

## Evaluation of Vitamin (D) Level in Children with Rheumatic Valvular Lesion

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### ABSTRACT

**Background:** Acute rheumatic fever (ARF) is an autoimmune response to GAS (Group A  $\beta$ -Hemolytic Streptococci) infection. (ARF) is the cause of Rheumatic heart disease.

**Aim:** The objective of this study was the assessment of serum vitamin D levels of children diagnosed with rheumatic valvular lesion.

**Patients & methods:** This is a case control study that was performed on 50 patients with valvular lesion who were diagnosed previously and 50 healthy children as (control), age & sex matched to the patients at the Cardiology Unit of the pediatric department at El-Hussein Hospital, Al-Azhar University in the period between January 2023 and January 2024. All the studied children were subjected to full history taking, general, cardiac examination. Lastly laboratory evaluation of serum vitamin D (25 OH), calcium, phosphorus, Mg, ALP, PTH, WBCs, ESR, CRP and ASO. level were done.

**Results:** There was highly statistically significant difference between patients, control groups according to Serum 25 (OH)D (ng/ml), WBCs (cell/ $\mu$ L), ESR (mm/h), CRP (mg/L), ASO (IU/L), Ca (mg/dL), P (mg/dL), Mg (mg/dl), ALP (U/L), and PTH (pg/ml). There was significant decrease in Serum 25 (OH)D (ng/ml), Ca (mg/dL), P (mg/dL), while there was significant increase in WBCs (cell/ $\mu$ L), ESR (mm/h), CRP (mg/L), ASO (IU/L), Mg (mg/dl), ALP (U/L), PTH (pg./ml) among rheumatic group compared with control group.

**Conclusion:** We found that WBCs, ESR, CRP, ASO, was elevated in children with rheumatic valvular lesion while Serum 25(OH)D, Ca and P was decreased.

**Key words:** Acute rheumatic fever; Vitamin (D) Level; Rheumatic Carditis; Echocardiography

## INTRODUCTION

ARF is an inflammatory disease that develops a few weeks after a throat infection caused by group A  $\beta$ -hemolytic streptococci, and involves organs such as the heart, joints, and brain, and is based on immune responses. ARF and rheumatic heart disease (RHD) are one of the most important causes of acquired heart diseases in our country and other developing countries, which emerge as a crucial public health problem. (Arvind B et al.2020)

ARF can manifest at any age, while the majority of cases occur in children aged five to fifteen. Annually, nearly 470,000 new patients of ARF and 275,000 deaths are attributed to RHD, worldwide. The majority of cases appear in low and middle-income nations, as well as among Indigenous groups. Regions with the greatest rates have the lowest exact information with substantial underreporting. (Lahiri S et al.2021)

The etiology of ARF through pathogenic mechanisms is currently inadequate. A pharyngeal infection caused by streptococci is necessary, and genetic

susceptibility may be shown. In this context, molecular mimicry is believed to be significantly contribute in the initiation of tissue damage. (Brouwer S et al.2023)

Lack of vitamin D is a worldwide health problem, specifically among children. vitamin D's immunomodulatory and anti-inflammatory impacts on a number of infectious & autoimmune disorders have also been documented. In children with autoimmune diseases, there have been reports of low levels of serum 25(OH)D in a restricted number of pediatric studies. Incidences of ARF and GAS infection make a seasonal peak in the spring & winter, when 25(OH)D levels are thought to be at their minimum. due to reduced sunlight exposure. In addition to the high risk of developing ARF children aged five to fifteen years are rapidly growing, with elevated vitamin D consumption. ( Güneş A et al. 2021)

The objective of this study was the Evaluation of levels of vitamin D in the blood of children diagnosed with rheumatic carditis.

## PATIENTS AND METHODS

### Ethical Consideration:

Approval by the ethical committee of the Pediatric department at the Faculty of Medicine at Al-Azhar University under the registration number was obtained before the study.

Patients were enrolled in the study after getting informed oral and written consent from their parents.

Patients data confidentiality was preserved during all study procedures.

The patients and parents have the right to withdraw any time.

There was no conflict of interest regarding the study or publication.

There is no financial support or sponsorship.

