Section: Biochemistry

Original Research Article

SERUM VITAMIN D LEVEL IN HIV INFECTED PATIENTS AND ITS RELATION WITH HIV DISEASE PROGRESSION

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Abstract

Background: Human Immunodeficiency Virus (HIV) infection is characterized by a progressive deterioration in immune function. Throughout the world, 39.9 million people have been infected to date by Human Immunodeficiency Virus (HIV). Vitamin D deficiency is of increasing concern in HIV- infected persons because it is seen to be associated with many negative health outcomes common in HIV. The present study was conducted to determine serum 25(OH) vitamin D level in HIV positive patients on antiretroviral therapy (ART) and to find out any correlation, if any, between serum vitamin D level and CD4 count. **Materials and Methods:** The study was conducted in Department of Biochemistry in collaboration with the Department of Medicine, Microbiology and ART centre, Jawaharlal Nehru Institute Of Medical Sciences, Porompat, Manipur among 175 confirmed cases of HIV infection on ART in the age group 18 years and above attending the ART centre from September 2017 to August 2019. The level of serum 25(OH) vitamin D was analysed and compared among the study groups.The evaluation of vitamin D level was done by LIAISON 25 OH vitamin D TOTAL chemiluminescent immunoassay (CLIA). CD4 count was determined by BD FACS Calibur Flow Cytometer using BD Trucount tubes by immunophenotyping. The statistical analysis was done by using IBM SPSS versio 16. **Result:** This study documents high prevalence of vitamin D insufficiency and deficiency of HIV – infected persons on ART. Low serum vitamin D level was found in 74.3% of patients. Serum vitamin D level was found to have a positive correlation with CD4 count. Also, the correlation between serum vitamin D concentration and the time of cumulative use of different antiretrovirals (years) was evaluated and was found to be negatively correlated. **Conclusion:** Our study shows high levels of vitamin D deficiency in patients on antiretroviral therapy. A positive correlation was found between serum vitamin D level and CD4 count and negative correlation between duration of antiretroviral theory and serum vitamin D level. Low levels of 25(OH)D among HIV-infected persons is seen to be associated with many chronic health conditions thereby highlighting the need for routine screening for vitamin D insufficiency or deficiency.

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is characterized by a progressive deterioration in immune function. Interventions that offset this impairment have the potential to slow HIV disease progression and improve quality of life.[1] The current surveillance definition categorizes HIV infection and CD4+T lymphocyte counts. From a practical standpoint, clinician should view HIV disease as a spectrum of disorders ranging from primary infection, with or without the acute HIV

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syndrome, to the asymptomatic infected state, to the advanced disease characterised by opportunistic infections and neoplasms. Throughout the world, 39.9 million people globally were living with HIV in 2023. 1.3 milllion people became newly infected with HIV in 2023. India has the third largest HIV epidemic in the world, with 2.1 million people living with HIV.[2] In India, adults and children living with HIV in 2023 is 2500 000. In 2023, HIV prevalence among adults was 0.2%. However in 2023, adults and children newly infected with HIV was found to be 68,000 and AIDS related deaths among adults were estimated to be 35000.[3] In 2024, 81% of people living with HIV were aware of their status,of whom 70% were on antiretroviral therapy,ART.[3] In India, the highest HIV prevalence is seen in the north east states Mizoram, Nagaland and Manipur.[2]

Vitamin D is a steroid hormone that is essential for calcium homeostasis and bone metabolism.[4] Vitamin D deficiency is associated with a number of comorbidities, including hypertension, cardiovascular disease, insulin resistance, diabetes, dyslipidemia, impaired immune function, and malignancies.[5,6] Currently, serum concentration of 25-hydroxyvitamin D(25[OH]D) is considered best indicator of vitamin D status, because it represents cumulative exposure to sunlight and dietary intake of vitamin D.[7]

Vitamin D deficiency is of increasing concern in HIV- infected persons because it is reported to be associated with HIV disease progression as well as various complications related with HIV.[8]

The introduction of ART has had a profound impact by reducing the viral load and reconstituting the immune system of HIV/AIDS patients. The treatment is a complex therapeutic regimen made up of a combination of at least 3 drugs that include the use of two nucleoside-analogue reverse-transcriptase inhibitors (NRTI) and one from another class, which is usually a non-nucleoside reverse-transcriptase inhibitor(NNRTI) or a (PI) protease inhibitor.[9] There seems to be evidence that antiretroviral therapy may be responsible for worsening of hypovitaminosis D.[10]

Vitamin D supplementation has proved recently that it plays a role in slowing disease progression and prevents mortality in HIV-infected individuals. Therefore a potential role of vitamin D in HIV-infected patients has been immensely investigated. In view of all these findings and observations of the possible role of vitamin D in HIV disease progression, the present study is taken up with the objective to estimate serum vitamin D level in HIV infected patients and its relation with HIV disease progression.

