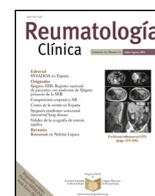




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Original article

## Investigating the comparative effect of vitamin D level with the type of complications in Henoch Schönlein purpura and Kawasaki disease



Mehrnoush Hassas Yeganeh<sup>a</sup>, Reza Sinaei<sup>b,c</sup>, Mitra Rouhi<sup>d,\*</sup>, Reza Shiari<sup>e</sup>, Vadood Javadi Parvaneh<sup>d</sup>, Khosro Rahmani<sup>f</sup>, Erfan Sheikhabaei<sup>g</sup>

<sup>a</sup> Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>b</sup> Department of Pediatrics, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

<sup>c</sup> Clinical Research Development Unit, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran

<sup>d</sup> Department of Pediatrics, School of Medicine, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>e</sup> Department of Pediatric Rheumatology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>f</sup> Department of Pediatric Rheumatology, School of Medicine, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>g</sup> School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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### ABSTRACT

**Introduction and objectives:** Henoch Schönlein purpura (HSP) and Kawasaki disease (KD) are two main inflammatory diseases among childhood vasculitis. Considering the anti-inflammatory effects of 25-hydroxyvitamin D3, we decided to investigate the association of serum 25-hydroxy vitamin D3 level with the type and severity of these conditions.

**Materials and methods:** The present study was performed as a historical cohort of 254 affected children with KD and HSP vasculitis. The required data were extracted, using a researcher-made questionnaire from patients' electronic file, and then they were analyzed after collecting information of the patients.

**Results:** In HSP group, 54% of participants were boys. Similarly, in KD group, boys were more affected than girls. The comparative 25-hydroxyvitamin D3 level in HSP patients with and without renal involvement ( $P=0.02$ ), hematuria ( $P=0.14$ ), and in two groups with and without heart disease, and also with and without coronary artery dilatation in KD patients ( $P<0.001$ ) were significant.

**Discussion and conclusions:** The findings showed that insufficient level of vitamin D3 were significantly associated with the exacerbation of complications of both diseases, and therefore it seems that vitamin D deficiency can be an effective predictive factor of severity in HSP and KD patients.

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## Investigación del efecto comparativo del nivel de vitamina D con el tipo de complicaciones en la púrpura de Henoch-Schönlein y la enfermedad de Kawasaki

### RESUMEN

**Introducción y objetivos:** La púrpura de Henoch-Schönlein (HSP) y la enfermedad de Kawasaki (EK) son dos patologías inflamatorias principales entre las vasculitis infantiles. Teniendo en cuenta los efectos antiinflamatorios de la 25-hidroxivitamina D3, decidimos investigar la asociación del nivel sérico de esta con el tipo y la gravedad de dichas afecciones.

**Materiales y métodos:** El presente estudio se realizó como una cohorte histórica de 254 niños afectados con vasculitis por EK y HSP. Los datos requeridos se extrajeron mediante un cuestionario elaborado por un investigador del expediente electrónico de los pacientes y se analizaron después de recopilar la información de los usuarios.

#### Palabras clave:

Púrpura de Henoch-Schönlein

Enfermedad de Kawasaki

Vitamina D

25-Hidroxivitamina D3

Complicaciones

\* Corresponding author.

E-mail address: [m.rouhi92@gmail.com](mailto:m.rouhi92@gmail.com) (M. Rouhi).

**Resultados:** En el grupo HSP, 54 y 46% de los participantes eran niños y niñas, respectivamente. De manera similar, en el grupo KD, los varones se vieron más afectados. El nivel comparativo de 25-hidroxivitamina D3 en pacientes con HSP con y sin afectación renal ( $p = 0,02$ ), hematuria ( $p = 0,14$ ), y en dos grupos con y sin enfermedad cardíaca, y en dos con y sin dilatación de la arteria coronaria en usuarios con EK ( $p < 0,001$ ) fueron significativos.

**Discusión y conclusiones:** Los hallazgos mostraron que los niveles insuficientes de vitamina D se asociaron significativamente con la exacerbación de las complicaciones de ambas enfermedades, por lo que parece que la deficiencia de vitamina D puede ser un factor predictivo eficaz de la gravedad en pacientes con HSP y EK.

