution of frequency of congenital heart diseases and the participants' serum vitamin D level in case group is illustrated in **Table.1**. The mean vitamin D serum level of all participants was 32.19 ng/ml (SD: 28.79). Kolmogorov-Smirnov showed that vitamin D levels in each group did not follow normal distribution; therefore, Mann-Whitney U test was used to compare vitamin D levels between the groups. The level of vitamin D in the case group was 16.82 ng/ml (29.85-9.38), and in the control group was 34.95ng/ml (46.60-26.52), and this difference was statistically significant (P<0.05). Male and female participants showed no significant difference in terms of vitamin D level in case and control group (P=0.718 and 0.670, respectively). Considering vitamin D serum levels, patients were divided into 4 subgroups. **Table.2** shows the number of patients in each subgroup. The Chi-square test showed a significant difference between groups considering level of serum vitamin D (P< 0.001). No difference was seen comparing vitamin D level in cyanotic and cyanotic children with CHD (P= 0.476 and T: 0.097).

Table-1: Distribution of frequency of congenital heart diseases in case group.

Congenital Heart Disease	Frequency	Percentage	Vitamin D serum levels
Ebstein	2	3.6	13.93
VSD	22	39.3	18.58
TOF	3	5.4	21.98
PS	1	1.8	15.6
PDA	9	16.1	22.65
ASD	14	25	22.37
AS	1	1.8	5.9
CoA	1	1.8	40.50
d-TGA	1	1.8	9.63
HCMP	1	1.8	30.33
MR	1	1.8	9.30
Total	56	100	

VSD: Ventricular septal defect, TOF: Tetralogy of Fallot, PS: Pulmonary (valve) stenosis, PDA: Patent ductus arteriosus, ASD: Atrial septal defect, AS: Aortic stenosis, CoA: Coarctation of the aorta, d-TGA: dextro-Transposition of the great arteries, HCMP: Hypertrophic cardiomyopathy, MR: Mitral (valve) regurgitation.

Table-2: Categorizing patients in two groups based on vitamin D level.

Groups	Vitamin D				Chi-Square	P value
	High	Insufficient	Normal	Deficient		
Case	5 (9%)	20 (36%)	16 (28%)	15 (27%)	22.88	< 0.001
Control	21 (37.5%)	28 (50%)	5 (9%)	2 (3.5%)		

Case group: Children with congenital heart disease.

4- DISCUSSION

In this study, we showed that children with CHD have a significantly lower level of 25(OH) vitamin D compared to healthy subjects. In accordance with our results, Noori et al. reported that CHD children had significantly lower serum vitamin D than healthy controls (27). However, the mean level of vitamin D in CHD children in Noori et al.'s study laid in normal range (27). In contrast, CHD children in our study had a mean level of vitamin D lower from the normal value. Although the precise etiology of CHDs is not well-established, genetic and environmental factors like higher maternal and paternal age at the time of conception, higher maternal weight, presence of maternal medical conditions during gestation, and maternal nutrient deficiency are believed to be involved. Vitamin D, a fat-soluble vitamin, plays a fundamental role in calcium and phosphate balance, and muscular and skeletal function (23).

