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VITAMIN D AND HIV INFECTION: THE CORRELATION & NEED FOR EVALUATION

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Abstract

Background: India is the country with the third highest HIV disease burden globally. One of the most common long-term complications of HIV infection is bone diseases. There is prevalence of reduced bone mineral density (BMD) and thus higher risk of fragility fractures among PLHIV. Further, many HIV-positive cohorts suggest Vitamin-D hypovitaminosis exposing to osteopenia/osteoporosis in this population. This detailed review would provide an insight on correlation of Vitamin-D hypovitaminosis and HIV infection.

Material & Methods: A thorough review of published research studies and literature work was conducted. These studies were selected on the basis of data available on HIV seropositive population and Vitamin D in peer reviewed indexed journals. Both prospective and retrospective studies with or without control groups and randomized-controlled trials (RCTs) reporting baseline vitamin D status in HIV seropositive patients were included.

Results: We reviewed the association of vitamin D deficiency with HIV progression, mortality, and AIDS events, increased incidence and severity of Mycobacterium tuberculosis (TB) and hepatitis C virus (HCV) infection. Low bone mineral density (BMD) is a challenging metabolic condition in PLHIV. Further, the impact of antiretroviral drugs on vitamin D metabolism was studied. The effect of body index mass and non- and nucleoside reverse transcriptase inhibitors effects with hypovitaminosis D was further reviewed along with supplementation therapy of the vitamin and its effect in HIV positive population.

Conclusion: The optimal levels of 1,25(OH)Vitamin D is necessary for regulation of calcium and phosphorus balance for bone mineralization and remodelling. Without its adequate level in bloodstream; dietary calcium cannot be absorbed and thus causes a low BMD.

Keywords: HIV; PLHIV; Bone Mineral Density; 1,25(OH)Vitamin D; Mineralization.

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1. Introduction

India is the country with the third highest HIV disease burden globally. The NACP is providing free antiretroviral therapy (ART) to more than 1.2 million PLHIV [1]. Since 2017, India adapted the routine viral load monitoring of treatment and Test & Treat policy. The rate of annual mortality since 2005 have significantly declined by almost 71% and the incidence of HIV infection also seen a decrease by 27% between 2010 and 2017 [2].

Increased life expectancy exposes People Living with HIV/AIDS (PLHIV) to chronic adverse drug reactions and to other age-related morbidities [3-5]. One of the most common long-term complications of HIV infection is bone diseases [6-8]. There is prevalence of reduced bone mineral density (BMD) and thus higher risk of fragility fractures among PLHIV [9-12]. Further, many HIV-positive cohorts suggest hypovitaminosis D exposing to osteopenia/osteoporosis in this population [13-19]. Additionally, the role of vitamin D can be also seen in non-skeletal functions, including cardiovascular and immune regulation, cancer prevention and brain health, apart from calcium homeostasis [20-24].

This detailed review would provide an insight on correlation of vitamin Dhypovitaminosis and HIV infection, thus giving us a way to consider the significance of Vitamin D monitoring in PLHIV. We first briefly describe VitaminD metabolism biological functions; then, we focus on the most recent epidemiological and experimental data dealing with the relationship between vitamin D deficiency and HIV infection. We analyse the extent of the problem, pathogenic mechanisms, clinical implications, and the potential effects of vitamin supplementation among PLHIV.

2. Methods

Selection Criterion & Data Analysis

A thorough review of published research studies and literature work was conducted. These studies were selected on the basis of data available on HIV seropositive population and Vitamin D in peer reviewed indexed journals. Both prospective and retrospective studies with or without control groups and randomized-controlled trials (RCTs) reporting baseline vitamin D status in HIV seropositive patients were included. Further, the search observed no geographical, language, race, age or gender restriction to consider wider distribution and outcome. However, Non-HIV seropositive group were excluded from review to prevent bias.

Vitamin D Metabolism

Vitamin D is a fat-soluble steroid, which is synthesized from a cholesterol precursor (7-dehydrocholesterol) [25]. The major forms of Vitamin D important to humans are Vitamin D2(ergocalciferol) and Vitamin D3 (cholecalciferol), synthesized from ergosterol in plants and naturally from cholesterol in animals respectively. These are available to body from the diet and Vitamin D-fortified products, among other sources [25,26].

