Mini review
Central Eur J Paed 2018;14(2):148-153
DOI 10.5457/p2005-114.213

Vitamin D and Immune Diseases in Children: A Mini-review

Srđana Čulić

Medical School University of Split, Split, Croatia

Correspondence:
srdjana.culic.sc@gmail.com
Tel.: + 385 98 4481 33
Fax.: + 385 21 556 256

Received: August 6, 2018
Accepted: September 12, 2018

Key words: Vitamin D ▪ Autoimmune Disease ▪ Children.

The purpose of this literature review was to summarize the knowledge about the effects of vitamin D on various autoimmune diseases. Research on the effects of vitamin D on the immune system increasingly shows that in cases of deficiency in vitamin D, adequate supplementing doses of this secosteroid, immunomodulatory hormone will enable us to prevent the onset or alleviate the symptoms of most autoimmune diseases. **Conclusion** – The importance of vitamin D's influence on the immune system and the consequences of its deficiency will be the interest of future research and will finally reveal the importance of this vitamin in the pathophysiology of immune events.

Introduction

Vitamin D (VD) deficiency is a leading cause of many adverse health effects in children. It has been associated with a wide spectrum of infections and autoimmune diseases in the recent scientific literature. This issue has gained increased interest among scientists who have discovered the important role of this hormone in immune regulation. VD acts as a balancing regulator of the cell-mediated Th1 and humoral Th2 immune response. It induces immune tolerance and control immune responses. This secosteroid hormone affects limphocyte T function and maturation via the vitamin D receptor (VDR). Immune cells such lymphocyte T, B, NK, dendritic cells express VDR and are capable of metabolizing VD, which plays an integral role in regulating the general immune response. Its function is realised by its genomic actions on the VDR. Looman's study in children revealed that higher 25(OH)D levels were associated with higher numbers of T effector memory lymphocytes. The author concludes that VD enhances celular immunity in children (1). High expression of VDR was also found in the intestine cells, beta islet cells of the pancreas, the nephrons, parathyroid gland, bronchi, thymus and the brain (2).

Inducing monocyte proliferation, expression and production of interleukines (IL-1, IL-12), extremely suppresses B-cell differentiation/proliferation and immunoglobulin production. VD decreases the production of interferon-γ, IL-17, and IL-2 and has strong immunomodulatory effect through modulation of helper and regulatory lymphocyte T function (3). VD is not only a vitamin but it is also a natural secosteroid hormon which is essential for the maintenance of the immune system.

Hypovitaminosis D is highly prevalent in children worldwide and an increased prevalence of deseases connected to imunodeficiency can be expected in this population. Inflamation of any type reduces utilization of VD while corticosteroids, anticoagulants and

antacides reduce its absorbtion or biologic activity. It gets taken up by fat cells so obesity reduces VD activity because it can be stored in adipose tissue. VD plays an important role in the adipogenesis process and inflammation status in adipocytes and adipose tissue (4, 5). Obese patients with low levels of VD have an increased risk of autoimmune diseases.

Hypovitaminosis D is defined as a condition in which the concentration of VD in serum is lower than 75 nmol/l (30 ng/ml). The optimal level for VD is recommended to be >75 nmol/L. Insufficiency is present with levels between 50 and 75 nmol/L. Levels ≤50 nmol/L are recognized as deficiency which may be strong (30 - 49.9 nmol/L), significant (20 – 29.9 nmol/L) or extreme (<20 nmol/L) (6). Recent research revealed that VD deficiency is linked to autoimmune diseases, such as multiple sclerosis, gastrointestinal autoimmune diseases, immune thrombocytopenia, systemic lupus erythrematodes (SLE), Hashimoto's thyroiditis and rheumatoid arthritis.

The purpose of this literature review was to present a short review about the impact of VD on autoimmune diseases and its importance in mastering these devastating conditions.

Autoimmune Thyroiditis

Hashimoto's autoimmune thyroiditis (AT) is the most common autoimmune disease. We know that obesity is associated with lower VD circulating levels and VD deficiency is significantly associated with AT in overweight and obese people (7). Bozkurt and colleagues revealed that serum 25OHD levels in patients with AT were significantly lower than controls, while 25OHD deficiency severity correlated with duration of AT, thyroid volume, and anti-TPO and anti-TG levels (8). Investigation of VD status in children with AT pointed that higher VD deficiency rates besides lower VD levels in the Hashimoto group together with the inverse correlation between VD and anti-TPO suggest that VD deficiency has a role in the autoimmune process in this population (9). VD suplementation may be beneficial for the management of AT patients with VD deficiency because low serum levels inversely corelate with serum anti-TPO antibodies. In AT patients with VD deficiency it was found that after 4 months suplementation a significant decrease (20.3%) of serum anti-TPO levels occured. These findings suggest that VD deficiency may be related to pathogenesis of AT and that its supplementation could contribute to the treatment of patients with AT (10).