It is regarded as a pleiotropic hormone, which inserts its influence on the nervous system, endocrine system, immune system, and cardiovascular system (28, 29). Recent studies have reported vitamin D as an important factor in the development and progression of cardiovascular disease alongside conventional risk factors. The possible causes of vitamin D deficiency in pediatric patients with congenital heart disease may be increased metabolism, increased energy, raw materials, vitamins, and minerals consumption, in comparison to healthy children. Furthermore, this condition is a result of a disease-related sedentary lifestyle with reduced outdoor activities and higher hospitalization leading to limited ultraviolet-induced vitamin D production in the skin. Previous articles have reported vitamin D deficiency in patients with various types of cardiovascular disorder like congestive heart failure (30), diastolic dysfunction (30), coronary heart disease (31), and peripheral arterial disease (32). Izumi et al. showed that vitamin D deficiency is commonly seen in patients with heart failure. Moreover, vitamin D deficiency exacerbates the condition of the patients (33). Giovannucci et al. showed the association of vitamin D deficiency with fatal or non-fatal myocardial infarction among men (34). Pilz et al. observed that vitamin D serum level is associated with cardiovascular mortality in the elderly population (35). Liu et al. reported that healthy controls had a higher 25[OH] vitamin D level than patients with coronary heart diseases; furthermore, they showed that vitamin D level decreased as the coronary disease increased (36). In a study conducted on children with cardiomyopathy, Maiya et al. showed that the mean serum level of 25 (OH) vitamin D was lower than normal level in those children (37). A 2-3 fold increase in the vitamin D concentration in mother's blood in early weeks of pregnancy as reported by Kaludjerovic et al. (38) may signify the importance of vitamin D on cardiogenesis, which occurs similarly in early pregnancy, between 2-7 weeks of gestation (39).

Kwon showed the importance of vitamin D for the development of the heart in the embryo of the animal model (40). As reported by Tanbacouchi et al., there is a meaningful positive relationship between vitamin D levels of mothers of term and preterm neonates during labor and vitamin D level of their neonates at birth ($P<0.001$) (41). A study conducted in Egypt illustrated that vitamin D deficiency in mother is significantly associated with the risk of CHD in offspring (42). Vitamin D increases anti-inflammatory cytokines like interleukin-10 while suppressing pro-inflammatory cytokines (43). The anti-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) have been recently considered as an important factor in the progression of cardiovascular diseases like

congestive heart failure (44). Shedeed showed that supplementation with vitamin D had beneficial improvements in clinical outcomes. It increased interleukin IL-10 and decreased IL-6, and TNF-α in the intervention group compared with the placebo group (45). Liu et al. showed a negative correlation between the level of serum 25-hydroxyvitamin D, and TNF-α ($r=-0.651$, $P<0.001$), IL-6 ($r=-0.457$, $P<0.001$), IL-8 ($r=-0.755$, $P<0.001$) and IL-1β ($r=-0.628$, $P<0.001$) (36).

Moreover, patients with CHD may need heart surgery which further decreases the serum vitamin D level. McNellie et al stated that the majority of the CHD patients have a postoperative lack of vitamin D due to a clear reduction of vitamin D during the operation (46). Vitamin D receptor-deficient mouse showed symptoms like cardiac hypertrophy, hypertension, and higher thrombogenicity (47), suggesting the important role of vitamin D and its receptor in the cardiovascular system (48). We reported that there was no meaningful difference considering vitamin D levels in males and females in the two groups. Like our study, males and females in Noori et al.'s study showed no significant difference in terms of vitamin D serum level (27). Sheikh et al.'s study also confirmed our findings (49). However, Nargesi et al., reported a significant difference between serum 25-hydroxyvitamin D of the sexes in Tehran (50), which may be due to large percentage (65%) of females in their study. Furthermore, we found no significant difference of vitamin D level in cyanotic and cyanotic patients. The results of Noori et al's study were dissimilar to ours because they reported that acyanotic patients had higher vitamin D level (27).

4-1. Study Limitations

Our study is subject to a number of limitations. First, the sample size was small. Second, we just assessed serum 25-hydroxyvitamin D, therefore, serum levels of parathyroid hormone, calcium and phosphate, and calcitonin hormone, which have a strong correlation with serum levels of vitamin D, and their impact on cardiovascular diseases remains unclear. We suggest similar studies considering further indices be conducted with a larger sample size. As recent studies reported that complications of vitamin D deficiency may be caused by a flaw in vitamin D receptor like a polymorphism in VDR gene Fok1 (42), we suggest that genetic assessment be taken into account for further studies.

5- CONCLUSION

Based on the results, children with CHD had a significantly lower level of vitamin D. Considering the results of the present study, it is suggested that the serum level of 25(OH) should be checked in CHD children, and higher vitamin D supplementation for children with CHD should be used compared to healthy children.

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7- CONFLICT OF INTEREST: None.

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