### Sample size calculation:

The sample size is calculated according to the following equation *with* 16% SD, alpha error 0.1 Prediction of 90%. It included 50 patients for control group and 46 patients for study group:

$$\text{Necessary Sample Size} = \frac{(Z - \text{score})^2 \times \text{StdDev} \times (1 - \text{StdDev})}{(\text{margin of error})^2}$$

*Keogh et al equation with 16% SD, alpha error 0.1 , for sample size calculation*

**Exclusion criteria:** Recent intake of vitamin D or calcium (for at least 2 weeks), Comorbidities recognized to impact the metabolism of vitamin D & other chronic, metabolic, endocrinal, or chronic diseases.

**Study procedure:**

**All patients were subjected to:**

**Complete history taking** (personal history, complaint & its duration, history of sensitivity to drugs, past surgical history and family history).

**Physical examinations including:**  
 Anthropometric measurements, cardiac examination (inspection, palpation, auscultation, blood pressure measurement, peripheral pulses, edema assessment, neck veins examination and abdominal examination).

**laboratory investigations including:** serum vitamin D (25 OH), calcium, phosphorus, Mg, ALP, PTH, WBCs, ESR, CRP and ASO level. **(Thorup L et al.2020)**

**Echocardiography:** All study participants were subjected to echocardiographic evaluation utilizing the echocardiography system that is commercially available in cardiology department unit, with a 1.5–3.6 MHz multi-frequency phased array probe.

**Statistical Analysis:** the statistical package for social sciences was utilized to analyze the documented data, version 23.0 (Illinois, SPSS Inc, USA, Chicago). For qualitative variables, information was shown as numbers and percentages, even for quantitative variables, they were means plus standard deviations (SD). Significance level: non-significant results are indicated by a P value greater than 0.05, whereas significant results are indicated by a P value lower than 0.05.

**RESULTS**

This table shows no statistically significant variation among studied groups according to age, BMI & sex (Table 1).

**Table 1:** distribution of demographic between studied groups.

	<b>Group (A) Rh. Patients N= 50</b>	<b>Group (B) (Control) N= 50</b>	<b>P value</b>
<b>age (years) Mean ± SD</b>	11.6±2.05	10.74±2.5	0.06
<b>Sex</b>			0.42
<b>male</b>	26 (52%)	22 (44%)	
<b>female</b>	24 (48%)	28 (56%)	
<b>BMI Mean ± SD</b>	27.8±6.07	26.8±5.8	0.4

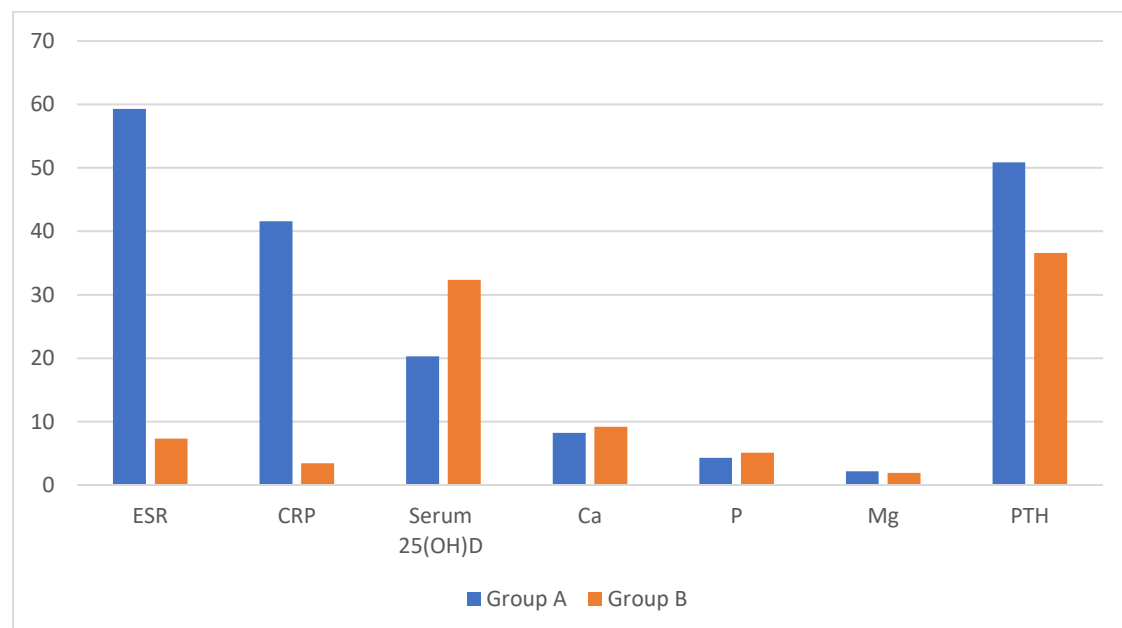
P value < 0.05 statistically significant.

