IAR Journal of Medical Case Reports
ISSN Print : 2709-3220 | **ISSN Online :** 2709-3239
Frequency : Bi-Monthly
Language : English
Origin : Kenya
Website : https://www.iarconsortium.org/journal-info/iarjmcr

OPEN ACCESS JOURNALS

Case Report

Clinical Utility of Vitamin D in the Treatment of Idiopathic Chronic Lymphopenia: A Possible Intervention

Article History

Received: 31.08.2021
Revision: 10.09.2021
Accepted: 20. 09.2021
Published: 30.09.2021

Author Details

José Arturo Álvarez Sánchez, Juan Pablo Díaz Bernal, Miriam Deyanira Rodríguez Piña and Hugo Mendieta Zerón*

Authors Affiliations

Faculty of Medicine, Autonomous University of the State of Mexico, Av Paseo Tollocan, esq. Jesús Carranza, Moderna de la Cruz, 50180 Toluca, Mexico

Corresponding Author*
Dr. Hugo Mendieta Zerón

How to Cite the Article:
Álvarez Sánchez JA, Díaz Bernal JP, Rodríguez Piña MD & Mendieta Zerón H. (2021); Clinical Utility of Vitamin D in the Treatment of Idiopathic Chronic Lymphopenia: A Possible Intervention. *IAR J Med Cse Rep. 2*(5),19-23.

DOI: 10.47310/iarjmcr.2021.v02i05.004

Abstract: ***Aim:*** To open the possibility of using vitamin D in cases of idiopathic lymphopenia. ***Background:*** In addition to its participation in the homeostasis of calcium and phosphorus, vitamin D has immunomodulatory mechanisms, so, its deficiency, apart from being associated with bone abnormalities, accompanies the development of certain autoimmune diseases. ***Case Description:*** It is a case of leukopenia associated with idiopathic lymphopenia of four years of evolution, in a 51-year-old woman, with history of hemithyroidectomy and osteopenia in the lumbar spine. Management initially consisted in supplementation with calcium and ibandronic acid. However, in the presence of hypercalciuria, vitamin D deficiency was suspected, so its serum levels were quantified, confirming the deficiency, then calcitriol was added to the treatment. Five months after the first dose of calcitriol, the leukocytes and lymphocytes levels were within normal range. ***Conclusion:*** There are many therapeutic schemes to treat vitamin D deficiency, however, nowadays no cases have been reported confirming the positive effect on lymphocytes count after vitamin D supplementation. ***Clinical significance:*** Until now, cases of idiopathic lymphopenia have not been given any specific therapeutic alternative, and vitamin D could have a positive effect if there is an autoimmune component, and perhaps even offer a greater spectrum of benefits.

Keywords: calcitriol, chronic leukopenia, idiopathic lymphopenia, immunomodulation, osteoporosis, vitamin D.

BACKGROUND

Vitamin D is involved in diverse processes other than calcium regulation, such as: antineoplastic actions, glucose metabolism, muscular activity and immune system regulation (Gómez de Tejada, M. J., 2014). Vitamin D deficiency is a high-prevalent condition worldwide due to alimentary, geographic and socioeconomic factors. As a matter of fact, this deficiency generates anomalies in the regulation of calcium, phosphorus and bone homeostasis.

It has been documented that a viable therapy to correct vitamin D deficiency and keep adequate serum levels is to administer vitamin D2 or D3 at a dose of 50,000 IU once a week for 2 months, following an adjustment in the maintaining dose to 50,000 IU at 2-4 weeks intervals. Since the availability of these capsules is insufficient, other alternative schemes which have demonstrated efficiency have been prescribed (Holick, M. F., 2007). Moreover, the Endocrine Society's Practice Guidelines Committee recommends that for optimal musculoskeletal health, serum vitamin D levels must be at least 30 ng/ml (Holick, M. F., 2017).

