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ORIGINAL ARTICLE – OPEN ACCESS

Evaluation of Vitamin D Levels in the Course of Acute Rheumatic Fever with Active Carditis

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ABSTRACT

Objective: Vitamin D is a hormone with immunomodulatory and anti-inflammatory effects besides calcium hemostasis. The present study aims to evaluate the relationship between acute rheumatic fever (ARF) attacks and vitamin D levels.

Materials and Methods: Acute phase reactants, vitamin D levels and echocardiographic parameters of 25 patients with active carditis were evaluated at the time of the acute attack and in 1, 2 and 6 months of follow-up and compared to a control group of 25 age-and sex-matched healthy children.

Results: At the time of diagnosis, WBC, ESR and CRP levels were significantly higher ($p<0.05$), and vitamin D levels were lower than the control group, not statistically significant ($p=0.07$). The mean vitamin D levels of the patients diagnosed in winter and spring-autumn seasons were 17.54±9.89 µg/L, and the rate of vitamin D deficiency was 47.3%. The mean vitamin D levels of the control group, in the same seasons, were 23.97±9.48 µg/L and the vitamin D deficiency rate was 19.1%. The vitamin D levels at the time of diagnosis of the ARF group were lower than the control group ($p=0.038$) and the attributed risk for vitamin D deficiency in ARF carditis in winter and spring seasons was found 3.46 (95% CI 1.1–5.14). Furthermore, cardiac parameters were significantly getting better, while vitamin D deficiency rates decreasing during the follow-up period.

Conclusion: ARF attacks were found to be more frequent in non-summer seasons when vitamin D levels were lower. Echocardiographic and laboratory parameters improved with increasing vitamin D levels. These findings suggest that anti-inflammatory and immunomodulatory effects of vitamin D.

Keywords: Rheumatic fever, vitamin D, carditis

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INTRODUCTION

Acute rheumatic fever (ARF) is the most common cause of acquired heart disease in developing countries (1). ARF is an inflammatory collagen tissue disorder that manifests symptoms in tissues, such as joints, heart, skin and nervous system, which show antigenic similarity to group A beta-hemolytic streptococci (2). The mechanism responsible for the development of ARF is an increased cellular and humoral response. In patients with acute rheumatic fever, intense infiltration of lymphocytes and macrophages was observed in the region of the lesion in the heart, and these cells proved to have an important role in the pathogenesis (3).

Vitamin D is a vital steroid formed hormone, which affects organisms in all life. The receptors of vitamin D are available on almost all cells and tissues of the human body, such as brain, muscle and bone tissues, also found in immune system cells, such as macrophages, T lymphocytes and monocytes (4, 5). Besides, its well-known effects on calcium and other mineral metabolisms on bone tissue, there are too many immunomodulatory and anti-inflammatory effects of vitamin D in the human body (6). It is thought to display these modulatory effects by regulating proliferation, maturation and cytokine/chemokine proliferation of immune system cells. Low vitamin D levels have been reported to be associated with increased cancer incidence and cardiovascular mortality, also immune disorders in recent years (7, 8). Many autoimmune and autoinflammatory diseases, such as systemic lupus erythematosus (SLE), Hashimoto thyroiditis, rheumatoid arthritis (RA) and inflammatory bowel diseases (IBD), were investigated by several researchers (9–11). The findings showed that vitamin D insufficiency contributes to the inflammatory process and that disease activity and vitamin D levels are inversely proportional.

Strong evidence shows that individuals with low vitamin D levels tend to have autoimmune disorders were reported in the current literature. However, to our knowledge, there is no adequate study about the link between vitamin D levels and ARF, which is the most common and pervasive reason for acquired heart disease among 5–15-year-old children in developing countries. The present study aims to monitor vitamin D levels in pediatric patients with ARF associated active carditis at the time of diagnosis and in the course of disease.

