Evaluation of vitamin D levels in patients with acute rheumatic fever

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Acute rheumatic fever (ARF) is a nonsuppurative complication of pharyngitis caused by group A beta-hemolytic streptococcus (GAS) whose underlying pathological mechanisms have not yet been fully elucidated (1). Vitamin D deficiency is a global health problem, particularly in the pediatric age group. Some immunomodulator and anti-inflammatory effects of vitamin D on various infectious and autoimmune diseases have also been reported. In limited number of pediatric studies low serum 25(OH)D levels have been reported in children with autoimmune diseases (2). Incidences of GAS infection and ARF make a seasonal peak at winter and spring months when 25(OH)D levels are expected to be lowest because of the lack of exposure to sunlight (3, 4). In addition to the high risk of developing ARF, children in the age group of 5–15 years are growing up rapidly, with increased vitamin D requirement. In present study, we evaluated the 25(OH) D levels in children with ARF in comparison with age-matched healthy controls to investigate the relationship between vitamin D deficiency and disease phenotype. Thirty patients admitted to our pediatric cardiology clinic and diagnosed with ARF using modified Jones criteria and 16 age-matched and sex-matched healthy controls evaluated for innocent murmur between December 2011 and March 2013 were prospectively recruited. Participants from the study and control groups were evaluated in the same seasonal period. None of our participants were on vitamin D replacement or had any comorbidities known to affect vitamin D metabolism. Study was approved by local ethics committee and an informed consent was obtained from the legal guardians of all participants. Age, sex, and anthropometric measurements of all participants were recorded. Serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), magnesium (Mg), parathormone (PTH), and plasma 25(OH)D levels were measured. All participants underwent echocardiographic examinations. Serum anti-streptolysin-O titers (ASO), erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) levels were measured only in the patient group. ARF diagnosis was considered according to the modified Jones criteria (5). The blood samples of ARF patients were obtained before initiation of anti-inflammatory therapy.

Plasma 25(OH)D levels measured with high-performance liquid chromatography method using commercial kits manufactured by ImmuChrom GmbH (Heppenheim, Germany) company. 25(OH) D levels of <20.0 ng/mL were considered to indicate vitamin D deficiency (6). Echocardiographic findings of ARF cases was assessed as absence of valvulitis, presence of mild, moderate, and severe regurgitation either in mitral or aortic valve. Carditis was classified into mild, moderate, and severe (7). Data was analyzed using SPSS software (version 16.0; SPSS Inc., Chicago, IL). There was no statistically significant differences between the groups in terms of age, sex, and BMI z-score (Table 1). None of subject from study group and controls had a BMI z-score (>2 SD) suggesting obesity. Distribution of the diagnostic criteria for ARF patients are shown in Table 2. Serum 25(OH)D levels were significantly lower in the study group than in the control group (14.56±8.31 ng/mL vs. 25.41±1.38 ng/mL, p=0.002). When considering 20 ng/mL as the cutoff for vitamin D deficiency, 23 out of 30 patients with ARF (77%) and 8 out of 16 controls (50%) had vitamin D deficiency (p=0.066). Thirteen of 29 patients with carditis (44.8%) had single valve involvement, 16 (55.2%) had both mitral and aortic valve involvement. Although there was no statistically significant difference among 25(OH)D levels of patients with mild (n: 20) (14.4±7.9 ng/mL), moderate (n: 5) (13.1±5.1 ng/mL), and severe (n: 4) (15.4±14.6 ng/mL) carditis (p=0.935), 25(OH)D levels of patients with carditis was lower than those with no carditis, including controls (25.1±13.5 ng/mL; p=0.054). The underlying biochemical and immunological mechanisms triggering ARF following GAS pharyngitis have not been fully elucidated (1, 8). It may result from endothelial injury in genetically predisposed subjects, which causes molecular mimicry and subsequent activation of cellular and humoral immune systems (1). Furthermore, vitamin D has also been defined as an immunomodulator agent decreasing T helper 1-mediated autoimmune response and symptoms of autoimmune diseases (9). To the best of our knowledge, this is the first study evaluating the vitamin D status in children with ARF who had lower 25(OH)D levels. The results of present study suggested the potential role of inflammatory and/or immune-mediated mech-

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Table 1. The demographic and biochemical characteristics of study and control groups*

Variable	Study group (n=30)	Control group (n=16)	*P*
Age, year	12±2.94	11±2.96	0.628
Sex, female%/male%	40%/60%	43.8%/56.2%	0.806
Height, cm	139.0±3.0	141±1.4	0.997
Weight, kg	44.8±2.3	35.1±1.3	0.221
BMI z-score	0.1±0.9	-0.5±1.2	0.104
Serum 25(OH)D, ng/mL	14.56±8.31	25.41±1.38	0.002
Calcium, mg/dL	9.46 ±0.62	9.53±0.38	0.679
Phosphorus, mg/dL	4.46±0.66	4.80±0.75	0.124
Magnesium, mg/dL	2.17±0.28	1.95±0.09	0.001
Serum ALP, IU/L	168 (89–389)	225 (79–368)	0.269
Serum PTH, pg/mL	37.83±2.63	47.91±2.32	0.205

*Variable shown as means±standard deviations or median (min-max). ALP - alkaline phosphatase; BMI - body mass index; PTH - parathormone

Table 2. Distribution of diagnostic (Modified Jones) criteria in study group*

	Study group (n=30)
Minor criteria	
Fever, n	12
Arthralgia (without arthritis), n	7
PR interval, sec	0.24
White blood cell count, per mL	18600
ESR, mm/h	74±48 (26–122)
CRP, mg/dL	69.8±5 (14.5–190)
Major criteria	
Arthritis (n)	20
Carditis (n)	29
Chorea (n)	3
Subcutaneous nodule	–
Erythema marginatum	–
Evidence for GAS infection	
ASO, IU/mL	760±3 (240–1760)

*Variable shown as means±standard deviations or (min-max). ASO- anti-streptolysin O; CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; GAS - group A beta-hemolytic streptococcus

anisms associated with vitamin D deficiency in ARF pathogenesis. However, vitamin D deficiency was not correlated with carditis severity. The risk factors for vitamin D deficiency in pediatric population include winter season, lack of outdoor activities, which limits sunlight exposure, non-white ethnicity, older age, puberty, and obesity (10). Vitamin D deficiency detected in our study group and controls were 77% and 50%, respectively. These findings were consistent with increased frequency of ARF during winter and spring seasons when the risk of vitamin D deficiency is highest. There is lack of food fortification and vitamin D replacement for the age group between 5 and 15 years in which ARF incidence is highest. In addition, the overlap of seasons with highest incidence of vitamin D deficiency and ARF may support our hypothesis stating that vitamin D deficiency may predispose to development of ARF.

In conclusion, vitamin D deficiency thereby decrease in its immunomodulator effect may trigger immune response and predispose developing ARF. Studies evaluating larger number of ARF patients with and without carditis are required to further elucidate the role of vitamin D deficiency in the pathogenesis of ARF and its impact on the disease phenotype.

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