Original Article
Central Eur J Paed 2021;17(1):1-7
DOI: 10.5457/p2005-114.280

Association of Vitamin D Status and Activity of Juvenile Idiopathic Arthritis: A Single Center Experience

Almira Ćosićkić, Adin Alić, Amela Selimović, Sanimir Suljendić, Dina Delibegović

Clinic for Children's Diseases Tuzla, University Clinical Centre Tuzla, Bosnia and Hezegovina,

Correspondence: *almiracosickic@gmail.com*; Tel: + 387 61 194 404; Fax.: + 387 35 303 740

Received: December 1, 2020; **Accepted:** December 29, 2020

Abstract

Objective – To evaluate a vitamin D [25-hydroxyvitamin D-25(OH)D] status in children with juvenile idiopathic arthritis (JIA), and its association with the activity of arthritis. **Materials and Methods** – Retrospective-prospective study was conducted at the Clinic for Children's Diseases, University Clinical Center Tuzla in the period from January 2018 to January 2020. The medical records of 51 children with JIA and 48 healthy children were analyzed. **Results** – The median serum levels of 25(OH)D in children with JIA were 35.4 nmol/L and 62.3 nmol/L in the control group, with a statistically significant difference (P=0.036). 11 of 51 children with JIA and 8 of 48 in the control group had values 25(OH)D <25nmol/L, while 8 of 51 children with JIA and 14 of 48 children in the control group had the adequate values of 25(OH)D. 40 of 51 children (median JADAS10 score 6.24) had active arthritis; 6 of them with insufficiency and 3 with deficiency of 25(OH)D had moderate disease activity at the time of evaluation. The values of 25(OH)D were negatively correlated with arthritis activity (r=-0.36, P=0.02), but no significant correlation between arthritis duration and 25(OH)D levels was found. There was significant difference between serum 25(OH)D concentrations and the form of arthritis (P<0.0001)**. Conclusions** – Our findings have shown the correlation between serum 25(OH)D concentrations and arthritis activity, however, prospective comprehensive studies are needed to further investigate the relationship between vitamin D and disease activity in JIA.

Key Words: Vitamin D ▪ Children ▪ Juvenile Idiopathic Arthritis.

Introduction

Juvenile Idiopathic Arthritis (JIA) is a group of clinically distinguishable subsets that share chronic, childhood-onset arthritis of unknown cause, as a unifying feature, unclear pathogeneses but likely multifactorial etiologies. The immune system is intimately involved in pathogenesis of JIA by abnormal immunoregulation, production of cytokine, development of inflammation as a hallmark of arthritis. Since vitamin D plays an important role in maintaining both skeletal and immune system, it has been implicated in the pathogenesis of JIA (1-4). Beside regulation of calcium homeostasis and bone turnover, vitamin D has proven antiproliferative, pro-differentiation, anti-bacterial, immunomodulatory and anti-inflammatory properties within the body in various cells and tissues (3-5). Cells involved in innate and adaptive immune responses such as macrophages, dendritic cells, T cells, and B cells express enzymes required to activate and respond to vitamin D (3, 6, 7). Since vitamin D tends to suppress the immune response, consequently low vitamin D concentrations are associated with an increase in pro-inflammatory mediators and more active disease (8, 9).

The aims of this study were to evaluate a vitamin D [25-hydroxyvitamin D-25(OH)D] status in children with JIA, and also to examine whether there was an association between serum levels of 25(OH)D and activity of arthritis.

Patients and Methods

This retrospective-prospective study was conducted at the Department of Rheumatology, Immunology and Allergology of the Clinic for Children's Diseases, University Clinical Center (UCC) Tuzla in the period from January 2018 to January 2020. The medical records of 51 children with JIA were analyzed. The diagnosis and classification of JIA was made based on the classification and diagnostic criteria for JIA 2001 by International League of Associations for Rheumatology (ILAR) (10). Exclusion criteria included failure to fulfill the diagnostic criteria for JIA, use of supplements containing vitamin D or calcium within the previous 3 months, associated chronic diseases (diabetes mellitus type 1, inflammatory bowel diseases, celiac disease and immunodeficiency disorders) and the parents' refusal for the child to take part in the study. Fifteen children met the exclusion criteria (nine used vitamin D supplements within the previous 3 months, two children had associated diseases, one had diabetes mellitus and one had celiac disease; the parents of two children refused to give informed consent for their children to participate in the study). Fifty-one children who met the study criteria were included in the study. In the JIA group, one child was taking chloroquine, 22 (43.1%) children were using disease-modifying anti-rheumatic drugs (DMARDs), seven (13.7%) children were using biological drugs, and no children were receiving glucocorticoids and/or biphosphonate at the time of evaluation.