**Table 2:** Distributions of laboratory investigations.

	<b>Group (A) Rh. Patients N=50</b>	<b>Group (B) Control group N=50</b>	<b>P value</b>
<b>WBCs (cell/<math>\mu</math>L) Mean<math>\pm</math> SD</b>	10532 $\pm$ 4314	6919 $\pm$ 1435	<0.001
<b>ESR (mm/h) Mean<math>\pm</math> SD</b>	59.3 $\pm$ 23.8	7.3 $\pm$ 2.8	<0.001
<b>CRP (mg/L) Mean<math>\pm</math> SD</b>	41.60 $\pm$ 14.8	3.4 $\pm$ 0.03	<0.001
<b>ASO (IU/L) Mean<math>\pm</math> SD</b>	960 $\pm$ 384	185 $\pm$ 53	<0.001
<b>Serum 25(OH)D (ng/ml) Mean<math>\pm</math> SD</b>	20.27 $\pm$ 5.68	32.37 $\pm$ 5.72	<0.001
<b>Ca (mg/dL) Mean<math>\pm</math> SD</b>	8.22 $\pm$ 0.52	9.2 $\pm$ 0.57	<0.001
<b>P (mg/dL) Mean<math>\pm</math> SD</b>	4.29 $\pm$ 0.5	5.1 $\pm$ 0.55	<0.001
<b>Mg (mg/dl) Mean<math>\pm</math> SD</b>	2.18 $\pm$ 0.25	1.9 $\pm$ 0.08	<0.001
<b>ALP (U/L) Mean<math>\pm</math> SD</b>	373.52 $\pm$ 76.02	261.28 $\pm$ 65.5	<0.001
<b>PTH (pg./ml) Mean<math>\pm</math> SD</b>	50.9 $\pm$ 8.18	36.58 $\pm$ 7.76	<0.001

P value <0.05 statistically significant

There was significant higher in Rh. Patients group than control group according to WBCs (cell/ $\mu$ L), CRP (mg/L), ESR (mm/h), Mg (mg/dl), ASO (IU/L), PTH (pg./ml), ALP (U/L). while there was highly statistically significant variation among studied groups in terms of WBCs (cell/ $\mu$ L), CRP (mg/L), ASO (IU/L), ESR (mm/h), Serum 25(OH)D (ng/ml), P (mg/dL), Ca (mg/dL), Mg (mg/dl), PTH (pg/ml) and ALP (U/L) (Table 2).



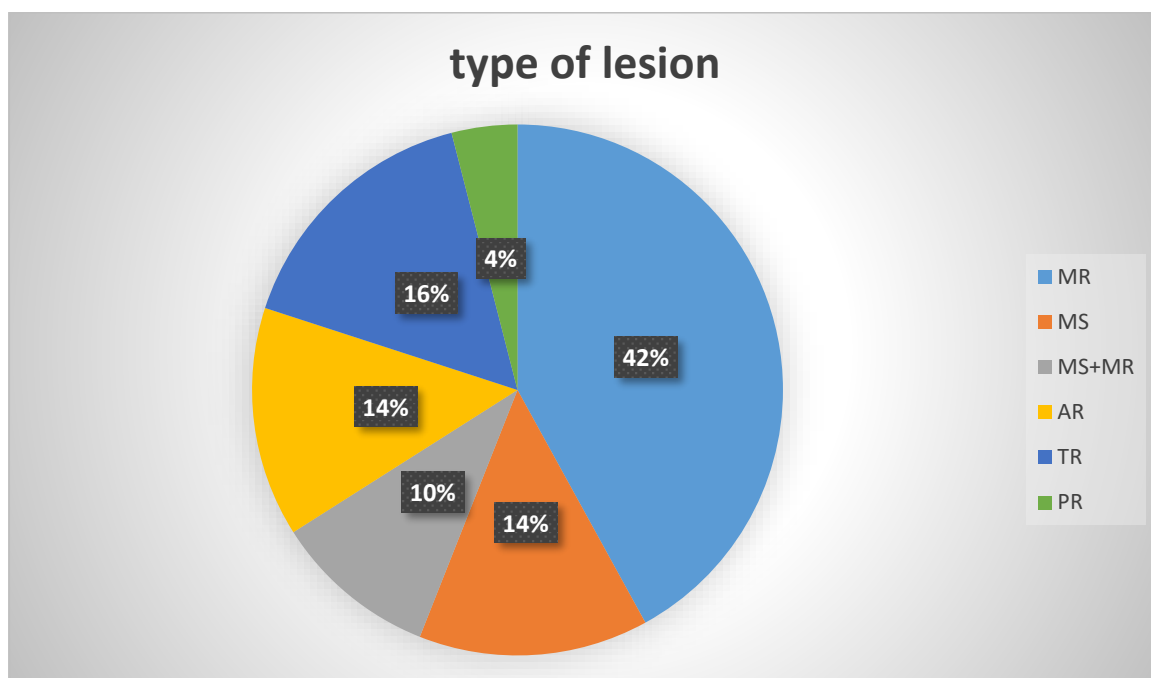
**Figure 1:** shows distribution of laboratory investigation.