Additionally, both the Spanish Agency for Medicines and Sanitary Products (AEMPS), and the United States Food and Drug Administration (FDA), indicate calcitriol use of in all those pathologies in which the synthesis capacity of this compound is abolished, such as: chronic renal insufficiency, idiopathic hypoparathyroidism, postsurgical hypoparathyroidism, pseudohypoparathyroidism, renal osteodystrophy, vitamin D-dependent rickets, vitamin D-resistant hypophosphatemic rickets and osteomalacia [Ficha técnica rocaltrol, 2021 & Calcitriol. 2021]. In fact, calcitriol therapy has demonstrated a greater increase in the bone mineral density in short and long term, and a decrease in fractures compared to colecalciferol therapy or placebo (Tanakol, R. *et al.*, 2018; Meier, C. *et al.*, 2004; & Tilyard, M. W. *et al.*, 1992).

On the other hand, the idiopathic lymphopenia diagnosis is established when the criteria given by the Center for Disease Control and Prevention (CDC) are met: 1) CD4 lymphocytes cellular depletion (absolute values <300 cells/mL or <20% of total lymphocytes in two different measures at least 6 weeks apart), 2) Absence of HIV serologic evidence, 3) Lack of any immunodeficiency or therapy associated with CD4 lymphocytes levels depletion. It is worth noting that there is an association between vitamin D deficiency with a decrease in the lymphocytes-leukocytes counts in the setting of infectious diseases (COVID-19 and HIV-AIDS) and autoimmune diseases, such as Type 1 Diabetes Mellitus (T1DM), Systemic Lupus Erythematosus (SLE) and rheumatoid arthritis; nevertheless, vitamin D deficiency has not been related to idiopathic lymphopenia, as suggested in the present case report.

Case Description

It is a case of a 51-year-old female patient, who since 2017 had leukopenia with initial values of 3,900 leukocytes/µL, associated with lymphopenia of 1,176 lymphocytes/µL, without any attributable cause. According to the important pathological personal antecedents, it stands out a hemithyroidectomy performed in 2014 due to a micro-macro follicular adenoma, as a consequence, she developed primary hypothyroidism, currently treated with levothyroxine. In 2017, she manifested osteoarticular discomfort, thus a densitometry was performed, identifying osteopenia at the lumbar spine level, initiating treatment with ibandronic acid and supplemental calcium. After confirming hipercalciuria in 2020, treatment was changed to alendronate and cholecalciferol. Throughout her periodic evaluations, bilateral renal lithiasis, segment V hepatic hemangioma, intramural and small element uterine myomatosis, colonic diverticulosis and persistent leukopenia associated with lymphopenia were recorded.

In august 2020, urinary calcium of 72 mg/day (100-300 mg/day) was determined; suspecting vitamin D deficiency, its serum value was quantified, obtaining 17.6 ng/ml of 25(OH) D (20-100 ng/ml) and it was decided to incorporate calcitriol to the initial treatment. Five months after this first dose, the leukocytes and lymphocytes values increased and reached the normal range (Figure 1).