MATERIALS and METHODS

Patients and Control Group

Twenty-five children aged between 4–17, who referred to the Pediatric Cardiology Department of our tertiary hospital with active rheumatic carditis, were included in this study. Patients were diagnosed as ARF using Modified Jones Criteria, who met two major or one major and two minor criteria (12). Twenty-five age- and sex-matched healthy children were included as a control group. They did not have any chronic diseases and did not receive vitamin D replacement. Demographic and anthropometric data of both groups, such as age, sex, weight and height measurements, were recorded. Also, the presence of clinical features, such as arthritis, arthralgia, carditis and Sydenham chorea, were noted in the patient group. All patients with active carditis received non-steroidal anti-inflammatory treatment following systemic steroid and aspirin; however, vitamin D replacement was not administrated.

Cardiological Evaluation

Detailed physical examination, blood pressure measurements, 12-lead electrocardiographic (ECG) and echocardiographic evaluations were performed for both groups. Cardiac murmurs, heart rate, blood pressure, P-R distances and presence of arrhythmias were noted. Echocardiographic evaluations of all individuals were assessed with the GE-Systems V brand machine by an expert pediatric cardiologist. Left ventricular functions in parasternal, apical four cavities and subcostal positions by M mode, B mode and color Doppler echocardiographic examination were performed at the time of diagnosis and at the end of 1st, 2nd and 6th months after diagnosing ARF. Echocardiography was performed only once for control group. Mitral and aortic valve regurgitations (MR, AR) left atrium (LA), aortic root (Ao), left ventricular end-diastolic and end-systolic diameters (LVEDd and LVESd) were evaluated in all visits. Physiological or pathological valvular regurgitations were evaluated by measuring regurgitated color length in color Doppler echocardiographic evaluation. If valvular insufficiency flow <1.5 cm, insufficiency was accepted as 1st degree (mild), 1.5–2.9 cm 2nd degree (medium) and 3–4.4 cm 3rd degree (heavy). If it was higher than 4.5 cm, it was considered as 4th degree (heavy) valvular regurgitation.

Laboratory Assessment

The blood samples were taken for the ARF group at the time of diagnosis and all visits during the follow-up period, at the end of 1st, 2nd and 6th months, and only once for the control group. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), 25-OH vitamin D levels, also calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) and parathormone (PTH) levels were evaluated for both groups and in all visits.

Vitamin levels were studied instantly as soon as blood samples were taken. The vitamin D levels were studied with 25-OH D2 HPLC (high-performance liquid chromatography) method using the Zivak ZV-4007-1000-10 device. The levels under 20 µg/L were accepted as vitamin D insufficiency according to the cut-off value in a recent study conducted by Munns CF et al. (13).

Statistically Analysis

Data were analyzed using IBM SPSS Statistics 22 statistical package program. The normal distribution of numerical variables was examined by the Shapiro-Wilk normality test. Median and interquartile range (25th percentile – 75th percentile) was used for non-normally distributed variables, whereas mean±SD values for normally distributed variables. Mann-Whitney U test was used for the data containing median values, and the Independent Samples Test was used for the comparison of mean values. During the follow-up, the statistical analysis of the recurrent data was performed with the Related Samples Friedman's Two-Way Analysis test. A p-value of <0.05 was considered statistically significant for all parameters evaluated.

Table 1. Demographic features and laboratory and echocardiographic results in ARF (n=25) and control groups (n=25) at the time of diagnosis

	ARF group n=25	Control group n=25	p
Gender	13 (52%) male 12 (48%) female	11 (44%) male 14 (56%) female	0.112
Age (years)	11.4±2.5	10.68 ±3.09	0.878
WBC (cell/µL)	**10765±4700***	**7050±1400***	**0.007**
ESR (mm/h)	**53.36±26.73***	**8.00 (2.00–12.00)****	**<0.001**
CRP (mg/L)	**24.6 (10.22–69.10)****	**3.45 (3.36–3.50)****	**<0.001**
Ca (mg/dL)	**9.29±0.48***	**9.6±0.41***	**0.03**
P (mg/dL)	4.44±0.47*	4.49±0.52*	0.67
ALP (U/L)	151.4±46.7*	171±46.1*	0.09
PTH (pg/ml)	37.8±21.3*	34.5±15.1*	0.64
D-vitamin (µg/L)	19.9±10*	24.2±9.4*	0.07
LVESd (Z-score)	0.29 (0.10–0.38)**	0.15±0.08*	0.264
LVEDd (Z-score)	**0.29 (0.13–0.74)****	**0.12 (0.03–0.24)****	**0.003**
La/Ao	1.3±0.28*	1.2±0.14*	0.077