The following were analyzed: gender, age, JIA activity and disease type, serum 25(OH)D concentrations, erythrocyte sedimentation rate (ESR). The level of disease activity was determined by means of the Juvenile Arthritis Disease Activity Score (JADAS10) (11). The JADAS10 is composed of the following four variables: physician global assessment of overall disease activity, parent global assessment of child's wellbeing, 10-joint reduced active joint count, and ESR. The JADAS10 is calculated as the sum of the scores of its individual components, which yields a global score of 0-40. The parent of each child was asked to make a global assessment of child's wellbeing on a 21-numbered circle visual analog scale-VAS (where 0=very good and 10=very poor) and to rate the intensity of child's pain on a 21 numbered circle VAS (where 0=no pain and 10=very severe pain); ESR ≤15 mm/h was considered as normal. Inactive disease (ID) is defined if the score is ≤1 in either oligoarthritis or polyarthritis. Low (or minimal) disease activity (LDA) is defined when JADAS10 is comprised between 1.1 and 2.0 in oligoarthritis, and between 1.1 and 3.8 in polyarthritis.

Moderate disease activity (MDA) is defined when the score is comprised between 2.1-4.2 in oligoarthritis and 3.9-10.5 in polyarthritis, since the state of high disease activity (HAD) is defined when the score is >4.2 in oligoarthritis and >10.5 in polyarthritis (12, 13). Forty-eight healthy children, matched for gender and age to the children with JIA, not using supplements containing vitamin D or calcium within the past three months, with no associated chronic diseases, were included as controls.

The assessment of 25(OH)D levels in serum was made, blood was taken by the standard procedure and analyzed at the Polyclinic for Laboratory Diagnostics of UCC in Tuzla. The blood samples for 25(OH)D were centrifuged at the speed of 3.000 turns per minute during a 10-minute period. After centrifuging, separated serum was kept in flacons at the temperature of -70°C until the procedure of determination. Values of 25(OH)D were determined by ADVIA Centaur assay. The values <25 nmol/L were considered as insufficiency, 25-50 nmol/L as deficiency, 50-75 nmol/L were insufficient values, since adequate vitamin D levels were ≥75 nmol/L.

Ethics Statement

The study protocol was approved by Ethics Committee of UCC Tuzla, No 01/1-37-473/18. The informed consent was signed by parents of all participants.

Statistical Analysis

Statistical data analysis was conducted using the biomedical software application "MedCalc for Windows, Version 15.11.4" (MedCalc Software,

Ostend, Belgium). The variables with distorted distribution were shown with a median as a measure of the central value. The Mann- Whitney and Kruskal-Wallis tests were used to test a statistically significant difference between the samples. Spearman's correlation coefficient was used to measure a correlation between the variables. The difference was considered significant when P<0.05.

Results

In the period from January 2018 to January 2020, 51 (10.6%) of 507 children, hospitalized at the Department of Rheumatology, Immunology and Allergology of the Clinic for Children's Diseases, UCC Tuzla, had JIA. There were 24 boys and 27 girls with a median age of 9.0 years (IQ range 2.6-12.6 years). Roughly the same number of children had the oligoarticular (2 of them had JIA associated uveitis) and polyarticular (2 of them were rheumatoid factor – RF positive) form of JIA. The clinical characteristics of 51 children with JIA are shown in Table 1.

The control group consisted of 48 healthy children (21 boys and 27 girls) with a median age of 10.6 years (IQ range 3.6-12.2 years). There were no statistically significant differences in age (P=0.22) or sex (P=0.26) between the children with JIA and the control group. The median levels of 25(OH)D were significantly lower in children with JIA, 35.4 nmol/L (IQ range 23.1-78.7 nmol/L), whereas those levels were 62.3 nmol/L (IQ range 22.8-77.2) in the control group, which was a statistically significant difference (P=0.036). Regarding serum 25(OH)D concentrations, it was found that 11(21.56%) children with JIA and 8(16.6%) children in the control group had 25(OH)D values of <25nmol/L; the levels of 25(OH)D were compatible with the adequate value in 8 children with JIA and 19 children in the control group (Table 2).

