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25-hydroxy Vitamin D Serum levels in Congenital Heart Disease (CHD) Children Compared to Controls

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Abstract

Background

25-hydroxy vitamin D [25(OH) VitD] deficiency is a highly prevalent condition, present in approximately 30% to 50% of the general population. A growing body of data suggests that low 25(OH) VitD levels may adversely affect cardiovascular health. The present study aimed to measure the serum levels of 25(OH) Vit D in Congenital heart disease (CHD) children compared to healthy children.

Materials and Methods

A case-control study performed on 270 children who equally distributed in case and controls and selected randomly from those who referred to the Ali Asghar Clinic and Ali Ebne Abi Talib Hospital in Zahedan, Iran, in the year of 2017. In patients, CHD diagnosed based on clinical manifestation and echocardiography by pediatric cardiologist, Serum 25(OH) Vit D measured by kit made of Italy.

Results

The level of 25(OH) Vit D serum means were lower in case (31.68±17.37) compared to controls (42.20±14.31) significantly (P<0.001); also in cyanotic and acyanotic were 23.689±12.317 and 33.772±17.924, respectively with lower level in cyanotic significantly (P=0.006). There was a significant difference in serum levels of 25(OH) Vit D in age groups of patients (P=0.117), so that it was lower in elder patients (26.07 ± 19.76) compared to youngers. The results showed that the levels of 25(OH) Vit D serum in patients were similar in male and females (p=0.782).

Conclusion

The present study concluded that serum level of 25(OH) Vit D was lower in CHD children, and among the patients, was lower in cyanotic. Considering the results of the present study suggested that the serum level of 25(OH) should be checked in CHD children specially those who suffered from cyanotic.

Key Words: Children, Congenital Heart Disease, 25-hydroxyvitamin D.

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1- INTRODUCTION

Congenital heart disease (CHD) is one of the main causes of death especially in the first year of life, and is one of the health problems that causes physical and mental disabilities in children (1). This disease is the most common congenital disorder in infants (2-4). Reported that Asia has the highest prevalence of CHD among other regions (9.3 per 1,000 live births), when in Europ and North of America are 8.2 and 6.9 in 1000 live births, respectively (5). In a study, the prevalence has been changed from 8.9 to 11.2 in 1000 live births in 8 years' duration in Northern Iran. In Sistan and Baluchestan province it has been reported by Noori et al., the rate of CHD in children as 5-40 in 1000 live births that the most common form of CHD are ventricular septal defect (VSD) that involved 35% of CHD patients; and the considerable type of cyanotic CHD is Tetralogy of Fallot (TOF) (1, 6). Recently, has been conducted a study in Khuzestan province of Iran, and resulted that the prevalence was 12 to 30 in 1000 live birth (1).

On the other hand, due to the high mortality of CHD in neonates with severe types and the burden due to not recognizing and treating the disease, and also problems and limitations in elders, the disease is known to be the most important congenital anomaly (7). Unfortunately, the cause of CHD is mostly unknown in neonates. Some of these defects are due to genetic changes and some combined of genetic and other risk factors such as exposure to environmental factors or maternal nutrition or maternal drug using (5). It is estimated that 15% of the causes of CHD are due to genetic impairments (1); and although a greater percentage of the disease is affected by environmental factors, much information is not available about these environmental factors that are effective in the development of CHD, which is why prevention of this disease has almost stopped because of the lack of information on these modifiable factors; and for most cardiac anomalies there is no effective primary prevention method (8). 25(OH) Vit D deficiency is a highly prevalent condition, present in approximately 30% to 50% of the general population. A growing body of data suggests that low 25(OH) Vit D levels may adversely affect cardiovascular health and shown a link between the levels of serum 25(OH) Vit D and cardiovascular disease (9). 25(OH) Vit D is a type of fat-soluble vitamin that is required for the proper functioning of many organs of the body (10), and expressed that it is not just one 25(OH) Vit D, but it can be said to be a steroid hormone that can be produced internally or it is achieved through diet. A large portion of 25(OH) Vit D is synthesized by ultraviolet radiation in the skin of the humans (11, 12). Identification of 25(OH) Vit D receptors in endothelial cells, smooth muscle cells, and myocytes from the heart has led to the hypothesis that this 25(OH) Vit D is involved in cardiovascular disease (11).