However, the main source of Vitamin D for the human body is its synthesis in the skin. Cutaneous 7-dihydrocholesterol is converted into pre Vitamin D3 following irradiation by ultraviolet (UV) light from the sun [26]. Then, by spontaneous isomerization of pre-Vitamin D3 forms cholecalciferol (Vitamin D3). Afterwards, Vitamin D3 is hydroxylated to 25-hydroxy-Vitamin D

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[25(OH)D] or calcidiol. This, 25(OH)D is then transported to kidneys, where it is hydroxylated to produce 1,25-dihydroxycholecalciferol [1,25 (OH)2D] or calcitriol. However, many other cell types can also produce 1,25(OH)2D and it is capable of regulating a wide variety of genes that are vital in regulating cell growth and differentiation.

The optimal levels of 1,25(OH)2D is necessary for regulation of calcium and phosphorus balance for bone mineralization and remodelling. Without its adequate level in bloodstream; dietary calcium cannot be absorbed and thus causes a low BMD. With its chronic deficiency in adults, there is greater risk of osteomalacia, osteoporosis, muscle weakness and increased risk of falls [26–33]. Thus, it is vital to maintain a normal level of vitD for skeletal benefits [27,28,34-36]. Moreover, vitamin D deficiency has also resulted in non-skeletal effects in many chronic diseases including, but not limited to, infectious diseases, autoimmune diseases, cardiovascular diseases, diabetes and cancer [34,37,38].Further, research studies also correlate vitamin D deficiency with increased risk of developing tuberculosis [39,40], otitis media [41], upper respiratory tract infections [42] and influenza [43]. Thus, assessing for its levels is all the more important to avoid any such abnormality.

Investigation

The fastest way to measure Vitamin D levels in the body is the quantification of 25(OH)D in serum or plasma. However, this method has some drawbacks due to the hydrophobic nature of Vitamin D, its high affinity to Vitamin D binding protein (DBP), and the low concentration in blood (44). Plasma 25(OH)D or calcidiol (a summation of D3 and D2 forms) is the most reliable marker of vitamin D status. Immunoassays such as radioimmunoassay (RIA), enzyme linked immunosorbant assay (ELISA), chemiluminescence immunoassay and protein binding assays are used in routine testing of 25(OH)D in clinical laboratories. Liquid chromatography tandem mass spectrometry (LCTMS) is the widely accepted reference method for 25(OH)D measurement. However, LCTMS is tedious, expensive and time consuming and therefore seldom used commercially.

The measurement unit of Vitamin D levels are nanogram per milliliter (ng/mL) or nanomol/liter (nmol/L). Vitamin D deficiency in adults is considered to be when total 25(OH)D levels are <25 nmol/L (10 ng/mL) and inadequate/insufficient if levels are <75 nmol/L (30 ng/mL); while >75 nmol/L (30 ng/mL) is considered to be a normal healthy level [45, 46].

HIV and Deficiency of Vitamin D

Several research studies and trials were made since past to estimate prevalence of vitamin D deficiency among PLHIV [47]. Mansuetoet al., presented that the prevalence of Vitamin D deficiency range from 70 to 85% in HIV-infected patients, based on a large number of epidemiological dataof on hypovitaminosis D with varying thresholds and a broad geo-localization of patients [48]. Studies had different range for assessing vitamin deficiency. Prevalence of hypovitaminosis with 25(OH)D levels be 10ng/mL, in 39.6%ofHIV-infectedpatients [49]. Studies also observe correlation of hypovitaminosis D with nonskeletal conditions, including cardiovascular, immune regulation, cancer, and neurocognitive disorders [50-52]. Moreover, some studies suggest that severe vitamin D deficiency is associated with HIV progression, mortality, and AID Sevents [53], increased incidence and severity of Mycobacterium tuberculosis (TB) and hepatitis C virus (HCV) infection [48, 54].

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Apart from many risk factors of vitamin D deficiency, as discussed above, the major risk factors among HIV infected population were associated with immune activation, chronic inflammation and antiretroviral treatment with potential interactions on the vitamin D metabolism[55-61].In regards to other infectious diseases, Vitamin D levels have not been associated with better immune response to hepatitis B or pneumococcal vaccination in HIV-infected patients [62].
However, conflicting data has also been found of prevalence of Vitamin D deficiency among HIV infected compared to non-HIV infected individuals. Where one study described that Vitamin D deficiency was more prevalent in HIV-positive than in HIV-negative individuals [63], other found no such evidence [64].