25(OH)D levels were analyzed with regard to gender, and it was found that the girls and the boys in both groups had deficiency of 25(OH)D, (Table 3). No statistically significant difference in the 25(OH)D concentration between the girls and boys were noticed, P=0.37 and P=0.13, respectively. There was a negative, moderate, statistically significant correlation between the age of children with JIA and the levels of 25 (OH)D (r=-0.36, P=0.004; 95%CI: -0.58-0.09), while the correlation between the age and serum 25(OH) D concentrations was not observed in the control group (r=-0.10, P=0.23; 95%CI: 0.38-0.18). The median duration of arthritis was 2.1 years (IQ range 9 months to 3.2 years); and looking into the correlation between arthritis duration and 25(OH)D serum levels in children with JIA, the negative but statistically nonsignificant correlation was found (r=-0.21,

Table 1. Clinical Characteristics of 51 Children with JIA* Included in the Study

Children's characteristics		N (%)
Gender	Male	24 (47,06)
	Female	27 (52.94)
Form of JIA*	Olygoarticular	22 (43.14)
	Polyarticular Rf +†	2 (3.92)
	Polyarticular Rf -	18 (35.3)
	ERA‡	7 (13.73)
	sJIA§	2 (3.92)
Disease activity	ID‖	-
	LDA¶	39 (76.47)
	MDA**	12 (23.53)
	HDA††	-

*Juvenile idiopathic arthritis; †Rheuma factor; ‡Enthesitis related arthritis; §Systemic juvenile idiopathic arthritis; ‖Inactive disease; ¶Low disease activity; **Moderate disease activity; ††High disease activity.

Table 2. Serum 25(OH)D Levels in Children with JIA* and Children of Control Group

Serum 25(OH)D levels	Children with JIA* N (%)	Children of control group N (%)
Insufficiency <25nmol/L	11 (21.56)	8 (16.67)
Deficiency 25-50 nmol/L	15 (29.42)	7 (14.58)
Inadequate levels 50-70nmol/L	17 (33.34)	14 (29.17)
Adequate levels ≥75 nmol/L	8 (15.68)	19 (39.58)

*Juvenile idiopathic arthritis.

Table 3. Serum 25(OH)D Levels in Children with JIA* According to a Form and Disease Activity

Children's characteristics		Serum 25(OH)D levels (nmol/L; mean (IQ range)
Gender	Male	47.3 (22.3-78.2)
	Female	44.5 (21.6-76.2)
Form of JIA*	Oligoarticular	38 (22.6-52.50)
	Polyarticular Rf+†	42 (24.3-42.9)
	Polyarticular Rf-	46.6 (22.2-77.3)
	ERA‡	59.4 (24.5-78.8)
	JIA§	50 (24.1-52.0)
Disease activity	ID‖	-
	LDA¶	45.2 (24.2-78.8)
	MDA**	33.1 (20.1-41.5)
	HDA††	-

*Juvenile idiopathic arthritis; †Rheuma factor; ‡Enthesitis related arthritis; §Systemic juvenile idiopathic arthritis; ‖Inactive disease; ¶Low disease activity; **Moderate disease activity; ††High disease activity.

P=0.15; 95%CI: 0.15-0.29). Analyzing 25(OH) D status with regard to the JIA form, significantly different serum concentrations were observed. The children with oligoarticular form had the lowest levels, while the children with ERA had the highest levels, although these levels were within the domain of inadequate levels (Table 3). There was a statistically significant correlation between the JIA form and 25(OH)D serum concentrations (r=0.31, P=0.032; 95%CI: 0.53-0.026). Forty out of fifty-one (78.43%) children with JIA were considered to have an active disease if the median JADAS10 score was 6.24 (IQ range 1.4 to 7.1), thus 11 children with oligoarticular and 6 with polyarticular form had LAD; six children had MDA, there were five children with oligoarticular and polyarticular form of JIA, and 2 with ERA. There were no children with ID or HAD. Six children with insufficiency and 3 children with deficiency of 25(OH)D had MDA disease at the time of evaluation. There was a significant negative correlation between serum 25(OH)D levels and arthritis activity (r=-0.36, P=0.02; 95%CI: -0.009-0.50).

Discussion

Interest and knowledge about defining the role of vitamin D in pathogenesis, activity and treatment of JIA has been increased, and the data indicate suboptimal vitamin D status in children with chronic arthritis (1). Also, recent meta-analysis, which included 19 papers reporting on values of 25(OH)D in JIA, could not find evidence to link vitamin D deficiency with JIA due to a lack of agreed definition of vitamin D deficiency in pediatric population (14). Nevertheless, it is an important and useful overview and provides further evidence of the relatively high prevalence of vitamin D deficiency in JIA children.