Multiple Sclerosis

Only 5% of patients experience Multiple sclerosis (MS) before the age of 18. The exact mechanisms involved in pediatric-onset MS pathogenesis have yet to be defined. There is strong evidence of the association between low VD and increased risk of adult-onset but there is a small number of studies examining this relationship in pediatric MS. An association between childhood obesity and risk of pediatric MS has been reported. It remains unclear whether the association between increased obesity and MS risk is mediated by lack of VD, which can be stored in adipose tissue (11). Gianfrancesco MA and coauthors reported strong evidence for a causal and independent association between hypovitaminosis D and increased BMI and risk of pediatric-onset MS. Their findings support a role of these independent parameters to disease susceptibility (12). Immunological findings in patients with MS revealed that VD significantly influences regulatory lymphocyte T, whose role is well known in the pathogenesis of SLE. Hypovitaminosis D is one of possible risk factors for the onset of MS (13). Protective effect of VD levels significantly reduced the risk of MS (14).

Gastrointestinal Autoimmune Diseases

A variety of gastrointestinal autoimmune conditions including the inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are known. The potential genetic links associated with VD metabolism increase the risk of the onset of gastrointestinal autoimmune diseases. CD is characterized as a gastrointestinal chronic immune-mediated inflammatory disorder and VD deficiency is common in CD patients. There is an inverse relationship between VD status and the onset or progression of CD (15). Supplementation appears to be beneficial in improving clinical symptoms reducing inflammation (16). Over 40% of patients used a VD supplementation but the dosages were inadequate to prevent deficiency. Appropriate VD screening and supplementation should be recomended in preventing exacerbation of CD symptoms (17). The meta-analysis research shows that IBD is significantly associated with higher VD deficiency (64%) when compared with controls, while patients with UC had more than double the odds of VD deficiency (18). Some randomised controlled trials suggest that people with IBD may remain in remission longer when treated with oral VD which may modify the immune response in IBD (19). VD deficiency is common among patients with active UC, particularly those requiring corticosteroids. VD deficient patients have increased disease activity than patients with normal VD levels (20).

Rheumatoid Arthritis

VD deficiency is also prevalent in patients with rheumatoid arthritis (RA). It is important to establish a relationship between serum VD level and disease activity in RA. Some studies revealed that serum VD levels were significantly lower in RA patients than in healthy controls and that VD deficiency had negative correlation with disease activity in RA. In high disease activity group VD levels were significantly lower compared to the patients with low and moderate disease activity (21). Lee and colleagues' meta-analysis suggests that the VD level is associated with susceptibility to RA and corelates inversely with RA activity (22, 23). Positive correlation between 25(OH)D and IL-6 was observed in RA in one Polish population study (24). Less is known about the role of VD in chronic arthritis in children. Of 38 studies reporting VD serum concentrations in childhood chronic arthritis, 32 (84.2%) reported that a significant number of children had suboptimal (<75 nmol/L) status (25). In juvenile idiopathic arthritis (JIA) VD values are reduced and the patients with more severe disease require higher supplementation to maintain normal VD serum levels (26).

Immune Thrombocytopenia

Paediatric immune thrombocytopenia (ITP) is characterized by acute onset and 75% of children achieve spontaneous remission within 6 months. There is the high rate of recovery from ITP between 7 to 12 months (27).

Significant differences in serum cytokine levels between pediatric patients and healthy controls were found and indicate that cytokine disturbances (IL-2, IL-3, TNF-α) might be involved in the pathogenesis of newly diagnosed ITP (28). Also VDR polymorphisms can be involved in pathogenesis of paediatric immune thrombocytopenia. Evaluating five VDR polymorphisms (Cdx-2, FokI, BsmI, ApaI and TaqI) genotyped in 44 children with ITP and in 100 healthy controls Yesil and colleagues found the association of the Cdx-2 VDR variant and ITP. The three Cdx-2 genotype groups (GG, GA, and AA) were significantly different distributed between

ITP patients and controls while the homozygous GG genotype of Cdx-2 was overrepresented in ITP patients. The frequency of the A allele of Cdx-2 was significantly different between patients and controls and was associated with a decreased risk of ITP (29). Hypovitaminosis D may result in immune abnormalities in the development of chronic form of ITP and supplementation of VD might reduce chronic disease risk by modulating the immune system (6). The mechanism by which vitamin D increase platelet count in ITP patients is unknown. Its immunomodulatory role may enhance different immune response in patients with ITP (30).