Also, new evidence suggests that the relationship between 25(OH) Vit D deficiency and increased risk of other diseases have been raised such as autoimmune diseases namely, diabetes type I, multiple sclerosis, rheumatoid arthritis, hypertension, infectious diseases and malignancies (12); 25(OH) Vit D deficiency is a common finding that is found in all age groups and in both genders (13), and as a health problem in the whole world (12). It has been reported that a billion people across the world have 25(OH) Vit D deficiency and even in India, it has been reported that, despite extensive sun exposure, most children have 25(OH) Vit D deficiency (12). Among 6-year-old children, 26% had 25(OH) Vit D deficiency (14). Considering the high prevalence of 25(OH) Vit D deficiency and its association with CHD

along high mortality and morbidity among CHD children in Iran, as well as the lack of adequate studies in this field, we decided to study measuring the serum levels of 25(OH) Vit D in CHD children compared to controls.

2- MATERIALS AND METHODS

This case-control study conducted on equal CHD and healthy children aged 6 months to 15 years' old who referred to Ali Asghar and Ali Ebne Abi Talib Hospitals in Zahedan southern city in Iran during the year of 2017. The participants were hospital randomized samples. The patients collected from the in-patient or out-patient from the cardiac clinic of these two hospitals and controls were selected from those who referred for routine checkup.

2-1. Criteria

Exclusion criteria in the case and control groups were using of drugs that affect calcium and bone metabolism, chronic liver or kidney disease, endocrine disorder such as hyperparathyroidism, insulin use, using of anticonvulsants.

2-2. Sample size

Considering the following formulae based on needed parameters derived 276, with 138 cases and 138 controls. In the duration of the data collection for case group derived 135 patients and we analyzed the data for this population that were considered equal with controls.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 (s_1^2 + s_2^2)}{(\bar{x}_1 - \bar{x}_2)^2} = \frac{3.2}{(1.5)^2} = 138$$

Where, first type error (α) = 0.05, Second type error (β) = 0.2, Levels of 25(OH) Vit D variance in case = 4.13, the level of 25(OH) Vit D in the controls = 4.8, average level of 25(OH) Vit D in case= 16.74, mean level of 25(OH) Vit D in the controls= 18.24.

2-3. Measurements

Patients were diagnosed via echocardiography (My lab 60, Italy) with a 3 to 8 MHz transducer. Patients were divided into two groups in terms of disease severity: cyanotic and acyanotic. This categorization performed based on the O_2 saturation. The patients who had O_2 sat lower than 85%, named cyanotic and others acyanotic; 3 ml of venous blood were taken from the children to measure 25 (OH) D serum levels. All serums were stored in a refrigerator at Ali ibn Abi Talib Hospital and then sent to one of the reputable labs in the city by storing the cold chain conditions. Serum samples were isolated after centrifugation and were kept at -80 °C until testing. The serum 25 (OH) D levels were measured using the ELISA method (Euroimmun kit, Medizinische Labordiagnostika AG, Germany, EQ 6411-9601).

2-4. Anthropometric measures

Participants' height and weight were determined according to standard anthropometric methods. Participants height over 2 years of age was measured to the nearest 0.1 centimeters (cm) in bare feet with participants standing upright against a Mounted Stadiometer and for the participant lower than two years of age height was measured with a wooden scaled table in supine position. Weight was measured to the nearest 0.1 kilogram (kg) with participants lightly dressed using a portable digital scale (Tanita HD 309, Creative Health Products, MI, and USA). Weight of participants lower that two years old, measured by Mika Mark recumbent weighing scale made in Japan with an error factor of 10 gr.

2-5. Ethics

Ethical notes were considered in all the stages of study such as sampling, collecting controls from hospital base and case collection from the neonate ward. The parents of children informed from the aims of the study and after taking signature

from them on the constant form, their children entered to the study. This study approved by Medical Research Ethics Committee of Zahedan University of Medical Sciences as a GP dissertation (ID-number: 1737).

2-6. Statistical method

Data were analyzed using SPSS software version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Descriptive statistics were expressed as mean ± SD for quantitative variables and frequency for qualitative variables. For inferential statistics, independent t test, one-way analysis of variance and Chi-square test (X^2) were used with considering 95% CI (5% error).