We found insufficiency of vitamin D in 21.6% children and deficiency in 29.4% children with JIA, which was similar to findings of other authors (15-17). The high percentage of children with pediatric rheumatic diseases has a vitamin D deficiency or insufficiency that might correlate with the disease outcome and flare-ups (18). Bouaddi et al. (15) reported that 52.5% of children with JIA were considered to have an active disease (48% of children with HDA), and 75% of those children had hypovitaminosis 25(OH)D. They emphasized that there was a strong inverse association between baseline levels of both serum 25(OH)D and disease activity. According to our results 78.43% of children had active arthritis, 13 children (25.5%) had MAD, but 6 of them had insufficiency and 3 children were with deficiency of 25(OH)D at the time of evaluation.

We also noticed the negative and statistically significant correlation (r=-0.36) between serum 25(OH)D concentrations and arthritis activity. Stagi et al. (18) noticed significantly reduced 25(OH) D levels in children with JIA who had an active disease and/or frequent relapses in comparison with children with JIA who had an inactive disease and infrequent flare-ups (P<0.005). Similarly, Çomak et al. (16) also emphasized a significant correlation between serum 25(OH)D concentrations and disease activity. There are some other reports on the relationship between serum 25(OH)D concentrations and disease activity. For instance, Dagdeviren-Çakir et al. (19) did not find any significant differences in serum 25(OH)D concentrations in children with JIA during active and remission periods of disease. Also, other authors did not notice reduced 25(OH) D values in children with active arthritis (16, 20). Analyzing serum 25(OH)D concentration values in newly diagnosed children with JIA, Pelajo et al. (21) found a negative but not significant correlation with disease activity. We noticed a significant difference between serum 25(OH)D concentrations and the form of arthritis (P<0.0001).

However, we did not find any correlation between serum 25 (OH)D and disease duration (P=0.032 and P=0.15). This result was unexpected taking into account effects of vitamin D on the modulation of the immune system. The average duration of arthritis in children included in our study was approximately two years, 43.1% of children received DMARDs, 13.7% biological, no children received glucocorticoids and/or biphosphonate at the time of evaluation. However, our results were in accordance with the results acquired by other authors (16, 17). They demonstrated that serum 25(OH)D was significantly correlated with disease activity in children with JIA but independent of age, gender, JIA subtype or medications (16). It is also important to emphasize that vitamin D deficiency is a current public health issue that is increasing, including healthy individuals of all ages in developed and developing countries (22, 23, 27).

In addition, many researchers assessing 25(OH) D status in children with JIA found lower values in healthy children included in control groups (18, 19, 25, 26). Our findings were similar to those – a decrease in vitamin D status was observed in both groups, but the median of serum 25(OH)D concentration was significantly lower in children with JIA than in the control group (P=0.036). Nevertheless, such low levels of vitamin D in the group of healthy children was not an unexpected result, since vitamin D deficiency has been recognized as a global health problem and now can be detected in children of all ages (27).

The Limitations of the Study

Our study had several limitations including the small sample size, lack of available information about diet and sun exposure which may have influenced the serum 25(OH)D levels, but also a lack of dynamic monitoring of serum 25(OH)D concentrations.

Conclusion

Our findings have shown the correlation between serum 25(OH)D concentrations and arthritis activity, however, prospective comprehensive studies are needed to further investigate the relationship

between vitamin D and disease activity in JIA. Considering the impacts of vitamin D on the modulation of the immune system, clinicians should be aware of vitamin D deficiency in this group of patients. It remains to be elucidated whether vitamin D supplementation in children with JIA might prevent relapses or diminish disease activity.

Authors' Contributions: Conception and design: AĆ, SS, AA and AS; Acquisition, analysis and interpretation of data: AĆ, AS, AA, DD and SS; Drafting the article: AĆ and AA; Revising the article critically for intellectual content: AĆ, AS, AA, DD and SS; Approved final version of the manuscript: AĆ, SS, AS, AA, and DD.