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## Introduction

Kawasaki disease (KD) which is formerly known as infantile mucocutaneous lymph nodes syndrome and neonatal polyarthritis is an acute childhood febrile vasculitis.<sup>1</sup> KD is the most common vasculitis in all children over the world especially children with Asian background. KD is a vasculitis with a preference of coronary artery involvement, in which approximately 20–25% of untreated patients and less than 5% of treated patients develop coronary artery disorder (CAD) including aneurysm. Therefore, it remains as the most common cause of acquired heart disease in children in developed countries such as the United States and Japan.<sup>2</sup>

Henoch Schönlein Purpura (HSP) as a leukocytoclastic vasculitis (LCV) is the most common form of small vessel vasculitis of childhood, ranging from 6 to 24 cases per 100,000 children. It is seen all over the world and involve all different racial groups, more commonly in whites and Asians.<sup>3</sup> The cause of the disease is probably an autoimmune reaction in the small blood vessels throughout the body, which causes inflammation and involvement of the arteries. Renal disease is the most important long-term complication of the disease and occurs in about 1–2% of affected children, up to near six months of diagnosis. Thereafter, it is recommended that the affected children should be followed up for several months after discharge for nephritis.<sup>4</sup>

Vitamin D is a steroid hormone and a fat-soluble vitamin, and naturally, few foods contain this vitamin. Therefore, skin synthesis is the main source of vitamin D supply. Several factors including strength of Ultraviolet (UV) rays, duration of UV exposure, season, age, physical activity, and the amount of skin pigments may contribute to the production of vitamin D3 in the skin. Although, several studies are in agreement with the relation between the seasonal changes and the vitamin D3 levels, in some others, the prevalence of vitamin D deficiency did not differ by seasons.<sup>5</sup> Vitamin D promotes bones' growth and its strength. It increases the absorption of phosphorus and calcium in the intestine and reduces their excretion by the kidneys. It also helps the cell growth through the alteration of cell nucleus genes. Recently, its anti-inflammatory and immunomodulatory roles have attracted much attention. Vitamin D inhibits cell proliferation and stimulates cell differentiation, activating the innate system, supporting the antimicrobial functions, and reducing inflammatory activities. It increases anti-inflammatory cytokine levels via stimulating T-helper (Th) 2 calls and via inhibiting Th1 and Th17 cells and proinflammatory cytokines. It acts as a nutria-epigenetic factor in autoimmunity. Reports of low serum vitamin D3 level predicting the course and facilitating the progression have been published. Disease activity has also been considered to correlate inversely with vitamin D3 level in several reports.<sup>6,7</sup>

Previous studies have also reported an anti-inflammatory effect for vitamin D, and its deficiency has exacerbated renal and CAD involvement in vasculitis affected children.<sup>8</sup>

Considering that HSP and KD are two common vasculitis of childhood, along with anti-inflammatory, immunomodulatory

properties of vitamin D, we aimed to investigate the possible effect of vitamin D on reducing both severity and complications of these two entities, which mainly include cardiac and renal impacts of these conditions.

## Materials and methods

The present study was performed as a historical cohort on 254 children with vasculitis of HSP and KD. The required data (including clinical status, Para clinical outcomes, renal complications in HSP patients, and cardiac complications, and the type of cardiac involvement in patients with KD who were hospitalized in Mofid Children's Hospital, Tehran, Iran, from September 2006 to March 2016) were extracted from the patients' electronic records, using a researcher-made questionnaire. Thereafter, the collected data were analyzed using STATA software by a statistics.

### Statistical analysis

Data analysis was performed using STATA software by Log Rank Test and survival analysis. The quantitative normal variables were displayed as mean (standard deviation=SD), and slightly with abnormal distribution in the middle (range between 25 and 25%). The qualitative variables were displayed as number (percentage). The statistical significant level was considered with  $P < 0.05$  in all analyzes.

### Ethics approval

Informed consent received from all patients before starting the work and the study approved by the ethics committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.MSP.REC.1398.748).

## Results

In the present study, 254 children with KD and HSP vasculitis were included in the study. Of these, 136 children had Kawasaki and 118 had HSP vasculitis. The gender distribution in both HSP and KD groups were compatible with more superiority of male patients. Accordingly, 54% out of 118 patients in HSP group, and 61% out of 136 patients in KD groups were boys.

In the context of KD, cardiac involvement has been expressed as coronary artery dilatation (0.218487) and left coronary artery dilatation (0.260504). In Henoch Schönlein Purpura, renal involvement has been expressed as proteinuria (0.126482), hematuria (0.3083), and glomerulonephritis (0.011858) (Fig. 1).

