World Nutrition Journal |eISSN 2580-7013

CASE REPORT

The effect of vitamin D supplementation on increasing CD4 levels in human immunodeficiency virus: evidence-based report

Dessy Suci Rachmawati[1], Diana Sunardi[1]

1. *Department of Nutrition, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo, General Hospital, Jakarta, Indonesia*

Received 15 March 2024
Accepted 28 May 2024
Published 30 August 2024

Link to DOI:
10.25220/WNJ.V08.i1.0004

Citation: Rachmawati D.S, Sunardi D. The effect of vitamin D supplementation on increasing CD4 levels in human immunodeficiency virus: evidence-based report. World Nutrition Journal.2024 August 30,8(i1): 21-28.

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Abstract

Introduction: Human immunodeficiency virus (HIV) is a retrovirus infection that attacks the immune system. According to world data in 2016, the number of HIV-infected patients reached 36.7 million, and 10 million people died due to acquired immunodeficiency syndrome (AIDS). Patients with HIV infection are susceptible to decreased levels of vitamin D (25(OH)D) by proinflammatory cytokines or as a result of the use of antiretroviral drugs. Vitamin D plays an important role in immune system, including reducing the production of pro-inflammatory cytokines and increasing the production of cathelicidin that inhibit viral replication. Oral vitamin D supplementation is an effort that can be made to increase vitamin D. To date, the relationship between vitamin D sufficiency and CD4 T cell count remains unclear, although most studies have shown a positive association. This study wanted to determine the effect of oral vitamin D supplementation on increasing CD4 levels in patients with HIV infection.
Methods: Literature search was carried out by advanced searching on Pubmed, Cochrane Library, and Science Direct using eligibility criteria determined by the authors.
Result: One systematic review and three randomized controlled trials (RCT) met the PICO and eligibility criteria that had been set. Three studies concluded that vitamin D supplementation can increase CD4 levels. One study shows that vitamin D supplementation dose of 5,000 IU daily could not increase CD4 levels.
Conclusion: Providing vitamin D supplementation at appropriate dose can increase serum vitamin D levels so that it can increase CD4 levels.

Keywords: vitamin D supplementation, CD4, human immunodeficiency virus

Clinical Scenario

A 28-year-old woman has been suffering from HIV for 4 months. The patient has not received antiretroviral therapy. The patient was treated for complaints of weakness that had worsened since 4 days before entering the hospital. At admission, the patient experienced anemia (7.7 g/dL), hyponatremia (135 mEq/L), hypokalemia (2.9 mEq/L), hypoalbuminemia (2.8 g/dL), and vitamin D deficiency (4.6 ng/mL). The patient was consulted by an internist to a physician clinical nutrition specialist for nutritional management and

Corresponding author:
Diana Sunardi
Department of Nutrition
Faculty of Medicine, Universitas Indonesia
Dr. Cipto Mangunkusumo General Hospital,
Jakarta, Indonesia
Email: diana_sunardi@yahoo.com

asked whether giving vitamin D supplementation could help immunological recovery by increasing of CD4 levels?

Introduction

The human immunodeficiency virus (HIV) is a retrovirus infection that attacks the immune system. According to world data in 2016, the number of HIV-infected patients reached 36.7 million, and 10 million people died due to acquired immunodeficiency syndrome (AIDS). The prevalence of HIV cases in Indonesia from 2005–2019 data recorded 338,363 people suffering from HIV and 1,536 people with AIDS. Patients with HIV are susceptible to vitamin D deficiency, this is caused by impaired renal 1α-hydroxylation of 25-hydroxyvitamin D3 mediated by proinflammatory cytokines or as a result of the use of antiretroviral drugs. Vitamin D plays a role in the immune system, both the innate immune system and the adaptive immune system.[1,2] There is an increased risk of morbidity and mortality in HIV-infected patients with low levels of vitamin D.[3] CD4 T cell counts in peripheral blood are useful to determine immune status and stage of HIV infection.[4]