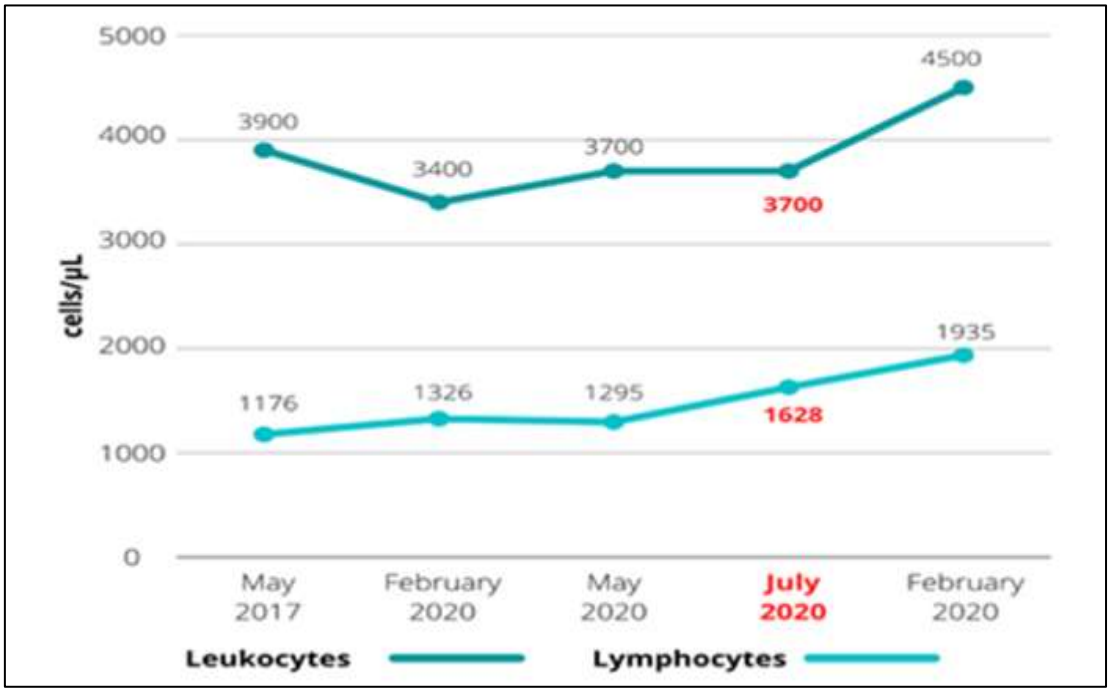

Figure 1: Leukocyte and Lymphocyte Levels Variations. One Month After Blood Count In July 2020, Treatment With Calcitriol Was Started.

Discussion

Based on available information, it is recommended that patients at risk of vitamin D deficiency or those who have a greater susceptibility to infections such as influenza and COVID-19, should be prescribed with vitamin D as a preventive dose (Romo, A., *et al.*, 2020). A study carried out in COVID-19 patients who required hospitalization, determined that, on average, their vitamin D levels were deficient (16.54 ± 7.37) and only 4.1% maintained optimal levels. Among the featured data, it was noticeable that none of the patients with adequate levels of this vitamin died and that the higher mortality rate was presented in the patients with deficient levels, despite the fact no significant statistical association was found between the different categories of vitamin D and mortality; nonetheless, it was reported

that patients with vitamin D levels below 8 ng/mL had 3.69 times higher risk to die (Reyes, R. A., *et al.*, 2020).

Vitamin D intoxication is an uncommon event, which can be caused by an excessively high ingestion, doses higher than >50 000 IU/day dose, elevate the values of 25(OH)D over 150 ng/ml and are related to hypercalcemia and hyperphosphatemia. Similarly, a dose of 10 000 IU/day of vitamin D3 for up to 5 months maximum does not carry toxicity risk (Holick, M. F., 2007).

The vitamin D endogenous production occurs by photochemical conversion of 7-dehydrocholesterol to cholecalciferol in the epidermis when exposed to UV-B rays, later it is hydrolyzed in the liver and is converted in 25-hydroxyvitamin D (25(OH)D), finally, in the kidney, this compound is converted into 1,25 dihydroxyvitamin D (1,25(OH)2D3), the active form of this hormone (Valero, M. *et al.*, 2007; & Zuluaga, N. *et al.*, 2011). It has been demonstrated that the vitamin D receptor (VDR) and the vitamin D activating enzyme, 1-alpha-hydroxylase (CYPB27B1), are expressed in different organs of the human body such as: bone, intestine, kidney, pancreas, prostate and even immune system cells (Sassi, F., *et al.*, 2018).