Bone Turnover in Patients with HIV Infection

Low bone mineral density (BMD) is a challenging metabolic condition in PLHIV [65]. Amongst PLHIV with Vitamin D deficiency, it may have an abnormal bone turnover, such that a non-synchronisation of bone resorption and bone formation is observed with increased markers of bone resorption and stable or decreased markers of bone formation [66,67]. The presence of a chronic high bone turnover state may lead to reduced BMD.

Literature review highlighted the existence of many studies supporting high prevalence of osteopenia and osteoporosis in PLHIV. A meta-analysis showed prevalence of 67% of osteopenia and 15% of osteoporosis in PLHIV-. It further indicated that the rate of BMD reduction was 6.4-fold higher, and that of osteoporosis 3.7-fold higher in PLHIV [68]. Another study indicated that more than 50% of PLHIVs had osteopenia, and roughly 35% had osteoporosis [69]. A higher prevalence of fractures in PLHIVs, in comparison to HIV-negative patients is also reported by Triantet al [70].

Another cross-sectional cohort study by Bonjochet al., of 671 PLHIV, indicated a high prevalence and considerable progression to osteopenia/osteoporosis. Their findings supported the importance of preventing bone demineralization and close monitoring of BMD in HIV-infected patients, specifically in at-risk patients who are on-ART (antiretroviral therapy) that affect bone mineralization. Their findings reported the rates for osteopenia and osteoporosis as 47.5% and 23% respectively, whilst BMD decreased in about 28% of patients in one 2.5 years of follow-up study[71]. Sharma et al., reported similar findings; where 42% and 12% PLHIVs were reported having osteopenia and osteoporosis respectively. The degree of osteopenia was three times higher compared with HIV negative subjects [72].

Vitamin D, Adaptive immunity and HIV infection

It is often challenging to establish a relationship between 25(OH)Dlevels, viral load and CD4+ T-cell count. Different mechanisms have been hypothesized to explain the association between 25(OH)D deficiency and severity of HIV disease.

Vitamin D may indirectly affect T-cell responses via modulation of the DC phenotype and its stimulatory capacity toward T cells [73]. The affect may also be observed on both naïve and resting memory T-cells [74]. T-cell activation increases the expression of VDR and CYP27B1, which allows 25(OH)D to be converted into 1,25(OH)2D to modulate effector functions of Vitamin D [75].

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Poowuttikul, Thomas et al., (2014) studied 160 HIV infected youth and found that severe low levels of vitamin D (25(OH)D≤10ng/mL) was related to lower CD4 counts and lower CD4%; however, it was unrelated to HIV plasma RNA. He also stated that CD4counts/ percentage had no effect upon vitamin supplementation. Very low vitaminD levels [25(OH)D≤10ng/mL] was related to lower CD4 counts and CD4% but not to HIV plasma RNA. CD4counts/CD4% did not increase under vitamin D supplementation [76].

Many studies suggested correlation between high HIV viral load and hypovitaminosis D in plasma [77-79]. Vitamin D deficiency is also found related to the decreased CD4+ T-cells in peripheral blood [80,81], rapid AIDS progression, and lower survival in HIV infected patients [82-86].Such correlation of decreased CD4 T-cell count with higher prevalence of hypovitaminosisD is supported by many other studies [87,88,89]. However, literature review showed three, well-designed trials conducted on a large scale no such association between these two factors [89,90,91]. Among other HIV-related risk factors, inconsistent correlations were observed between HIV viral load, duration of ART treatment and duration of HIV infection [86,87,88,92,93,94].

Mortality rates were studied in 1103 PLHIVs for over 24months at a research in Tanzania. The study revealed that <20 ng/ml levels of 25(OH)D was significantly associated with increased mortality as compared to 25(OH)D levels of >30ng/mL. However, Vitamin D status was found unrelated to the changes in CD4 T-cell count after ART initiation [82].