Systemic Lupus Erythrematodes

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease and VD deficiency has been proposed as a trigger of disease onset. Immune dysfunction with loss of self-tolerance can lead to autoimmunity with multiple organ disfunction. Multiple studies have shown that there is a connection between SLE and hypovitaminosis D and revealed that the majority of patients with SLE have insufficient levels of VD and that there is a connection between SLE and VD status. Lower 25(OH)D levels were found in 123 cases with newly diagnosed SLE compared with 240 controls (Caucasians), and it was statistically significant (31). SLE patients have deficits in endothelial functions such as dilatation. VD as a nuclear hormone regulates vascular endothelial nitric oxide synthase activity and expression. Many SLE patients have insufficient levels of VD and the effect of this hormone on vascular endothelial function in SLE patients is not known. Kamen and Oates designed a study to determine the effect of VD levels on endothelial function in patients with SLE and VD deficiency. The results of this study suggest a potential role for VD in SLE-related endothelial dysfunction (32). VD actions are extremely important not only for the field of immunity but also for endothelial functioning. Endothelial diseases are one of the frequent causes of mortality nowadays therefore research in this area could give us very interesting and usefull conclusions. Young and colleagues genotyped six single nucleotide polymorphisms (SNPs) in four VD genes involved in VD transport (*GC* (rs7041), *CYP27B1* (rs10877012), *CYP24A1* (rs4809959), and *VDR* (rs1544410, rs11568820, and rs7975232)) in individuals who transitioned to SLE and were VD deficient. They found that individuals with VD deficiency and CYP24A1 may have increased risk of transitioning to SLE. This discovery may help identify patients at increased risk of transitioning to SLE (33). Genetic polymorphism in combination with VD deficiency is important and VD supplementation may decrease the risk of transitioning to autoimmune disease.

Conclusion

Vitamin D is an immunomodulating secosteroid hormone which has the potential to be effective in preventing and treating autoimmune diseases. VD supplementation is a promising strategy for decreasing the incidence and symptoms of variuos autoimmune disease. Immune modulating effect and the action of VD on the immune system today is a topic of ample research. Unfortunately, medicine has not solved many dilemas related to the immune system diseases that are a leading cause of morbidity in the world. There is hope that future research will show how important it is to compensate for the lack of VD with the aim to prevent immune disease, its reactivation and deterioration. It is important to emphasize that the VDR polymorphism study will link genetic defects with the occurrence of autoimmune disease.

Conflict of interest: The author declares that she has no conflict of interest.