Aside from its main role in calcium homeostasis and skeletal system regulation, in recent decades the immunomodulatory mechanisms that vitamin D exerts on the immune system have been clarified. Regarding innate immunity, 1,25(OH)2D3 improves the β2-defensin and the antimicrobial cathelicidin peptide (CAMP) production by keratinocytes, macrophages, monocytes and neutrophiles. It also stimulates chemotaxis and phagocytosis mechanisms, likewise, it improves macrophages differentiation and maturation (Sassi, F., *et al.*, 2018; & Skrobot, A., *et al.*, 2018). Regarding adaptive immunity, it reduces antigen presentation, activation of effector T lymphocytes (Th1, Th17) and secretion of proinflammatory cytokines such as IL-17, TNFα, IL-22 e IFN-ɣ; simultaneously, it induces Th2 and T regulatory cells activation, both involved in the proinflammatory reactions reduction. Moreover, 1,25(OH)2D3 inhibits the post-change and plasma B cells production, thus causing a decrease in the immunoglobulins secretion (Skrobot, A., *et al.*, 2018; & Höck A. D., 2014). (Figure 2).

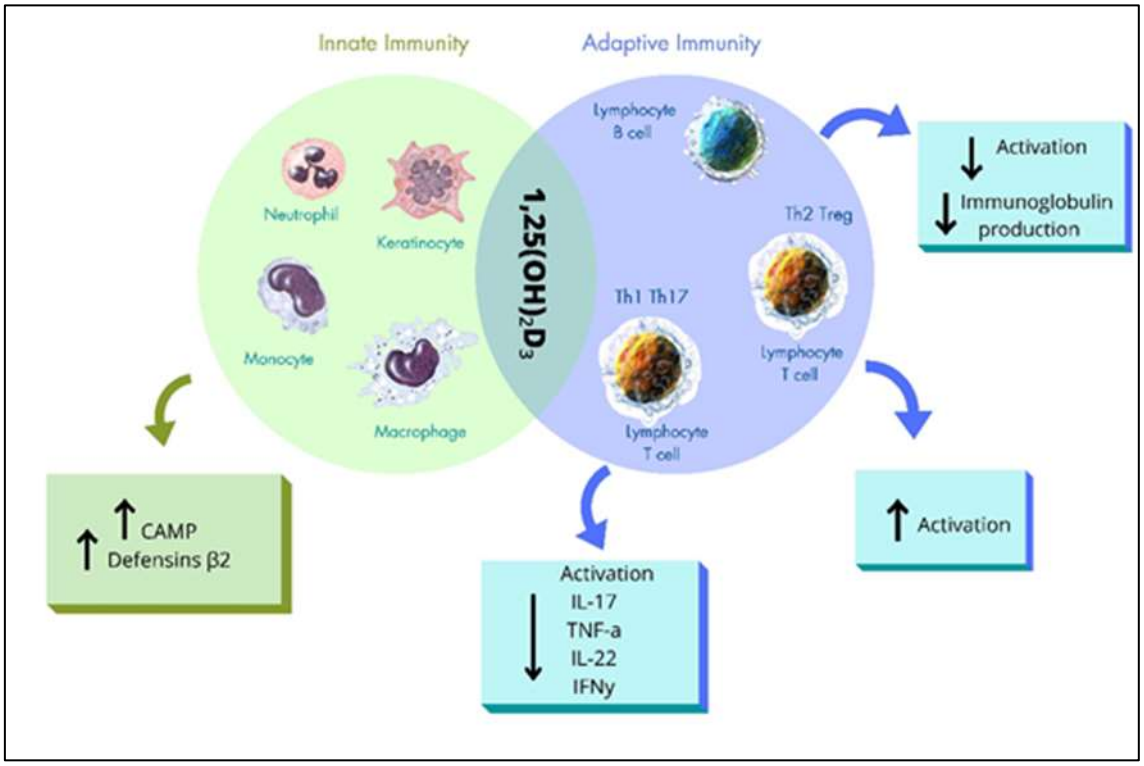

Figure 2: Vitamin D actions. 1, 25 dihydroxyvitamin D roll in adaptive immunity produces different effects over the variety of lymphocytes, for instance, it influences lymphocytes B to downregulate the activation and production of immunoglobulin as well as reducing Th1 and Th17 activation of cytokines Interleukin 17, Interleukin 22, Interferon gamma, and Tumor Necrosis Factor; on the contrary it increases the activation of Th2 and regulatory T cells. On the other hand, 1,25 dihydroxyvitamin D acts on the innate immunity by increasing the cyclic adenosine monophosphate and the production of beta-defensin-2.