3- RESULTS

Of participants 48.9% were male and of patients 20.7% were cyanotic. The mean age of CHD and healthy children were 6.04 ± 4. 52 and 5.24 ± 3.29 years, respectively with non-significant difference (t = 1.65, P = 0.101). The means of weight were lower in case (18. 02 ± 10.39 kg) compared to controls (20.55 ± 10.56 kg) significantly (t = -1.98, p = 0.049). The mean of 25(OH) Vit D was lower in case (26.07 ± 19.76 ng/ml) compared to controls (42.20 ± 14.31 ng/ml) significantly (t = -7.62, p= 0.001).

The means of age were 6.24± 5.09 and 5.98± 4.38 years in cyanotic and acyanotic, respectively; but non-significant (t = 0.27, P = 0.787). The mean weight of patients was 14.59± 9.23 and 18.92± 10.53 kg between the two groups of cyanotic and acyanotic respectively (t = -1.99, P = 0.049). The serum levels of 25(OH) Vit D in cyanotic and acyanotic groups were 14.49±6.18 and 29.11 ± 2.03 ng/ml, respectively; and the difference was significant in favor of cyanotic (t = -3.14, P = 0.004). The serum levels of 25(OH) Vit D in males and females were 25.23±17.71 and 26.91±21.70 ng/ml, respectively and the different was significant in favor of cyanotic (t = -0.49, P = 0.622) (**Table.1**). **Table.2** showed the levels of 25(OH) Vit D in different age groups of patients. The patients categorized based on the ages of 0-2, 2-5, 5-10 and > 10 years, and the mean levels of 25(OH) Vit D in these age groups were 256±16.61, 31.52±29.00, 30.55±17.60 and 19.35±13.82 ng/ml, respectively that this dereference was significant (f=2.815, p=0.042); but the follow up Tukey tests did not show any significant different between the groups.

Table.3 showed the means of weight and 25(OH) Vit D in cyanotic and acyanotic patients in different age groups. In patients aged < 2 years, weights' mean was 5.72±1.15 and 8.30±1.60 kg in cyanotic and acyanotic patients respectively (t=-4.432, p<0.001). In patients aged 2-5 2 years, weights mean was 9.003±2.83 and 12.80±3.25 kg in cyanotic and acyanotic patients, respectively (t=-2.195, p=0.037). In patients aged 5-10 years, weights mean was 14.40±2.70 and 20.11±5.50 kg in cyanotic and acyanotic patients (t=-2.25, p=0.032); and in patients aged >10 years, the weights mean was 24.900±6.136 and 31.56±8.48 kg in cyanotic and acyanotic respectively (t= -2.285, p=0.028).

In patients aged < 2 years, the serum levels of 25(OH) Vit D were 16.64±4.93 and 28.98±18.12 ng/ml in cyanotic and acyanotic, respectively (t= -3.14, p=0.004). Similar to patients aged < 2 years, in the patients aged 2-5 years, the serum levels of 25(OH) Vit D were 15.80±10.86 and 34.14±30.36 ng/ml in cyanotic and acyanotic, respectively (t= -2.225, p=0.044). Patients with cyanotic who aged 5-10 years had higher serum levels of 25(OH) Vit D (15.78±4.10 ng/ml) compared to acyanotic with similar age (32.60±17.89 ng/ml) significantly (t= -4.378, p=<0.001). The patients higher than 10 years had lower level of serum 25(OH)

Vit D (11.54±5.59 ng/ml) when they had cyanotic diseases compared to those who had acyanotic (21.95±14.81 ng/ml) significantly (t= -3.228, p=0.003).

Table-1: The age, weight and 25(OH) Vit D comparison between groups of participants.

Variables	Group of participants	Mean ± SD	t-value	P-value
Age (year)	Case	6.035±4.517	1.646	0.101
	Control	5.244±3.289		
Weight (kg)	Case	18.024±10.393	-1.978	0.049
	Control	20.546±10.560		
25(OH) Vit D, (ng/ml)	Case	26.07 ± 19.76	-7.62	<0.001
	Control	42.198±14.310		
Weight (kg)	Cyanotic	14.589±9.226	-1.986	0.049
	Acyanotic	18.922±10.532		
Age (year)	Cyanotic	6.242± 5.092	0.271	0.787
	Acyanotic	5.981± 4.378		
25(OH) Vit D (ng/ml)	Cyanotic	14.49 ± 6.18	-3.64	<0.001
	Acyanotic	29.11 ± 2.03		
25(OH) Vit D (ng/ml)	Male	25.23 ± 17.71	-0.494	0.622
	Female	26.91 ± 21.70		

SD: Standard deviation; 25(OH) Vit D: 25-hydroxy vitamin D.