Vitamin D plays a role in the innate and adaptive immune system, and the vitamin D receptor (VDR) is expressed in almost all cells of the immune system, namely CD8+ T lymphocytes, CD4+ T lymphocytes, as well as B lymphocytes and monocyte/macrophage cells. The active form of vitamin D, namely 1,25(OH)2D, will influence the differentiation of innate immune cells, which increases the development of regulatory T lymphocytes with suppressive activity. Additionally, pathogen elimination is increased through increased intracrine 1,25(OH)2D production by monocytes and macrophages, leading to increased phagocytosis and expression of pathogen recognition receptors. This signaling will increase the transcription of cathelicidin, which have antimicrobial properties, and defensins, which has both antimicrobial and antiviral properties. Cathelicidin is also known to inhibit HIV replication in CD4+ T cells and macrophages.[5-7]

Based on previous research, vitamin D can influence both innate and adaptive responses through the expression of its receptors on various immune cells, such as monocytes, dendritic cells, and lymphocytes. Through this process, vitamin D is known to increase CD4 levels. According to two randomized controlled trials and one systematic review, vitamin D supplementation can increase CD4 levels in HIV patients. Several studies state that giving vitamin D supplementation at the appropriate dose can improve vitamin D levels and the patient's immune system.

Clinical Questions

P : Patients with HIV infection
I : Vitamin D supplementation
C : Placebo or no vitamin D supplementation
O : CD4 level
Clinical question: Can oral vitamin D supplementation reduce CRP levels in patients with HIV infection?

Methods

The literature search was carried out by advanced searching using a combination of MesH terms and title/abstract on the PubMed database, Cochrane Library, and advanced search on Science Direct. The search was carried out on January 4, 2024. The keywords used were vitamin D supplementation, CD4, and human immunodeficiency virus. Critical appraisal tools and determination of the level of evidence are based on the Oxford Center for Evidence Based Medicine.

Eligibility Criteria

Inclusion criteria included subjects over 18 years of age with a diagnosis of HIV infection. The study used a randomized controlled trial (RCT) design and systematic review/meta-analysis from an RCT. The intervention was the supplementation of vitamin D, while the control group was given placebo or no vitamin D supplementation, published from 2019 to 2024, and was written in English. Exclusion criteria include research that

was not conducted in humans and articles not available in full text.

Critical Study Method

The critical review method was carried out on all selected articles by examining the *validity*, *importance*, *applicability* (VIA) using CEBM (*Centre for Evidence Based medicine*) in accordance with the type of therapeutic study.

Results

Based on the results from the database, which was conducted with advance searching, the author found 9 literatures from PubMed, 65 literatures from Cochrane Library, and 147 literatures from Science Direct. As shown in **Figure 1**, there are1 SR/MA and 3 RCTs selected to be included in this evidence-based case report. Based on criteria from the Oxford Centre for Evidence Based Medicine, the level of evidence of 1 article with the SR/MA study is level 1a, while 3 articles with the RCT study is level 1b. The subjects in 4 study articles were patients with HIV infection who received vitamin D supplementation in the intervention group, compared to the control group given placebo or no vitamin D supplementation, to assess the outcome of CD4 levels. The study characteristics of these articles are listed in Table 2. The level of evidence for these articles is presented in **Table 3**.