An inflammatory response with high concentrations of pro-inflammatory cytokines has been observed in patients with severe forms of COVID-19 who present lymphopenia, especially in cases of T lymphocytes and vitamin D deficiency, conditions associated with the development of multiple organ failure, responsible for death in a significant proportion of these patients (Romo, A. *et al.*, 2020).

There are several autoimmune diseases associated with vitamin D deficiency, such as T1DM, SLE and Hashimoto's thyroiditis; in which, a therapeutic benefit has been evidenced with the use of vitamin D supplements. The vitamin D immunomodulatory effects include pancreatic-cells apoptosis prevention, leading to insulin secretion improved function in T1DM; fatigue symptoms and disease activity reduction, and adaptive immunity activation enhancement in SLE; as well as the reduction in anti-thyroid peroxidase (TPOAb) and anti-thyroglobulin (TgAb) antibodies levels in Hashimoto's thyroiditis (Bellan, M., *et al.*, 2020).

Another pathology in which vitamin D deficiency has been extensively documented is Multiple Sclerosis (MS), especially during recurrent episodes; through the analysis of various cohort studies in large population groups, it has been suggested the use of vitamin D supplementation to reduce the risk of appearance and development of this disease (Munger, K. L., *et al.*, 2004; VanAmerongen, B. M., *et al.*, 2004; & Ascherio, A., *et al.*, 2010).

In the present case, within the approach of the patient with vitamin D, its possible effect for the treatment of idiopathic lymphopenia is analyzed. Vitamin D insufficiency corresponds to values of 21-29 ng/ml of 25 (OH) D and has a high prevalence worldwide, affecting approximately 50% of the population and 67.1% of women with osteoporosis in Mexico. On the other hand, vitamin D deficiency is considered when serum 25 (OH) D values are <20 ng/ml (Holick, M. F., 2007; & Lips, P. *et al.*, 2006).

In our patient, it was ruled out that the decrease in the leukocyte-lymphocyte cellular counts was caused by malignant etiologies, in the same way, complementary studies were carried out in search of autoimmune diseases, HIV infection and other attributable causes, without positive results. According to the criteria established by the CDC, it was classified as idiopathic lymphopenia, for which treatment with calcitriol was started. Vitamin D supplementation improved the patient's clinical setting regarding musculoskeletal discomfort; likewise, in the hematic biometry performed five months after starting the treatment, an increase in the number of leukocytes and lymphocytes was found, reaching the normal range.

A limitation of this case report is the lack of determination of lymphocyte subpopulations, however the elevation of the total leukocyte and lymphocyte counts, allow us to infer a favorable effect of vitamin D. It is mandatory to perform controlled studies with a larger sample size to determine vitamin D deficiency in patients with autoimmune diseases; as well as identifying the levels of vitamin D in patients with idiopathic lymphopenia, and to make a close record of the lymphocyte count after the prescription of this hormone.

CONCLUSION

According to the reviewed literature, taking into account the vitamin D immunomodulatory functions, and considering the evidence in favor of supplementation in pathologies that are deficient in this vitamin and the findings obtained in the present case, it is suggested that Vitamin D supplementation as a treatment in patients with idiopathic lymphopenia and autoimmune diseases, should be considered in the comprehensive management of these patients, due to its effect associated with increased serum levels of lymphocytes, improving the symptoms and clinical course of the disease.

Clinical Significance

Until now, cases of idiopathic lymphopenia have not been given any specific therapeutic alternative, and vitamin D could have a positive effect if there is an autoimmune component, and perhaps even offer a greater spectrum of benefits.

Conflict of interest statement

All authors do not have any conflict of interest.