*Mean±SD; **Median (25 percentage–75 percentage); WBC: White blood cell; ESR: Erythrocyte sedimentation rate; CRP: C- reactive protein; Ca: Calcium; P: Phosphor, ALP: Alkaline phosphatase; PTH: Parathormone; LVEDd: Left ventricular end-diastolic diameter; LVESd: Left ventricular end-systolic diameter; LA/Ao: Left atrium and aortic root ratio

RESULTS

Demographic and Clinical Features

Of the 25 patients included in this study, 13 (52%) was male and 12 (48%) was female, the male/female ratio was 1.1 in the ARF group. The mean ages of ARF and control groups were 11.4±2.5 and 10.68±3.09 years, respectively. Three-quarter of patients (76%) were aged between 10–15 years. There was no significant difference between ARF and control groups concerning gender and age (Table 1). All patients had active carditis and arthritis, and five of them (20%) had Sydenham chorea. Regarding the seasonal evaluation of diagnosis time, 76% of the patients were diagnosed as ARF in winter and spring-autumn seasons, while only 24% were in summer.

Laboratory Results at the Time of Diagnosis

White blood cell count, ESR and CRP levels were statistically higher in the ARF group than in the control group at the time of diagnosis ($p<0.05$ for all parameters). Vitamin D levels were

Table 2. Laboratory and echocardiographic results of ARF group (n=25) in the follow-up period

	At the time of diagnosis	At the end of the 1st month	At the end of the 2nd month	At the end of the 6th month	p
WBC (cell/μL)	**10765±4700^{a*}**	**10983±5770^{bc*}**	**8916±3863^{c*}**	**8046±1678^{b*}**	**<0.0011**
CRP (mg/L)	**24.6 (11.26–68.55)^{a**}**	**3.45 (3.36–3.67)^{b***}**	**3.45 (3.36–6.70)^{b***}**	**3.45 (3.36–3.5)^{b***}**	**<0.0012**
ESR (mm/h)	**50 (34–71)^{a**}**	**14 (4.5–21)^{bc**}**	**9 (5–19)c****	**8.5 (2–13)^{c**}**	**<0.0012**
LVESd (Z-score)	**0.16 (0.10–0.370)^{a}**	**0.13 (0.09–0.20)^{ac}**	**0.07 (0.02–0.19)^{b}**	**0.06 (0.03–0.17)^{bc}**	**<0.001***
LVEDd (Z-score)	**0.29 (0.13–0.71)^{a}**	**0.18 (0.05–0.67)^{ab}**	**0.12 (0.02–0.53)^{c}**	**0.11 (0.01–0.50)^{c}**	**<0.001***
La/Ao	1.33 (1.17–1.54)**	1.33 (1.18–1.51)**	1.19 (1.10–1.49)**	1.16 (1.05–0.36)**	0.66*
Vitamin D	18.26 (7.15–21.16)**	16.12 (10.11–18.25)**	19.16 (12.01–23.18)**	20.31 (14.02–25.17)**	0.09

*Mean±SD; **Median (25 percentage–75 percentage); WBC: White blood cell; ESR: Erythrocyte sedimentation rate; CRP: C- reactive protein; LVEDd: Left ventricular end-diastolic diameter; LVESd: Left ventricular end-systolic diameter; LA/Ao: Left atrium and aortic root ratio

lower in the ARF group (19.9±10 μg/L) than control (24.21±1.88 μg/L), but the difference was not statistically significant (p=0.07) (Table 1). However, when we compared vitamin D levels of both groups regarding diagnosis time, we found that the patients who were diagnosed in spring-autumn and winter months (n=19) had lower vitamin D levels (17.54±9.89 μg/L) than healthy controls (23.97±9.48 μg/L) in the same months (n=23), and the difference was statistically significant (p=0.038). Furthermore, the rate of vitamin D insufficiency was statistically higher in the ARF group diagnosed in winter and spring months (47.3%) than in the control group (19.1%) (p<0.05). The odds ratio for vitamin D insufficiency in patients diagnosed with ARF carditis in non-summer seasons was calculated as 3.46 (95% CI 1.1–5.14).