Another analytical study in the larger EuroSIDA cohort also stated similar findings. Outcomes were compared of vitamin D tertiles of <12 ng/mL, 12.1 ng/mL to 20 ng/mL and >20 ng/mL. When compared PLHIVs in the lowest tertile with higher tertiles, it was found that the patients in former tertilehad statistically significant greater risk for progression to AIDS and to death and a non-statistically significant increased risk for progression to non-AIDS-related events[95].

Hypovitaminosis D and Antiretroviral therapy

Several in vitro and in vivo studies and clinical trials tried to evaluate the impact of antiretroviral drugs on vitamin D metabolism. Both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been long associated with the impairment of vitamin D metabolic pathways. Considering the major findings and research undertaken in large populations, only particular ART classes of drug were clearly found to be related to hypovitaminosis D [86,87,90]. Several authors demonstrated that (NNRTI) use was associated with 25(OH)D deficiency [96-100].

A well designed cross-sectional assessment found that Serum 25(OH)D was negatively correlated with body mass index, insulin resistance, HIV duration, and cumulative use of antiretroviral therapy, non- and nucleoside reverse transcriptase inhibitors. As refers to NNRTIs, for efavirenz (EFV)in particular, an association with low 25(OH)D concentration has often been suggested due to compromised vitamin D homeostasis. EFV has been described indeed to increase 25(OH)D catabolism, through the induction of CYP2494,95 and reduced transcription of CYP2R1, a 25-hydroxylase [97].

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Pasquetet al., examined the association between decreased 25(OH)D and NNRTIs consumption), however he could not find any correlation with EFV and nevirapine (NVP). However, based on its regression models, he suggested a NNRTI class effect, rather than a specific EFV impact 25(OH)D levels [96]. Another study by Bovenet al., [101] showed that vitamin D levels did not significantly change in comparison with baseline values among patients receiving the new NNRTI rilpivirine over 48 weeks, whereas a significant decrease was observed among those starting EFV-based regimen. Similarly, Allavenaet al.,[102] and Brown et al.,[103] found decline in 25(OH)D serum levels after initiation of EFV-based regimen, in comparison with a non-EFV-based regimen.

On the contrary, one of the cross-sectional studies performed on 262 individuals, presented 25(OH)D levels as higher in patients exposed to NVP and PIs), in comparison with those exposed to EFV. Moreover, of the patients with baseline 25(OH)D insufficiency, a smaller proportion developed severe 25(OH)D deficiency with rilpivirine than EFV [104].Similar but less consistent findings were observed for some nucleoside reverse transcriptase inhibitor (NRTIs), such as emtricitabine, tenofovirdisoproxilfumarate (TDF)and zidovudine [87, 90, 105].

A small prospective observational study of 96weeks, examined the consequence of ART regimen changes on vitamin D values, and demonstrated a beneficial effect (increase of 25OHD level) in switching from efavirenz (NNRTI) and/or zidovudine (NRTI) to darunavir/ ritonavir (PIs) [106].However, one of the studies observed that patients who were prescribed TDF/EFV (NRTI/ NNRTI) did not have lower vitamin D levels [107].

A randomized 12 week controlled trial in HIV+ youth treated with TDF, assessed for effect of Vitamin D3 supplementation on fibroblast growth factor-23 (FGF-23). The findings clearly indicated an increase in the fibroblast growth factor 23 (FGF23) response to vitamin D supplementation in HIV-infected youth. The findings were supported by similar studies in vitamin D-deficient PLHIVs treated with TDF, where open-label vitamin D supplementation was associated with a trend toward increased FGF23 [108], in contrast to what was observed in non-HIV infected persons with vitamin D deficiency [109].

Additionally, different studies associate vitamin D and TDF-linked hyperparathyroidism, emphasizing that both influence in PTH values. One of the studies suggests that the increased hydroxylation rates and tubular phosphate losses, which drive calcium preservation and possibly altered bone metabolism, are dependent on vitamin D status [110]. Moreover PTH elevations have been observed in patients taking both NNRT and PI[111-113].Results for PIs suggested a protective effect against hypovitaminosis D [87,91,95].