### Evaluation of 25-hydroxyvitamin D3 levels in patients with HSP

Wilcoxon rank sum (Mann-Whitney) test was used to compare 25-hydroxyvitamin D3 levels in the groups. Comparison of 25-hydroxyvitamin D3 levels in the two groups with and without

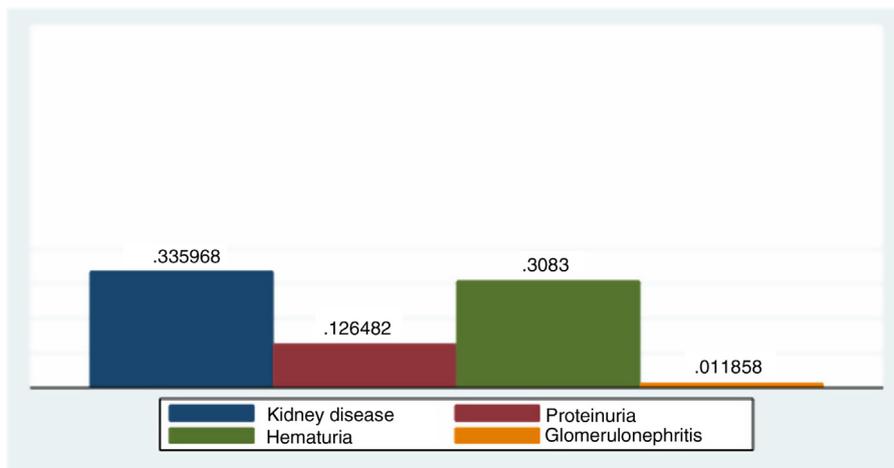


Fig. 1. Frequent distribution of kidney problems in Henoch Schönlein.

Table 1

Vitamin D levels in the two groups with and without renal involvement in Henoch Schönlein Purpura patients.

Kidney disease	Obs	Rank sum	Expected
0	124	11,371.5	10,726
1	48	3506.5	4152
Combined	172	14,878	14,878

z = 2.207.

Prob > |z| = 0.0273.

Table 2

Vitamin D levels in both groups with and without hematuria in Henoch Schönlein Purpura patients.

Hematuria	Obs	Rank sum	Expected
0	131	12,013.5	11,331.5
1	41	2864.5	3546.5
Combined	172	14,878	14,878

z = 2.455.

Prob > |z| = 0.0141.

Table 3

Vitamin D levels in the two groups with proteinuria and non-proteinuria in Henoch Schönlein Purpura patients.

Proteinuria	Obs	Rank sum	Expected
0	154	13,237	13,321
1	18	1641	1557
Combined	172	14,878	14,878

z = -0.421.

Prob > |z| = 0.6738.

renal involvement in HSP patients in Table 1 with 0.0273 (z = 2.207) and comparison of 25-hydroxyvitamin D3 levels in both groups with and without hematuria in HSP patients in Table 2 with 0.0141 (z = 2.455) were significant.

Comparison of 25-hydroxyvitamin D3 levels in the two groups with and without proteinuria in HSP patients in Table 3 has been shown. These levels in two groups were not statistically significant, and glomerulonephritis occurred only in three cases.

Evaluation of 25-hydroxyvitamin D3 levels in patients with KD

Comparison of 25-hydroxyvitamin D3 levels in two groups with and without heart disease in Kawasaki patients in Table 4 with z = 4.561, (z > Prob, 0.0000) and 25-hydroxyvitamin D3 levels in

Table 4

Vitamin D levels in two groups with and without heart disease in Kawasaki patients.

Cardiac disease	Obs	Rank sum	Expected
0	77	4867.5	4196.5
1	31	1018.5	1689.5
Combined	108	5886	5886

z = 4.561.

Prob > |z| = 0.0000.

Table 5

Vitamin D levels in the two groups with and without coronary dilatation in Kawasaki patients.

Coronary dilatation	Obs	Rank sum	Expected
0	82	5045	4469
1	26	841	1417
Combined	108	5886	5886

z = 4.143.

Prob > |z| = 0.0000.

Table 6

Comparison of vitamin D levels in the two groups with and without coronary wall irregularities in Kawasaki patients.

Irregularity	Obs	Rank sum	Expected
0	103	5708.5	5613.5
1	5	177.5	272.5
Combined	108	5886	5886

z = 1.390.

Prob > |z| = 0.1645.

the two groups with and without coronary dilatation in Table 5 with (z = 4.143, Prob > |z| = 0.0000) were significant.

Comparison of 25-hydroxyvitamin D3 levels in the two groups with coronary wall irregularities and without coronary wall irregularities in Table 6 showed that 25-hydroxyvitamin D3 levels were not significant in the two groups.