Echocardiographic Results at the Time of Diagnosis

Active carditis was determined in all patients in the ARF group and all of them had mitral valve involvement. In addition, 48% of them had aortic valve involvement at the time of diagnosis. The median Z-score of left ventricular end-diastolic diameter (LVEDd) was 0.29 in the ARF group and 0.12 in the control group. The difference was statistically significant (p<0.05). Also, left ventricular end systolic diameters were higher in the ARF group; however, there was no statistical significance (p>0.05). The left atrium and aortic root ratio (LA/Ao), which is a good marker for cardiac involvement in ARF, was 1.3±0.28 and 1.2±0.14 in ARF and control group, respectively. There were higher LA/Ao ratios in the ARF group; however, the difference was not statistically significant (p>0.05) (Table 1).

Laboratory and Cardiac Parameters in the Follow-up Period

In the course of the disease, the biochemical and echocardiographic markers were getting better in the ARF group. White blood cell counts, ESR and CRP values decreased in six months period (p<0.05 for all values). Moreover, the cardiac parameters, such as LVEDd, LVESd and LA/Ao, decreased in the course of the follow-up period (Table 2).

We had heterogeneous results about the levels of vitamin D, due to seasonal variability in the follow-up period for the patient group, and no statistically significant results could be obtained. However, we determined that the vitamin D levels of 19 patients that diagnosed in winter and spring months were statistically increased for a six-month follow-up period (p<0.05). The vitamin D levels were 17.54 μg/L at the time of diagnosis, 15.08 μg/L at the end of the first month, 17.54 μg/L at the end of the second month and 23.47 μg/L at the end of the 6th month in this group. ESH and CRP values were decreasing in ARF patients who diagnosed in winter and spring months, while vitamin D levels were increasing (p<0.05). Similarly, cardiac parameters, such as mitral and aortic regurgitations, were getting better in the ARF group that diagnosed in winter and spring months, while vitamin D levels were increasing (p<0.05). The median degree of mitral valvular regurgitation decreased from 2.6 grade at the time of diagnosis to 1.3 grade at the end of the 6th month. In addition, the median degree of aortic valvular regurgitation decreased from 0.88 to 0.32 at the same time. These improvements were statistically significant for ARF group (p<0.05).

The rates of vitamin D insufficiency statistically decreased in the follow-up period for ARF group, regardless of the seasonal variation (p<0.05). This rate was 48% at the time of diagnosis, while it was 44% at the end of the first month, 40% at the end of the second month and 20% at the end of the 6th month. Clinical, laboratory and echocardiographic parameters were getting better while the rate of vitamin D insufficiency was decreasing in the ARF groups follow-up period for all patients.

DISCUSSION

Vitamin D has an important role in regulating immunity and resisting autoimmune disorders. In other words, insufficiency of vitamin D increases the tendency to autoimmune diseases (14, 15). We found that insufficiency of vitamin D was more common in children with ARF and active carditis than in the healthy group. In addition, clinical, laboratory and echocardiographic features of patients with ARF were getting better while vitamin D levels were increasing, in the course of disease.

Acute rheumatic fever is a cross-reactional immune disorder to group A streptococcal infections, which may be an endemic problem in spring-autumn and winter months (1, 15). Vitamin D levels also have the lowest values in the mentioned seasons because UV sunlight cannot be benefited adequately. Lower levels of this immunomodulatory agent may be one of the contributing factors in the development and progression of this disease. In the current

study, 76% of the patients with ARF with active carditis referred to a hospital in spring-autumn and winter seasons, and the vitamin D levels of these patients were statistically lower than controls. In the literature, there were many studies about seasonal variation in the course of autoimmune disorders (16, 17, 18, 19). Multiple sclerosis, as an autoimmune disorder of the central nerve system and IBD, the autoimmunity of the digestive system was found to be influenced by seasons. In winter and spring months, they had a progressive clinic due to lower vitamin D levels and other environmental factors (17).