**Table 3:** Types of valvular lesions by echocardiographic results among studied groups.

Type of lesion	Group (A) Rh. Patients N= 50
MR	21 (42%)
MS	7 (14%)
MS+MR	5 (10%)
AR	7 (14%)
TR	8 (16%)
PR	2 (4%)

MR means mitral regurgitation, MS: mitral stenosis, AR: aortic regurgitation, TR: tricuspid regurgitation, PR: Pulmonary regurgitation. LVEDd: Left ventricular end-diastolic diameter; LVESd: Left ventricular end-systolic diameter; LA/Ao: Left atrium and aortic root ratio.

This table show that the most frequently affected valve in the ARF group was the mitral valve, followed by aortic, tricuspid, and pulmonary valves. 21 had mitral regurgitation (42%), 7 had mitral stenosis (14%), and 5 had both mitral regurgitation and stenosis (10%), 7 had aortic stenosis (14%), 8 had tricuspid regurgitation (16%) and 2 had Pulmonary regurgitation (4%).



**Figure 2:** shows type of lesion in ARF group.

**Table 4:** Correlation of Vit D level and type of lesions.

	vit D (ng/ml)	
	Mean	±SD
MR	20.4	5.5
AR	21.7	6.2
MS	23.5	8.2
TR	20.6	2.1
MS+MR	18.0	6.9
PR	18.3	3.5
<b>P-value</b>	0.65	

MR means mitral regurgitation, MS: mitral stenosis, AR: aortic regurgitation, TR: tricuspid regurgitation, PR: Pulmonary regurgitation.

This table shows no statistically significant variation between vit d level & vit D level was markedly decreased in double M. lesions (Table 4).

### DISCUSSION

ARF is an autoimmune reaction to infection with GAS that is characterized by a constellation of signs and symptoms, involving arthritis or arthralgia, skin manifestations, fever, & carditis (involving valvulitis most frequently affects the aortic and/or mitral valves). (Sika-Paotonu D, et al, 2017)

ARF doesn't necessarily manifest in all streptococcal pharyngitis patients. Probability of ARF developing is 0.5-3%. As carditis is the most important cause of morbidity & mortality of the disease, it can cause cardiac failure and death due to pan carditis during acute phase. (Auala T et al. 2022)

Vitamin D is an essential steroid hormone that has an impact on all living organisms. The human body contains vitamin D receptors on the vast majority of cells and tissues, including muscle, brain, & bone tissues, as well as immune system cells including T lymphocytes, monocytes & macrophages. (Dominguez LJ et al. 2021) Particularly, there is evidence to suggest that hypovitaminosis D is linked to an elevated susceptibility to infections, including pharyngitis caused by GAS, as well as the development of autoimmune disorders. Additionally, associations have been established between rheumatic mitral stenosis & ARF. (Dupuis ML et al, 2021)

**The main results of this study were as follows:**

According to the present study, the average age of the ARF group was 11.6±2.05 years, twenty-six (52%) were males and twenty-

four (48%) were females while the average age of control group 10.74±2.5 years, twenty-two (44%) were males and twenty-eight (56%) were females. We found that there was no statistically significant difference among studied groups regarding age, sex, & BMI.

(Thorup et al. 2020) who evaluated levels of vitamin D in RHD patients. They revealed that there wasn't statistically significant variance among studied groups according sex and age. While there was statistically significant variance among studied groups according BMI.

(Rémond et al. 2015) who aimed to determine the significance of minor echocardiographic variations by assessing whether they were correlated with an elevated risk of ARF or progressive heart defect consistent with the progression of Certain RHD. They revealed that the median age (IQR) of cases group was 13.7 (11.9–15.7) years, 59.0% cases were females while the median age of control group was 13.7 (11.8–15.5) years, 57.2% participants were females. They found that there was no statistically significant difference among the two studied groups according sex and age.