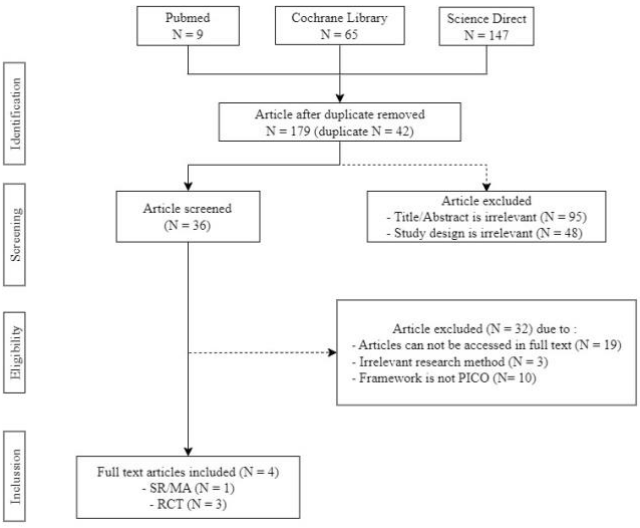

Figure 1. Prisma's Flowchart

Discussion

In HIV patients, the prevalence of vitamin D deficiency and insufficiency is quite high, ranging from 24% to 72%. This deficiency can be attributed to malabsorption, chronic inflammation, poor intake, and liver dysfunction. Vitamin D is a micronutrient that plays a role in regulating the innate and adaptive immune systems. One of its functions is to enhance the transcription of cathelicidin, which can inhibit HIV replication in CD4+ T cells and macrophages. The relationship between vitamin D sufficiency and the increase in CD4 levels in HIV patients is still uncertain, so further research on this matter is needed for clarification.[8]

CD4+ T cell counts and viral load are essential indicators for determining the clinical course of HIV-1 infection. CD4+ T lymphocytes are the primary target cells of HIV, followed by dendritic cells, monocytes, and macrophages. The acute infection is characterized by the destruction of gut-associated lymphoid tissue (GALT) that harbors a high number of CD4+ effector memory cells. Destruction leads to both anatomical and functional alterations of the gut mucosal barrier, facilitating the passage of commensal microorganisms into the circulation system, which in turn, promotes continuous immune activation.[9]

Vitamin D in humans is obtained through three main pathways: the synthesis of vitamin D in the skin, consuming food sources of vitamin D, and supplementation in the form of vitamin D2 or D3. Ultraviolet B (UVB) can convert 7-dehydrocholesterol into previtamin D3 in the skin, and then quickly converted it into cholecalciferol (D3). Vitamin D3 goes to the liver to be converted into 25-hydroxyvitamin D (calcidiol) by the enzyme 25-hydroxylase. Calcidiol goes to the kidneys and is converted into 1,25-dihydroxyvitamin D3 (calcitriol) by the enzyme 1-α-hydroxylase. Calcitriol is the active form of vitamin D which works on target cells and binds to the vitamin D receptor (VDR).[10]

Based on studies by Almeida-Afonso R, et al.,[11] Teixeira NDSCCA, et al.,[12] and Permata M, et al.,[13] vitamin D supplementation can increase

Table 1. Literature Search Strategy

We conducted a comprehensive analysis of existing research using advanced search methods in Pubmed, Cochrane Library, and Science Direct. This process includes combining MeSH Terms and Title/Abstract searches to ensure a thorough search strategy that targeted the population, intervention, comparison, and outcome.

Database	*Search Strategy*	*Hits*	*Selected Article*
Pubmed	("vitamin d supplementation"[Title/Abstract] OR "vitamin d3 supplementation"[Title/Abstract] OR "cholecalciferol supplementation"[Title/Abstract]) AND "2014/01/19 00:00":"3000/01/01 05:00"[Date - Publication] AND (("cd4 antigens"[MeSH Terms] OR "cd4"[Title/Abstract]) AND "2014/01/19 00:00":"3000/01/01 05:00"[Date - Publication]) AND (("hiv"[MeSH Terms] OR "human immunodeficiency virus"[Title/Abstract] OR "hiv"[Title/Abstract])	9	3
Cochrane Library	#1 (vitamin d supplementation):ti,ab,kw #2 (vitamin d3 supplementation):ti,ab,kw #3 (cholecalciferol supplementation):ti,ab,kw #4 MeSH descriptor: [CD4 Antigens] explode all trees #5 (cd4):ti,ab,kw #6 MeSH descriptor: [HIV] explode all trees #7 (human immunodeficiency virus):ti,ab,kw #8 (hiv):ti,ab,kw #9 #1 OR #2 OR #3 #10 #4 OR #5 #11 #6 OR #7 OR #8 #12 #9 AND #10 AND #11	65	1
Science Direct	(vitamin d supplementation OR vitamin D3 supplementation OR cholecalciferol supplementation) AND (cd4) AND (human immunodeficiency virus OR HIV)	147	0