MATERIALS AND METHODS

This study was a cross-sectional analysis carried out in the Department of Biochemistry in collaboration with the Department of Medicine, Microbiology and ART centre, Jawaharlal Nehru Institute of Medical Sciences, (JNIMS) Porompat, Manipur from September 2017 to August 2019. Confirmed cases of HIV infection in the age group 18 years and above on ART who gave consent to participate in the study attending the ART centre, Jawaharlal Institute of Medical Sciences, Imphal were included in the study.

All those who did not give informed consent, acutely ill patients, patients with renal failure, chronic liver disease, tuberculosis, sarcoidosis, hepatitis B and C positive cases, advanced age group , pregnant women, taking vitamin D supplements were all excluded from the study. Based on a prevalence of 87%[11] of hypovitaminosis D with a precision of 5% at 5% significance level, sample size was calculated as 173 rounded off to 175.

After taking informed consent, about 6ml of venous blood was drawn from the median cubital vein under aseptic precaution from selected subjects. 3ml was transferred to a sterile K_3EDTA containing vacutainer tube for the analysis of CD4 cell count. The remaining 3ml of blood was transferred to a sterile plain vial for estimation of vitamin D. Serum vitamin D level was evaluated by the method LIAISON 25 OH vitamin D TOTAL chemiluminescent immunoassay (CLIA). It is a direct competitive chemiluminescence immunoassay (CLIA) for quantitative determination of total 25 OH vitamin D in serum.

Normal range cutoffs for screening are based on the Institute of Medicine (IOM) Committee's 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D[12]

Vitamin D status 25 OH Vitamin D

1. Deficiency < 20ng/ml
2. Insufficiency < 30ng/ml
3. Sufficient > 30ng/ml

Determination of CD4 count

It was determined by BD FACS Calibur Flow Cytometer using BD Trucount tubes by immunophenotyping.

WHO immunological classification for established HIV infection is based on the value of CD4 count [13]:

HIV- associated Immunodeficiency	CD4 count values for 5 years and above(cells/µL)
1)None or not significant	>500
2)Mild	350 - 499
3)Advanced	200 - 349
4)Severe	< 200 or 15 %

Statistical analysis was done using IBM SPSS ver 16. Association between two continous data was done using Pearson correlation after checking for linearity and also presented in scattered diagram. Test of significance for quantitative data was performed using chi square test. Probability value (P-value) of less than 0.05 was taken as significant. The study was done after getting approval from Institutional Ethics Committee, JNIMS, Imphal(Ref no – Ac/06/ IEC/JNIMS/2017(PGT).

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RESULTS

[Table 1] shows that majority of the patients were in the age group (31-50) years which constituted 54.3% followed by (18-30) years group with 30.3% and >50 years group having 15.4%. Mean age was 38.8 years with a standard deviation of 11.7 years.

Out of the 175 cases, 110 were male and 65 were female. Male were the majority in 62.9% of cases and females in 37.1% of cases as shown in [Table 2].

Low serum vitamin D level was found in 74.3% of patients as shown in [Table 3]. Mean serum vitamin D level was 25.4 ng/ml with a standard deviation of 9.54 ng/ml. It ranges from 9 to 75 ng/ml.

CD4 count of less than 200 cells/µ was seen in 21 (12%) of cases, between 200-349 cells/µl in 35 (20%) of cases, between 350-499 cells/µl in 60 (34.3%) of cases and >500 cells/µl in (59) 33.7% of cases in this study as shown in [Table 4]. Mean CD4 count was 470.16 cells/µl with a standard deviation of 266.75 cells/µl.

[Table 5] shows that insufficient vitamin D was seen in more than 50% in all the regimes. In our study, four different regimen each containing Efavirenz, Nevirapine, Tenofovir and Ritonavir were studied. In our study, insufficient vitamin D was seen in more than 50% in all the regimes. And also,insufficient vitamin D was more among nevirapine (78.8%) containing regimen followed by efavirenz (68.9%), ritonavir (68.1%) and tenofovir (65.4%)which is shown in table above. This finding was statistically significant (p<0.05).This finding is also represented by the bar diagram showing relation between serum Vitamin D and ART regimen [Figure 1]