Discussion

The results of the study of patients with HSP showed that the most common complications of patients are renal problems that occurred in 6.33% of patients, including hematuria (in 8.30% of patients), proteinuria (in 6.12% of patients), and glomerulonephritis (in 1.1% of Patients). The lower vitamin D level in HSP patients with renal involvement was statistically significant than non-affected patients (P = 0.02). Similarly, the group with hematuria

had a significant difference with non-affected patients ( $P=0.01$ ). The vitamin D level in patients with and without proteinuria did not show a significant difference ( $P=0.67$ ).

In one study on 50 children with HSP, Fan et al. found that children with HSP and with low vitamin D levels had a higher risk of renal involvement than those with normal vitamin D levels. Surprisingly, the length of these patients' hospitalization stay was longer.<sup>9</sup> In another study that conducted by Zhang et al. the vitamin D levels in patients with HSP were significantly diminished, and usually were accompanied by joint and digestive symptom involvements.<sup>10</sup>

Both aforementioned studies have confirmed the effect of vitamin D on the increase of the complications of HSP disease, which is fully consistent with the results of our study. Of course, the role of vitamin D deficiency on Hematuria, proteinuria, and glomerulonephritis as the main renal problems is an important subject that has been investigated in detail in our study and it has been never studied cumulatively in any other study.

In another part of our study, the role of vitamin D in children with KD was investigated. Gender distribution in Kawasaki patients was with superiority of male patients.

The most common problems in Kawasaki affected patients were heart problems (in 26.05% of patients), including coronary dilatation (21.8% of patients), coronary irregularity (in 4.2% of patients), and left coronary dilatation (in 1.7% in patients), in descending order.

The results of our studies showed that the level of vitamin D was significantly different in the two groups with and without heart disease and in the two groups with and without coronary dilatation in Kawasaki patients ( $P<0.001$ ). Nevertheless, the level of vitamin D had no significant difference among patients with and without irregularity of the coronary walls ( $P=0.16$ ).

In an earlier study by Suzuki Yasu et al., which aimed to evaluate the effect of anti-inflammatory and de-hydroxy properties of vitamin D on coronary artery endothelial cells in patients with KD, showed that vitamin D levels could modify the inflammatory response of coronary arteries of affected patient.<sup>8</sup>

Another study that conducted by Stagi et al. on 79 children aged 5.1–5.7 years revealed that the blood levels of vitamin D in children with Kawasaki were significantly lower than in normal children.<sup>11</sup>

In 2016, Yang et al. conducted a study on the relationship between vitamin D and Kawasaki disease. Considering the effective role of vitamin D in reducing cardiovascular problems and inflammation, they concluded that vitamin D deficiency in KD was effective on the inflammatory response, function of endothelial cells, platelets, DNA methylation, and increased risk of coronary artery complications. Similarly, vitamin D reduced the complications of this disease.<sup>12</sup>

Fifty-seven adult patients with systemic small and medium vessel vasculitis in a Turkish study were evaluated for their 25-hydroxy vitamin D3 levels. The mean vitamin D3 level was  $21.8 \pm 14.2$  ng/mL and  $42.7 \pm 27.6$  ng/mL in vasculitis and healthy groups, respectively. There was a negative correlation between vitamin D and C-reactive protein levels in this study ( $P=0.007$ ). The renal involvement was significantly associated with diminished vitamin D levels in patients with vasculitis, just like the results of our study.<sup>13</sup>

The serum vitamin D3 levels of 663 children hospitalized with HSP and 400 healthy children in a retrospective Chinese study showed a significantly lower vitamin D in vasculitis group ( $P<0.01$ ). The vitamin D3 level was reduced in the nephritis and gastrointestinal subgroups. Conversely, those with joint involvement did not a significant reduction in their vitamin D3 levels. The vitamin D3 levels were significantly lower spring and winter seasons than fall and summer. They evaluated some novel parameters such as season and extra-ordinary symptoms that did not evaluated in our study.<sup>14</sup>

The seasonal epidemic of KD in winter in Japan resulted to a cross-sectional study comparing the 25-OH vitamin D3 levels in 290 controls and 86 KD patients. The vitamin D3 level was lower in KD patients ( $P<0.001$ ). In winter, the vitamin D3 level in KD patients were lower than in summer,<sup>15</sup> what we did not included in our study. In this study, the status of vitamin D3 at diagnosis was not associated with intravenous immunoglobulin resistance or CAD. However, the comparative 25-hydroxyvitamin vitamin D3 level in two groups with and without heart disease, and also with and without coronary artery dilatation in KD patients in our study were significant.