Table-2: The results of Analysis of Variance test of the serum levels of 25(OH) Vit D in different age groups of patients.

Variables	Age Groups (year)	Mean ± SD	Lower Bound of mean	Upper Bound of mean	F- value	P- value
25 (OH) Vit D (ng/ml)	0-2	25.64 ± 16.61	19.85	31.44	2.815	0.042
	2-5	31.52 ± 29.00	20.27	42.76		
	5-10	30.55 ± 17.60	23.81	36.29		
	>10	19.35 ± 13.82	14.93	23.76		
	Total	26.07 ± 19.76	22.71	29.44		

SD: Standard deviation; 25(OH) Vit D: 25-hydroxy vitamin D.

Table-3: Weight and 25(OH) Vit D comparison in various age groups of patients (cyanotic versus acyanotic children).

Variables	Age group (year)	CHD	Number	Mean ± SD	t-value	P- value
Weight (kg)	< 2	Cyanotic	9	5.722 ± 1.149	-4.432	0.000
		Acyanotic	25	8.304 ± 1.598		
	2-5	Cyanotic	4	9.000± 2.828	-2.195	0.037
		Acyanotic	24	12.800 ± 3.252		
	5-10	Cyanotic	5	14.400 ±2.701	-2.250	0.032
		Acyanotic	28	20.107± 5.499		
	>10	Cyanotic	10	24.900 ± 6.136	-2.285	0.028
		Acyanotic	30	31.560± 8.480		
25(OH) Vit D (ng/ml)	< 2	Cyanotic	9	16.64 ± 4.93	-3.14	0.004
		Acyanotic	25	28.95 ± 18.12		
	2-5	Cyanotic	4	15.80 ± 10.86	-2.225	0.044
		Acyanotic	24	34.14 ± 30.36		
	5-10	Cyanotic	5	15.78 ± 4.10	-4.378	<0.001
		Acyanotic	28	32.60 ± 17.89		
	>10	Cyanotic	10	11.54 ± 5.55	-3.228	0.003
		Acyanotic	30	21.95 ± 14.81		

SD: Standard deviation; 25(OH) Vit D: 25-hydroxy vitamin D; CHD: Congenital heart disease.

4- DISCUSSION

The results of the present research showed weight, the level of 25(OH) Vit D serum in children with CHD and healthy based on different age groups. In all age groups of patients, the levels of serum 25(OH) Vit D were lower in cyanotic patients. Recognizing the 25(OH) Vit D receptor in endothelial cells, smooth muscle cells, and myocytes in the heart has prompted the theory that 25(OH) Vit D is engaged with cardiovascular illness (12), and actually, debilitated capacity of this receptor in cardiovascular cells unsettling influences in diastole, and in the end cardiovascular complications (14,15). 25-hydroxyvitamin D inadequacy is a typical finding in all age scope of both genders (12). The aftereffects of this investigation demonstrated that there was a huge distinction between serum 25(OH) Vit D levels in youngsters with CHD contrasted and controls, which was bring down in the patients. Different investigations have analyzed the connection between 25(OH) Vit D and coronary illness. In an investigation by Maiya et al., that led an examination on babies with dilated cardiomyopathy, demonstrated that the mean serum levels of 25(OH) Vit D was lower than ordinary status and the seriousness of the disease related with the rate of 25(OH) Vit D inadequacy (16). Patange et al., discovered that 25(OH) Vit D inadequacy pervasive in the patients and this deficiency was straightforwardly identified with the expansion in left ventricular mass and diastolic brokenness (17). In the investigation of Shedeed et al., babies with HF bring down serum levels of 25(OH) Vit D contrasted with typical kids and 25(OH) Vit D supplementation was related altogether to enhance cardiovascular capacity (18). In an examination by Uysal et al., on 27 babies

with an analysis of 25(OH) Vit D inadequacy in rickets contrasted and healthy newborn children, demonstrated that 25(OH) Vit D insufficiency in infants with left ventricular dysfunction was related with extreme left ventricular dysfunction and with clear clinical signs (19). McNally et al., led two examinations on CHD patients who experienced surgery and came about that expanding 25(OH) Vit D inadequacy was a result of losing it amid surgery and have been related with more awful clinical outcomes (20, 21). In an examination by Graham et al., on neonates with CHD who were hospitalized for cardiopulmonary sidestep cardiomyopathy surgery, the mean serum 25(OH) Vit D level in all neonates who partook in the investigation were lower than ordinary level (22). In the investigation of Izumi et al. on patients with CHD, the levels of 25(OH) Vit D in CHD patients was uncovered and bring down level of 25(OH) Vit D was related with a higher seriousness of the illness (serum levels of 25(OH) Vit D are characterized as under 50 nmol/l) (23).