References

1. Finch SL, Rosenberg AM, Vatanparast H. Vitamin D and juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2018;16(1):34.
2. Tang T, Zhang Y, Luo C, Liu M, Xu L, Tang X. Adjunctive vitamin D for the treatment of active juvenileidiopathic arthritis: An open-label, prospective, randomized controlled trial. Exp Ther Med. 2019;18(6):4921-6.
3. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr. 2004;80(Suppl 6):S1689-96.
4. White JH. Vitamin D metabolism and signaling in the immune system. Rev Endocr
5. Cutolo M, Pizzorni C, Sulli A. Vitamin D endocrine system involvement in autoimmune rheumatic diseases. Autoimmun Rev. 2011;11(2):84-7.
6. Vojinovic J. Vitamin D, receptor agonists' anti-inflammatory properties. Ann NY Acad Sci. 2014;1317:47–56.
7. Arkema EV, Hart JE, Bertrand KA, Laden F, Grodstein F, Rosner BA, et al. Exposure to Ultraviolet-B and risk of developing rheumatoid arthritis among women in the Nurses' Health Study. Ann Rheum Dis. 2013;72(4):506-11. Epub 2013 Feb 4.
8. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Curr Opin Pharmacol. 2010;10(4):482-96.
9. Sabbagh Z, Markland J, Vatanparast H. Vitamin D status is associated with disease activity among rheumatology outpatients. Nutrients. 2013;5(7):2268-75.
10. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25(10):1991-4.
11. Consolaro A, Ruperto N, Bazso A, Pistoro A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum. 2009;61(5):658-66.
12. Consolaro A, Negro G, Chiara Gallo M, Bracciolini G, Ferrari C, Schiappaprieta B, et al. Defining Criteria for Disease Activity States in Nonsystemic Juvenile Idiopathic Arthritis Based on a Three Variable Juvenile Arthritis Disease Activity Score. Arthritis Care Res. 2014;66(11):1703-9.
13. Consolar A, Bracciolini G, Rupeto N, Pistorio A, Magni-Manzoni S, Mallatia C, et al. Remission, minimal disease activity and acceptable symptom state in juvenile idiopathic arthritis. Arthritis Rheum. 2012;64(7):2366-74.
14. Nisar MK, Masood F, Cookson P, Sansome A, Östör AJK. What do we know about juvenile idiopathic arthritis and vitamin D? A systematic literature review and meta-analysis of current evidence. Clin Rheumatol. 2013;32(6):729-34.
15. Bouaddi I, Rostom S, El Badri D, Hassani A, Chkirate B, Abougal R, et al. Vitamin D concetrations and diease activity in Moroccan children with juvenile idiopathic arthritis. BMC Musculosceletal Disorders. 2014;15:115.
16. Çomak E, Doğan ÇS, Gökçeoğlu AU, Akbaş H, Özdem S, Koyun M, et al. Association between vitamin D deficiency and disease activity in juvenile idiopathic arthritis. The Turkish Journal of Pediatrics. 2014;56(6):621-6.
17. RV Munekata, MTRA Terreri, OAB Peracchi, C Len, Lazaretti-Castro M, ROS Sarni, et al. Serum 25-hydroxyvitamin D and biochemical markers of bone metabolism in patients with juvenile idiopathic arthritis. Braz J Med Biol Res. 2013;46(1):98-102.
18. Stagi S, Bertini F, Cavalli L, Matucci-Cerinic M, Brandi ML, Falcini F. Determinants of vitamin D levels in children, adolescents, and young adults with juvenile idiopathic arthritis. J Rheumatol. 2014;41(9):1884-92.
19. Dagdeviren-Çakir A, Arvas A, Barut K, Gür E, Kasapçopur Ö. Serum vitamin D levels during activation and remission periods of patients with juvenile idiopathic arthritis and familial mediterranean fever. Turk J Pediatr. 2016;58(2):125-31.
20. Reed A, Haugen M, Pachman LM, Langman CB. Abnormalities in serum osteocalcin values in children with chronic rheumatic diseases. J Pediatr. 1990;116(4):574-80.
21. Pelajo CF, Lopez-Benitez JM, Kent DM, Price LL, Miller LC, Dawson-Hughes B. 25-hydroxyvitamin D levels and juvenile idiopathic arthritis: is there an association with disease activity? Rheumatol Int. 2012;32(12):3923-9.
22. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. Pediatrics. 2009;124(3):362-70.

23. Gordon CM, Feldman HA, Sinclair L, Williams AL, Kleinman PK, Perez-Rossello J, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med. 2008;162(6):505-12.

24. Peters BSE, dos Santos LC, Fisberg M, Wood RJ, Martini LA. Prevalence of vitamin D insufficiency in Brazilian adolescents. Ann Nutr Metab. 2009;54(1):15-21.

25. Shevchenko N, Khadzhynova. Juvenile idiopathic arthritis and vitamin D status in Ukrainian patients. Georgian Med News. 2019;294:88-91.

26. Rosiles VH, Salazar CD, Velazquez RM, Ruiz RR, Clark P. Determination of 25(OH)D serum levels in children with systemic lupus erythematosus and juvenile idiopathic arthritis. Bol Med Hosp Infant Mex. 2015;72(2):99-105.

27. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3)266-81.