Table 2. Assessment of Literature Characteristics

Author	Study Design	Population Characteristics	Intervension	Outcomes	Research Results
Almeida-Afonso R, et al.[11] (2021)	*Randomized Controlled Trial*	37 patients in the intervention group (supplemented once a week with 50,000 IU vitamin D) and 36 patients in the placebo group	Patients with HIV infection were given vitamin D dose 50,000 IU/week supplementation compared to placebo for six months.	T CD4 cells count, vitamin D levels, calcium, phosphorus, glucose, urea, osteocalcin level	Supplemented active group achieved a small increase in T CD4+ lymphocytes at the end of the six months follow-up time, compared to the placebo group (p = 0.05)
Ashenafi S, et al.[14] (2019)	*Randomized Controlled Trial*	95 patients were allocated to the intervention group (daily oral supplementation 5,000 IU) and 102 patients were allocated to the placebo group.	The intervention group took daily dose vitamin D3 supplementation (5,000 IU), and those in the control group received matching placebo tablet from good	HIV viral load, CD4 T cell count, CD8 T cell count, BMI, MUAC, vitamin D status	The study does not show that vitamin D supplementation dose 5,000 IU daily can increase CD4 T cell count. There was no significant changes in CD4 T cell count in this study

Author	Study Design	Population Characteristics	Intervensions	Outcomes	Research Results
			manufacturing. The intervention was carried out for 16 weeks.		
Teixeira NDSCCA, et al.[12] (2019)	*Systematic Review*	Total 198 articles and after selection process 5 articles were identified eligible. Total sample from those 5 articles were 4470. The PICO strategy of the following guiding question: does vitamin D supplementation lead to improvements in the clinical picture of HIV patients?	The intervention group got vitamin D supplementation ranged from 2,000 to 50,000 IU per week, and the duration of intervention ranged from 12 weeks to 3 years	The main variables investigated were: 25(OH)D, BMI, CD4 count, but some studies went further and included biochemical tests and immunological data	The results of the five clinical trials demonstrated a positive effect of supplementation on CD4 lymphocytes count supporting the vitamin D benefit in immunological recovery.
Permata M, et al.[13] (2020)	*Randomized Controlled Trial*	10 patients in the intervention group (supplemented calcitriol 0,5 mcg per day for eight weeks) and 10 patients in the placebo group	The patients in intervention group received vitamin D (calcitriol 0,5 mcg per day) for 8 weeks.	This study aims to determine whether the addition of vitamin D affects increasing the CD4 counts of HIV/AIDS infection patients	There was a significant increase in the CD4 cell count of the vitamin D group, but not in the CD4 cell count of both groups. In the vitamin D group, the mean CD4 count before the addition of vitamin D was 361.3+185.2 cells/mm^3 increased to 400.1 + 185.2 cells/mm^3 ($p = 0.046$)

Table 3. Relevance Criteria

Authors	Population similarity	The similarity of the determining factors	Outcomes similarity
Almeida-Afonso R, et al. (2021)[11]	+	+	+
Ashenafi S, et al. (2019)[14]	+	+	+
Teixeira NDSCCA, et al. (2019)[12]	+	+	+
Permata M, et al. (2020)[13]	+	+	+

After the identification and screening process, articles that are suitable for population, intervention, comparison, and outcome are then critically reviewed. Four articles were found to have appropriate setting to the clinical scenario. Among these articles, three are randomized controlled trials (RCTs) and 1 is a systematic review (SR). These four articles identified the validity criteria based on quality and level of evidence according to the Oxford Center for Evidence-Based Medicine (CEBM).

Table 4. Validity Criteria

	PICO	Review Strategy	Study Design	Study Quality Assessment	High Quality	Results in Tables/Forest Plots	Similarity of Study Results	Quality of evidence*	Level of evidence**
Almeida-Afonso R, et al.[11]	+	+	+	+	-	+	+	Moderate	1b
Ashenafi S, et al.[14]	+	+	+	+	+	+	+	Moderate	1b
Teixeira NDSCCA, et al.[12]	+	+	+	+	-	+	+	High	1a
Permata M, et al.[13]	+	+	+	+	+	+	+	Moderate	1b

*Quality of evidence according to GRADE guidelines, https://www.ncbi.nlm.nih.gov/pubmed/21208779
**Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), http://www.cebm.net.
+ clearly mentioned in the article; - not done; ? Not stated clearly

CD4 levels significantly in HIV patients. Meanwhile, a different statement from a study by Ashenafi S, et al.,[14] shows that vitamin D supplementation does not show significant changes in CD4 levels in HIV patients.