References

1. Looman KIM, Jansen MAE, Voortman T, van den Heuvel D, Jaddoe VWV, Franco OH, et al. The role of vitamin D on circulating memory T cells in children: The Generation R study. Pediatr Allergy Immunol. 2017;28(6):579-87.
2. Clarke MC, Cole K, Sutter A. Vitamin D3: Clinical overview and applications from 10 years of research reviews. Central Eur J Paed. 2018;14(2):130-9.
3. Ariganjoye R. Pediatric Hypovitaminosis D: Molecular Perspectives and Clinical Implications. Glob Pediatr Health. 2017;4:2333794X16685504.
4. Ruiz-Ojeda FJ, Anguita-Ruiz A, Leis R, Aguilera CM. Genetic Factors and Molecular Mechanisms of Vitamin D and Obesity Relationship. Ann Nutr Metab. 2018;73(2):89-99.
5. Peterson CA, Belenchia AM. Vitamin D deficiency & childhood obesity: a tale of two epidemics. Mo Med. 2014;111(1):49-53.
6. Čulić S, Markić J, Petrović D, Konjevoda P, Pavelić J. Serum vitamin D levels in children with newly diagnosed and chronic immune thrombocytopenia. Semin Hematol. 2016;53 (Suppl 1):S67-9.
7. De Pergola G, Triggiani V, Bartolomeo N, Giagulli VA, Anelli M, Masiello M, et al. Low 25 Hydroxyvitamin D Levels are Independently Associated with Autoimmune Thyroiditis in a Cohort of Apparently Healthy Overweight and Obese Subjects. Endocr Metab Immune Disord Drug Targets. 2018: 6. doi: 10.2174/1871530318666180406163426.
8. Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, et al. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract. 2013;19(3):479-84.
9. Camurdan OM, Döğer E, Bideci A, Celik N, Cinaz P. Vitamin D status in children with Hashimoto thyroiditis. J Pediatr Endocrinol Metab. 2012;25(5-6):467-70.
10. Mazokopakis EE, Papadomanolaki MG, Tsekouras KC, Evangelopoulos AD, Kotsiris DA, Tzortzinis AA. Is vitamin D related to pathogenesis and treatment of Hashimoto's thyroiditis? Hell J Nucl Med. 2015;18(3):222-7.
11. Sundström P. Managing Epstein-Barr virus and other risk factors in MS-Future perspectives. Acta Neurol Scand. 2017;136 (Suppl)201:31-3.
12. Gianfrancesco MA, Stridh P, Rhead B. Evidence for a causal relationship between low vitamin D, high BMI, and pediatric-onset MS. Neurology. 2017;88(17):1623-9.
13. Pierrot-Deseilligny C, Souberbielle JC. Is hypovitaminosis D one of the environmental risk factors for multiple sclerosis? Brain. 2010;133(Pt 7):1869-88.
14. Salzer J, Hallmans G, Nyström M, Stenlund H, Wadell G, Sundström P. Vitamin D as a protective factor in multiple sclerosis. Neurology. 2012;79(21):2140-5.
15. Ghaly S, Lawrance I. The role of vitamin D in gastrointestinal inflammation. Expert Rev Gastroenterol Hepatol. 2014;8(8):909-23.
16. Basson A. Vitamin D and Crohn's disease in the adult patient: a review. JPEN J Parenter Enteral Nutr. 2014;38(4):438-58.
17. Suibhne TN, Cox G, Healy M, O'Morain C, O'Sullivan M. Vitamin D deficiency in Crohn's disease: prevalence, risk factors and supplement use in an outpatient setting. J Crohns Colitis. 2012;6(2):182-8.
18. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2015;21(11):2708-17.
19. O'Sullivan M. Vitamin D as a novel therapy in inflammatory bowel disease: new hope or false dawn? Proc Nutr Soc. 2015;74(1):5-12.
20. Blanck S, Aberra F. Vitamin d deficiency is associated with ulcerative colitis disease activity. Dig Dis Sci. 2013;58(6):1698-702.
21. Sharma R, Saigal R, Goyal L, Mital P, Yadav RN, Meena PD, et al. Estimation of vitamin D levels in rheumatoid arthritis patients and its correlation with the disease activity. J Assoc Physicians India. 2014;62(8):678-81.
22. Lee YH, Bae SC. Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: a meta-analysis. Clin Exp Rheumatol. 2016;34(5):827-33.
23. Meena N, Singh Chawla SP, Garg R, Batta A, Kaur S. Assessment of Vitamin D in Rheumatoid Arthri-

tis and Its Correlation with Disease Activity. J Nat Sci Biol Med. 2018;9(1):54-8.

24. Polasik K, Piotrowska E, Lipińska B, Witkowski JM, Bryl E, Tukaj S. Vitamin D status in patients with rheumatoid arthritis: a correlation analysis with disease activity and progression, as well as serum IL-6 levels. Acta Biochim Pol. 2017;64(4):667-70.

25. Finch SL, Rosenberg AM, Vatanparast H. Vitamin D and juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2018;16(1):34.

26. 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.

27. Imbach P, Kühne T, Müller D, Berchtold W, Zimmerman S, Elalfy M, et al. Childhood ITP: 12 months follow-up data from the prospective registry I of the Intercontinental Childhood ITP Study Group (ICIS). Pediatr Blood Cancer. 2006;46(3):351-6.

28. Čulić S, Salamunić I, Konjevoda P, Dajak S, Pavelić J. Immune thrombocytopenia: serum cytokine levels in children and adults. Med Sci Monit. 2013;19:797-801.

29. Yesil S, Tanyildiz HG, Tekgunduz SA, Toprak S, Fettah A, Dikmen AU, et al. Vitamin D receptor polymorphisms in immune thrombocytopenic purpura. Pediatr Int. 2017;59(6):682-5.

30. Bockow B, Kaplan TB. Refractory immune thrombocytopenia successfully treated with high-dose vitamin D supplementation and hydroxychloroquine: two case reports. J Med Case Rep. 2013;7:91.

31. Singh A, Kamen DL. Potential benefits of vitamin D for patients with systemic lupus erythematosus. Dermatoendocrinol. 2012;4(2):146-51.

32. Kamen DL, Oates JC. A Pilot Study to Determine if Vitamin D Repletion Improves Endothelial Function in Lupus Patients. Am J Med Sci. 2015;350(4):302-7.

33. Young KA, Munroe ME, Guthridge JM, Kamen DL, Niewold TB, Gilkeson GS, et al. Combined role of vitamin D status and CYP24A1 in the transition to systemic lupus erythematosus. Ann Rheum Dis. 2017;76(1):153-8.