There is intimate knowledge about a strong negative correlation between vitamin D levels and inflammation, as well. Dendritic cells and macrophages via inhibiting IL-12, a critical agent in Th1 development, mediate the regulatory role of vitamin D on inflammation (20, 21). In addition, active vitamin D affects T-cell polarization by inhibiting T helper 1 and IFN-gamma production, also promoting Th2 cell development for IL-4, IL-5, and IL-10 production from naïve T-cells (22). T helper 1 cells, which express CD 4+ surface antigen is an important liable agent for developing ARF, especially with valvular involvement (23). In addition, deficiency of anti-inflammatory CD4+ T cells contributes to clinical and increasing acute phase reactants in the ARF (24). In this study, there were higher acute phase reactants, such as ESR and CRP, with higher WBC values in the ARF group than controls at the time of diagnosis, while there were lower vitamin D levels. Furthermore, levels of vitamin D were increasing during the follow-up period of ARF group, while laboratory markers of inflammation were getting better. We further speculate that increased vitamin D levels might have a positive effect on decreasing inflammation and acute phase reactants in the course of ARF. There are many studies about the relationship between acute phase reactant values and vitamin D levels. In a study conducted by Onan et al. (18), it was reported that pediatric patients with ARF had lower vitamin D levels than healthy controls; however, there was no correlation between carditis and vitamin levels. Mok et al. (19) reported that lupus patients with lower vitamin D levels had higher acute phase reactant values and higher disease activity; they also emphasized the immunomodulatory effects of vitamin D in autoimmune diseases. Another study by Di Franco et al. (25) reported that there was a negative correlation between rheumatic arthritis patient's disease activity and responsiveness to treatment and vitamin D levels. Similarly, a metanalysis about the relation between IBD and vitamin D demonstrated that IBD patients with lower vitamin D levels had higher disease activity, lower life quality, higher acute phase reactants and clinically active disease (26).

Environmental factors, especially vitamin D, may play an important role in cardiac health. Clinical and echocardiographic outcomes of many cardiac diseases, such as heart failure, rheumatic valvular disease, pulmonary hypertension and coronary artery disease adversely affected by vitamin D insufficiency (14, 16, 26). This positive effect of vitamin D on the heart can be thanked to inhibiting the renin-angiotensin system, blockage of matrix-metalloproteinase producing, besides inhibiting inflammatory system (27). In the current study, we found that there were lower vitamin D levels at the time of diagnosis with higher valvular regurgitations, LVESd, LVEDs and LA/Ao values. Therefore, these echocardiographic parameters were getting better in the course of the disease when levels of vitamin D were increasing in addition to their anti-inflammatory treatment. Yusuf et al. (15) reported an inverse correlation between active vitamin D levels and mitral valve stenosis related to rheumatic fever. Matter et al. (26) studied the link between vitamin D and myocardial functions and reported that LVEDd and LVESd were higher in healthy adolescents with vitamin D deficiency. A similar study by Sheeded et al. (28), about infants with heart failure reported that vitamin D supplementation promoted to getting better the echocardiographic parameters, such as ejection fraction of LV, LVEDd and LVESd. They also emphasized the cardioprotective effects of vitamin D and it can be used for supportive care in infancy heart diseases.

Monitoring the levels of vitamin D was difficult throughout the year because of the seasonal variability. The fluctuation of this value was a disadvantage for our study; eventually, we could not find statistically significant results about all ARF patients' vitamin D states in the course of the disease. However, healthy results could be obtained when seasonal variability was disabled and comparing the patients and control groups who applied in the same seasons. In addition, another handicap of our study was ignoring vitamin D receptor polymorphism (VDRP). VDRP is an indicator as strong as levels, about the bioactivity of vitamin D.

To our knowledge, this study was the first study about the progression of vitamin D levels during the disease period of rheumatic fever with active carditis in children. We think this study may lead the way for future studies about the link between nutrition and ARF that is the most important acquired heart problem in the childhood period. Maybe vitamin D will be used in rheumatic carditis for immunomodulation effects soon.

Ethics Committee Approval: Ethical approval was obtained from the decision of ethics committee of Erciyes University Clinical Research Ethics Committee, numbered 2014/38 and dated 24 January 2014.

Informed Consent: Informed consent forms were taken for all children's parents in both patient and control groups.

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