Supplementation of vitamin D

In the general population, current recommended dietary allowances (RDA) of vitamin D are 700-800 IU cholecalciferol/day 55. Serum 25(OH)D levels generally increase by approximately 1 ng/ml for every 100 IU of vitamin D intake [114]. However, efficacy of vitamin D repletion in PLHIVs is evaluated through few small cohorts studies. Some clinical trials assessing Vitamin D supplementation have demonstrated a positive impact on BMD in subgroups of PLHIVs who were initiating ART or on suppressive ART regimens. However, significant heterogeneity exists between studies; and data are less consistent with other clinical outcomes.

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Van den Bout et al., treated 20 vitamin D deficient PLHIVs with 2000 IU cholecalciferol/day for 14 weeks, after which the dosage was lowered to 1000 IU/day until 48 weeks. The evaluation of 25(OH)D3 and 1,25(OH)2D3 levels at 24 weeks showed normalized values, but after 48 weeks only serum 25(OH)D3 was significantly different from baseline, whereas 1,25(OH)2D3 returned to baseline levels, probably because of the reduction in cholecalciferol dose [115].

Arpadiet al., reported the benefits of oral doses (twice in a month) of 100,000 IU cholecalciferol and 1g/day calcium in a cohort of HIV-infected children and adolescents during a year long study. In this study, 25(OH)D levels were found significantly higher among supplemented subjects, in comparison with individuals receiving placebo; 44.4% of subjects in the group receiving cholecalciferol and calcium had 25(OH)D > 30 ng/ml after 1 year [93].Similarly, Havens et al., studied a cohort of 207 PLHIVs, when orally administering vitamin D3 (50000 IU in three doses at monthly intervals) showed a rapid increase in 25(OH)D serum concentration [116].

A well designed controlled study in India, evaluates the relationship between vitamin-D, zinc and copper supplementation and the CD4 counts in HIV-positive mothers. The study was conducted for three year period, where 195 HIV-positive antenatal cases were studied for effect of vitamin D supplementation and other mineralson CD4 count. The first group of 49 cases were evaluated for CD4 count at their first visit to facility, then received 400 I.U/day of vitamin-D supplementation and re-evaluatedat 36 weeks of gestation and at six weeks post-partum, irrespective of the outcome of pregnancy. Significant improvement in CD4 counts was observed in the group where Vitamin D supplementation was given as compared to the control. Thus, the study established a significant relationship of improved CD4 counts with vitamin D supplementation [117].

Another rdouble-blind, placebo-controlled study of 48 weeks evaluated the effect of high dose vitamin D3 (4000 IU daily) plus calcium supplementation (1000 mg calcium carbonate daily) on BMD in HIV-infected subjects initiating ART with efavirenz/emtricitabine/tenofovir. The primary endpoint was percentage change in total hip BMD over 48 weeks. Results showed that vitamin D/calcium supplementation mitigated the loss of BMD seen with initiation of efavirenz/emtricitabine/tenofovir, particularly at the total hip [118].

Further, another study concluded that vitamin D supplementation in HIV-infected patients is safe and valid for correcting vitaminD abnormalities and to improve raised PTH levels, but not enough for normalizing them, especially in patients exposed to tenofovir or protease inhibitors [119]. However, others did not find that vitamin D (in any possible formula) supplementation can increase CD4+ count [120,121]. One of the research studies pointed out, that only 40% of patients receiving oral vitamin D supplements had 25(OH)D levels >30 ng/ml after a median 16 week follow up. Supporting this claim, one of the studies showed only 46% reduction in hypovitaminosis D was observed in a cohort of HIV-positive young adults receiving 50000 IU vitamin D3/week for 12 weeks [122].

Although arguments may be found against wide spread screening for vitamin D deficiency in HIV-infected patients, it include the unclear benefit of vitamin D replacement for non-musculoskeletal outcomes with potential toxicities of some supplementation approaches [123]. The optimal repletion and maintenance dosing regimens remain to be established as well as the impact of vitamin D supplementation in preventing comorbidities [124].

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3. Conclusion

Vitamin D deficiency is emerging as a matter of great concern among HIV-infected population. Although no clear consensus have been reached on its effect on the life expectancy of PLHIVs, given the overlapping risk for potential chronic diseases and immune-modulatory impact from both HIV infection and Vitamin D deficiency; the clinical role of Vitamin D for this population needs attention and further assessment. Also, given the widespread presence of this deficiency in PLHIV, the benefit of screening vitamin D deficiency and its replacement needs a systematic evaluation.

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