In a cohort study conducted by Nargesi et al., on patients with essential hypertension with the aim of evaluating the association of 25(OH) Vit D deficiency and CHD. They found that the serum levels of 25(OH) Vit D and the coronary events were correlated and those with the lowest levels of 25(OH) Vit D have experienced the highest severity of the disease (24). Roy et al., reported that people with acute MI and control had high incidence of 25(OH) Vit D deficiency, but severe deficiency 25(OH) Vit D (less than 10ng / ml in this study) was significantly higher in the people with acute myocardial infarction (MI) than controls (12). In a randomized, double blind clinical trial that conducted on a population with a higher age group than our study by Trivedi et al., found that the rate of cardiovascular events and the associated deaths were similar in the groups of receiving 25(OH) Vit D supplementation and controls that did not consume 25(OH) Vit D (25). The results were different with our study that might be was due to inadequate supplementation of 25(OH) Vit D and also a higher age group than our study. In a study by Izumi et al., on individuals with CHD with higher age group than ours, it has been shown that the difference between mean serum levels of 25(OH) Vit D in different age was similar (23) that this finding was not consistent with the results of our studies, which is probably due to differences in age groups, different population with a gap in life style and society Nargesi et al. (24) found a significant difference between the different age groups in patients consistent with the results of present study. Kim and colleagues determined a significant relationship between serum 25(OH) Vit D level and hypertension in different age groups and gender and concluded no significant difference in serum levels of 25(OH) Vit D in the gender (26). Izumi et al., found no statistically significant difference between the serum levels of 25(OH) Vit D in gender (23).

Sheikh et al., In Pakistan, suggested that the distribution of 25(OH) Vit D deficiency between male and female groups in healthy people were same (27) but in a study by Vahabzadeh et al., in West Azerbaijan province, Iran showed that the level of 25(OH) Vit D deficiency increases in healthy females (28). Despite of the different geographic and cultural conditions, Sheikh et al., results was in relation with ours (27). Also, in the study of Nargesi et al., in Tehran, found that the serum level of 25(OH) Vit D was significantly different between the two sexes (24); which was dissimilar with the results in our study, and this difference may be due to the greater percentage of female participants (65%) in Nargesi et al., study, in addition to different geographical and cultural conditions than our study

population. According to the findings of this study there was a significant difference between the serum levels of 25(OH) Vit D in the two groups of patients (cyanotic and non-cyanotic), which was significantly lower in the cyanotic group. Also revealed that the age range of 6 months to 2 years and more than 10 years were significant. A study by Izumi et al., found that lower levels of 25(OH) Vit D were associated with a higher incidence of CHD (23), consistent with our findings. Our findings indicated that the mean weight in children with CHD was significantly lower than the mean weight in healthy children, which found similar results by Okoromah et al., in Nigeria (29).

Also, in our study, among children with CHD, the mean weight in the cyanotic group was significantly lower than the acyanotic group, which was consistent with Okoromah et al. (29). They noted that Z-score of weight for age (WAZ), weight for height (WHZ) and height for age (HAZ) were significantly higher in children with CHD compared the controls (29). In the study by Noori et al., on 60 children with CHD and 30 healthy, the BMI of children with CHD was significantly lower than the BMI of healthy children (30). These findings were also consistent with the results of our study. Also, in another study by Noori et al., on children with CHD 72% of the patients under the age of 5 had low weight and 57.8% of children under the age of 5 were lower in height and 49.6% were below the 5th percentile in weight and height (31).

4-1. Limitations of the study

The study limitation was lack of Proper Corporation by participants especially controls.

5- CONCLUSION

In this study, it was generally observed that serum levels of 25(OH) Vit D in children with CHD were significantly lower than the controls. There was no significant difference between serum levels of 25(OH) Vit D in both sexes and in patients with different age groups. The value of 25(OH) Vit D was significantly different between the two groups of cyanotic and acyanotic, so that in the group of children with CHD, cyanotic had lower.

6- CONFLICT OF INTEREST: None.

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