The study by Almeida-Afonso R, et al.,[11] show that vitamin D supplementation was found to be effective in normalizing blood levels after six months (>30 ng/mL) for 80% of the patients in the study. None of the patients exhibited blood levels considered dangerous (>100 ng/mL). A weekly oral dose of 50,000 IU of vitamin D was sufficient to safely normalize vitamin deficiency with good adherence among HIV-1-infected subjects. The study also indicated that vitamin D supplementation in the intervention group achieved a small increase in T CD4+ lymphocytes at the end of the six-month follow-up period compared to the placebo group.

According to a systematic review by Teixeira NDSCCA, et al. with 5 eligible articles (4470 samples), it also states findings consistent with the Randomized Controlled Trial (RCT) by Almeida-Afonso R, et al. With vitamin D supplementation ranging from 2,000 to 50,000 IU per week, and the intervention duration ranging from 12 weeks to 3 years, it can improve vitamin D levels. The relationship between chronic viral infections and hypovitaminosis D is well known. Vitamin D deficiency is associated with a low TCD4 cell count and a viral load higher than 50 copies/mL. In addition, vitamin D deficiency occurs more frequently in patients with more severe disease progression. Thus, patients with vitamin D deficiency increase the risk of morbidity and mortality in HIV patients. Based on this systematic review, sufficient levels of 25(OH)D are positively correlated with the number of CD4+ cells and a reduction in infection levels.[12]

According to several previous studies, vitamin D deficiency is associated with increased inflammation and immune activation, low peripheral blood CD4+ T cells, faster progression

of HIV disease, and shorter survival time in HIV-infected patients.[15,16] A study by Ashenafi S, et al.,[14] states that supplementation with vitamin D3 at a dose of 5000 IU per day for 16 weeks can significantly increase serum vitamin D levels. Given these prior findings, the study hypothesized that daily nutritional supplementation with vitamin D3 could reduce viral replication and restore immune and nutritional status in HIV infection.

However, the results of the study by Ashenafi S, et al.,[14] indicate somewhat different outcomes. The study does not demonstrate that a daily vitamin D supplementation dose of 5,000 IU can increase CD4 T cell count. The difference in results from this study could be due to an inadequate number of doses or an insufficient length of intervention. Apart from that, when compared with research conducted by Permata, et al. even though the study was for a period of 8 weeks, the intervention given was vitamin D in the active form (calcitriol).[13]

In addition to supplementation, vitamin D needs can be fulfilled by consuming foods that are natural sources of vitamin D and by sun exposure. Vitamin D is a fat-soluble vitamin naturally present in some foods and is also produced endogenously when ultraviolet (UV) from sunlight hits the skin, triggering vitamin D synthesis. Fatty fish (such as trout, salmon, tuna, and mackerel) and fish liver oil are the best sources of vitamin D. Beef liver, egg yolks, and cheese contain small amounts of vitamin D. Some foods are fortified to provide vitamin D, such as beverages made from soy, almonds, oats, and cow's milk. Several studies suggest that approximately 5–30 minutes per day or at least twice a week, especially between 10 a.m. and 4 p.m., on the face, arms, hands, and legs without sunscreen usually leads to sufficient vitamin D synthesis.[17]

Conclusion

The relationship between chronic viral infections and hypovitaminosis D is well known. Patients with HIV are susceptible to vitamin D deficiency. Vitamin D deficiency is associated with a low TCD4 cell count and a higher viral load. Vitamin D supplementation can increase 25(OH)D levels in plasma, and adequate levels of 25(OH)D are positively associated with the number of CD4. Several articles state that vitamin D supplementation can increase serum vitamin D levels which has a positive relationship with increasing CD4 levels. However, some different results are still found so future trials need to be conducted to prove the benefits of vitamin D to increase CD4 levels in HIV.

Conflict of interest

The authors declare there is no conflict of interest regarding this article.

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