REFERENCES

1. Gómez de Tejada Romero, M. J. (2014). Acciones extraóseas de la vitamina D. *Revista de Osteoporosis y Metabolismo Mineral*, *6*, 11-18.
2. Holick, M. F. (2007). Vitamin D deficiency. *New England journal of medicine*, *357*(3), 266-281.
3. Holick, M. F. (2017). The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Reviews in Endocrine and Metabolic Disorders*, *18*(2), 153-165.
4. Ficha técnica rocaltrol 0,25 mcg capsulas blandas. Retrieved September 6, 2021, from: https://cima.aemps.es/cima/dochtml/ft/55973/FichaTecnica_55973.html
5. Calcitriol. (2021). En StatPearls publishing. Retrieved July 1, 2021 from: https://www.ncbi.nlm.nih.gov/books/
6. Tanakol, R., Gül, N., Üzüm, A. K., & Aral, F. (2018). Calcitriol treatment in patients with low vitamin D levels. *Archives of osteoporosis*, *13*(1), 1-9.
7. Meier, C., Woitge, H. W., Witte, K., Lemmer, B., & Seibel, M. J. (2004). Supplementation with oral vitamin D3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial. *Journal of Bone and Mineral Research*, *19*(8), 1221-1230.
8. Tilyard, M. W., Spears, G. F., Thomson, J., & Dovey, S. (1992). Treatment of postmenopausal osteoporosis with calcitriol or calcium. *New England Journal of Medicine*, *326*(6), 357-362.

9. Romo-Romo, A., Reyes-Torres, CA, Janka-Zires, M., & Almeda-Valdes, P. (2020). The role of nutrition in the coronavirus disease 2019 (COVID-19) The role of nutrition in the coronavirus disease 2019 (COVID-2019). *Rev Mex Endocrinol Metab Nutr* , *7* , 132-43.
10. Tort, AR, Mercado, EAM, Cuazitl, AM, Nieto, AVP, & Pérez, RAR (2020). Vitamin D deficiency is a risk factor for mortality in COVID-19 patients. *Revista de Sanidad Militar* , *74* (1), 106-113.
11. Zanuy, M. V., & Carranza, F. H. (2007). Metabolismo, fuentes endógenas y exógenas de vitamina D. *Revista Española de Enfermedades Metabólicas Óseas*, *16*(4), 63-70.
12. Zuluaga Espinosa, NA, Alfaro Velásquez, JM, Balthazar González, V., Jiménez Blanco, KE, & Campuzano Maya, G. (2011). Vitamin D: new paradigms. *Med. Lab* , 211-246.
13. Sassi, F., Tamone, C., & D'Amelio, P. (2018). Vitamin D: nutrient, hormone, and immunomodulator. *Nutrients*, *10*(11), 1656.
14. Skrobot, A., Demkow, U., & Wachowska, M. (2018). Immunomodulatory role of vitamin D: a review. *Current Trends in Immunity and Respiratory Infections*, 13-23.
15. Hoeck, A. D. (2014). Vitamin D3 deficiency results in dysfunctions of immunity with severe fatigue and depression in a variety of diseases. *in vivo*, *28*(1), 133-145.
16. Bellan, M., Andreoli, L., Mele, C., Sainaghi, P. P., Rigamonti, C., Piantoni, S., ... & Marzullo, P. (2020). Pathophysiological role and therapeutic implications of vitamin D in autoimmunity: focus on chronic autoimmune diseases. *Nutrients*, *12*(3), 789.
17. Munger, K. L., Zhang, S. M., O'reilly, E., Hernan, M. A., Olek, M. J., Willett, W. C., & Ascherio, A. (2004). Vitamin D intake and incidence of multiple sclerosis. *Neurology*, *62*(1), 60-65.
18. VanAmerongen, B. M., Dijkstra, C. D., Lips, P., & Polman, C. H. (2004). Multiple sclerosis and vitamin D: an update. *European journal of clinical nutrition*, *58*(8), 1095-1109.
19. Ascherio, A., Munger, K. L., & Simon, K. C. (2010). Vitamin D and multiple sclerosis. *The Lancet Neurology*, *9*(6), 599-612.
20. Lips, P., Hosking, D., Lippuner, K., Norquist, J. M., Wehren, L., Maalouf, G., ... & Chandler, J. (2006). The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *Journal of internal medicine*, *260*(3), 245-254.