The current study revealed that the mean WBCs in ARF group was 10532 ± 4314 cell/μL, ESR 59.3± 23.8 mm/h, CRP was 41.60 ±14.8 mg/L, ASO was 960± 384 IU/L, Serum 25(OH)D was 20.27± 5.68 ng/ml, Ca 8.22± 0.52, Mg was 2.18± 0.25 mg/dl, P was 4.29± 0.5 mg/dL, ALP was 373.52 ± 76.02 U/L, and PTH was 50.9 ± 8.18 pg./ml. We found that there was

significant higher level of WBCs, ESR, CRP, ASO, Mg, ALP and PTH in ARF group than control group. Also, there was highly statistically significant difference among studied groups according to Serum 25(OH)D, Ca, and P.

The present study is consistent with (Thorup et al. 2020) who demonstrated that there was statistically significant variance among the two studied groups related to Serum 25(OH)D level.

Similarly, our findings can be supported by (Onan et al. 2016) who clarified that the average erythrocyte sedimentation rate in ARF group was  $90 \pm 3$  ranging from 27 to 122 mm/h, the mean CRP was  $69.8 \pm 5$  ranging from 14.5 to 190 mg/dl, the mean ASO was  $760 \pm 3$  ranging from 240 to 1760 IU/L, the mean Serum 25(OH)D was  $25.41 \pm 1.38$  ng/ml, the mean calcium was  $9.46 \pm 0.62$  mg/dl, the mean phosphorus  $4.46 \pm 0.66$  mg/dl, the mean magnesium was  $2.17 \pm 0.28$  mg/dl, serum ALP was 168 (89-389) IU/L and the mean serum PTH was  $37.83 \pm 2.63$  pg/ml.

They found that serum Mg levels and Serum 25(OH)D in patient group were significantly greater than in control group while there was no statistically significant difference among the two studied groups according to P, ALP, PTH and Ca. Also, they revealed that 77% cases with ARF and 50% of the control group lacked vitamin D ( $p=0.066$ ).

(Turkucar et al. 2020) who revealed that the average WBC of ARF group was  $10765 \pm 4700$  cell/ $\mu$ L, the mean ESR was  $53.36 \pm 26.73$  mm/h, the median CRP was 24.6 (10.22–69.10) mg/L, the mean Ca level was  $9.29 \pm 0.48$  mg/dL, the mean

phosphorous was  $4.44 \pm 0.47$  mg/dL, the mean ALP was  $151.4 \pm 46.7$  U/L, the mean PTH was  $37.8 \pm 21.3$  pg/ml and the mean D-vitamin was  $19.9 \pm 10$   $\mu$ g/L. They found that ARF group had statistically significant higher levels of WBCs, ESR, CRP when compared to control and ARF group had statistically significant lower level of Ca. While no statistically significant variance among the two studied groups related to P, ALP, PTH and D-vitamin.

Our results indicated that ARF group had significant greater level of LVEDd (Z-score) than control group, while no statistically significant among studied groups according to LVESd (Z-score) and La/Ao. As regards type of lesions, we reported that the most frequently affected valve in ARF was the mitral valve group, followed by, aortic, pulmonary and tricuspid valves. We found that 21(42%) had mitral regurgitation, 7 (14%) had mitral stenosis, and 5(10%) had both mitral regurgitation and stenosis, 7 (14%) had aortic stenosis, 8(16%) had tricuspid regurgitation and 2 (4%) had Pulmonary regurgitation.

(Turkucar et al. 2020) who reported that ARF group had significant higher level of LVEDd (Z-score) 0.29 (0.13–0.74) than control group 0.12 (0.03–0.24) while no statistically significant variance among studied groups related to LVESd (Z-score) and La/Ao. They revealed that all patients in the ARF group were found to have active carditis and mitral valve involvement was present in all cases. Furthermore, aortic valve involvement was observed in 48% of the patients during diagnosis.

### CONCLUSION

The present study assessed vitamin D levels in the serum in children diagnosed with rheumatic carditis. We found that WBCs, ESR, CRP, ASO, was elevated in children with acute rheumatic fever while Serum 25(OH)D, Ca and P was decreased. Also,

the mitral valve was the most frequently impacted valve in patients with ARF. We concluded that the Lack of vitamin D can decrease in its immunomodulator effect, which can activate the immune system and increase developing ARF.

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