## Conclusions

From the results of our study and previous studies on the effect of vitamin D levels in patients with Henoch and Kawasaki, it was found that insufficient levels of this vitamin are significantly associated with exacerbation of complications from both diseases. Therefore, it seems that vitamin D deficiency can be a predictor factor of Henoch and Kawasaki disease. Based on these findings, it is suggested that the prescription of vitamin D for these patients and its role in reducing the complications caused by these diseases can be investigated in the next study. It is hoped that using this strategy can be effective in reducing the pain caused by both diseases in patients.

## Authors' contributions

M.H.Y. and M.R. were involved in conception and design of study. M.R. were contributed to analysis and interpretation of data. M.R. and R.S. were contributed to drafting of the article. R.Sh., V.J.P., Kh.R. and E.Sh. were contributed to critical revision of the article for important intellectual content. All authors read and approved the final version of the manuscript.

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## Conflict of interest

The author(s) declare that they have no conflict of interest.

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## References

1. Saket S, Mojtahedzadeh S, Karimi A, Shiari R, Shirvani F. Relationship between electrolyte abnormalities, ESR, CRP and platelet count with severity of Kawasaki disease. *Sci Mag Yafte*. 2009;11:5–14.
2. Nelson textbook 20 ed 2016. p. 1209–18.
3. Dalili A, Gholamveisi B, Rahimi S, Ebrahimi A, Sadeghi M. Henoch-Schonlein purpura with multiple symptoms in adult patient: a case report. *Med Sci J Islamic Azad Univ*. 2020;30:453–8.
4. Hassas Yeganeh M, Shiari R. IgA vasculitis in Henoch-Schönleinpurpura. *J Pediatr Nephrol*. 2016;4:8–13.
5. Heidari B, Mirghassemi MB. Seasonal variations in serum vitamin D according to age and sex. *Caspian J Intern Med*. 2012;3:535.
6. Sanlier N, Guney-Coskun M. Vitamin D, the immune system, and its relationship with diseases. *Egypt Pediatr Assoc Gazette*. 2022;70:39.
7. Mazur A, Frączek P, Tabarkiewicz J. Vitamin D as a nutri-epigenetic factor in autoimmunity – a review of current research and reports on vitamin D deficiency in autoimmune diseases. *Nutrients*. 2022;14:4286.
8. Suzuki Y, Ichiyama T, Ohsaki A, Hasegawa S, Shiraishi M, Furukawa S. Anti-inflammatory effect of  $1\alpha, 25$ -dihydroxyvitamin D3 in human coronary arterial

- endothelial cells: Implication for the treatment of Kawasaki disease. *J. Steroid Biochem. Mol. Biol.* 2009;113:134–8.
9. Fan L, Liu H, Wang Y-C, Chen L, Zhou J-J, Cui Y-X. Association of serum vitamin D level with severity and treatment in children with Henoch-Schönlein purpura. *Zhongguo Dang dai er ke za zhi.* 2017;19:796–9.
  10. Zhang YD, Dong QW, Li RM, Ji CY, Chu YT, Ma L, et al. Changes in 25-hydroxyvitamin D3 level in children with Henoch-Schönlein purpura. *Zhongguo Dang Dai Er Ke Za Zhi.* 2017;19:292–5.
  11. Stagi S, Rigante D, Lepri G, Cerinic MM, Falcini F. Severe vitamin D deficiency in patients with Kawasaki disease: a potential role in the risk to develop heart vascular abnormalities? *Clin. Rheumatol.* 2016;35:1865–72.
  12. Yang X, Dong X-Y. Research advances in association between vitamin D and Kawasaki disease and related mechanisms of action. *Zhongguo Dang dai er ke za zhi.* 2016;18:1319–23.
  13. Korkmaz FN, Ozen G, Unal AU, Odabasi A, Can M, Ascioglu E, et al. Vitamin D levels in patients with small and medium vessel vasculitis. *Reumatol Clin (Engl Ed).* 2022;18:141–6.
  14. Wang J, Ye WP. The comparisons of vitamin D3 levels in IgA vasculitis across different subgroups and healthy children: a comparative study. *Transl Pediatr.* 2023;12:938.
  15. Okazaki N, Ikeda H, Honda T, Tsuno K, Inoue F, Takahashi S, et al. The impact of vitamin D on the onset and progress of Kawasaki disease. *Pediatr. Int.* 2022;64:e15191.