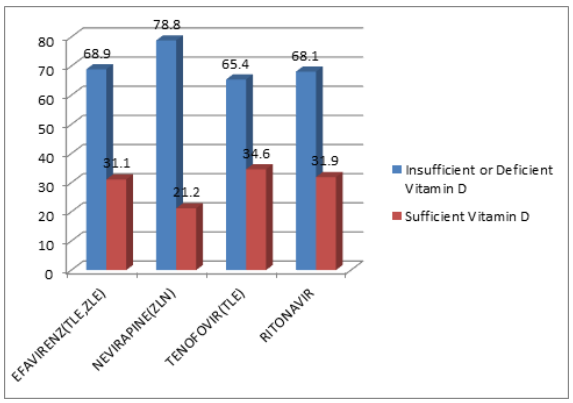

Figure 1: Bar diagram showing relation between serum Vitamin D and ART regimen

Pearson correlation between vitamin D and duration of ART indicates negative correlation (rp= -0.015) and the finding was statistically insignificant (p> 0.05). This negative correlation was shown in the scattered diagram below as slight clumping of dots. [Figure 2]

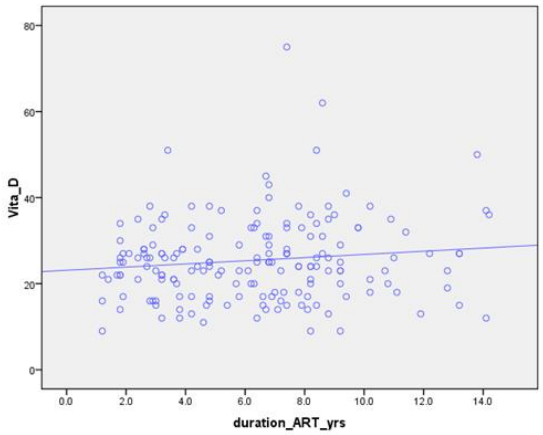

Figure 2: Scattered diagram showing relation between Vitamin D level and duration of ART

[Table 6] shows that with increasing age there was chance of decreasing vitamin D level (poor negative correlation rp= -0.010) but the finding was statistically insignificant.This negative correlation was shown in the scattered diagram as slight clumping of dots.(Figure 2)

Pearson correlation between vitamin D and CD4 count indicates positive correlation (rp= 0.198) and the finding was statistically significant (p< 0.05) [Table 7]. This correlation was shown in the scattered diagram below. [Figure 3]

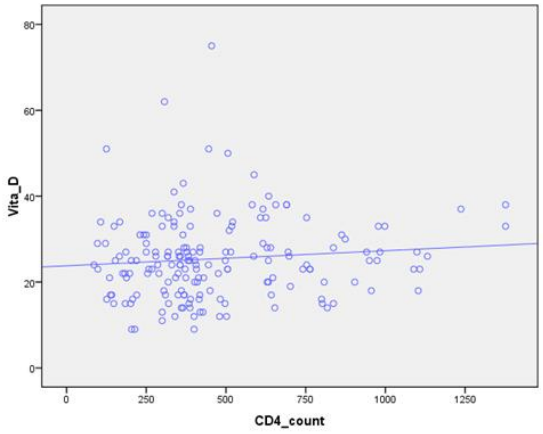

Figure 3: Scattered diagram showing relation between Vitamin D level and CD4 count

Table 1: Age distribution of the respondents.

Age in years	Frequency	Percentage
18-30	53	30.3
31-50	95	54.3
>50	27	15.4
Total	175	100.0
Mean ±SD	38.8±11.7	

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Table 2: Sex distribution of the respondents

Sex	Frequency	Percentage
Male	110	62.9
Female	65	37.1
Total	175	100.0

Table 3: Distribution of the respondents serum vitamin D level

Serum Vitamin D (ng/ml)	Frequency	Percentage
<30	130	74.3
≥30	45	25.7
Total	175	100.0
Mean ± SD	25.44 ± 9.54	
Median (minimum-maximum)	25 (9-75)	

Table 4: Distribution of the respondents by CD4 count

CD4 count (cells/µl)	Frequency	Percentage
>500	59	33.7
350-499	60	34.3
200-349	35	20.0
<200	21	12.0
Total	175	100.0
Mean±SD	470.16±266.75	
Median (minimum maximum)	389 (86-1377)	

Table 5: Relation between serum Vitamin D and ART regimen

ART regimen	Insufficient or Deficient Vitamin D	Sufficient Vitamin D	Total	Chi-square test
EFAVIRENZ(TLE,ZLE)	60 (68.9)	27(31.1)	87(100.0)	Value=8.771
NEVIRAPINE(ZLN)	52(78.8)	14(21.2)	66(100.0)	df-3
TENOFOVIR(TLE)	34(65.4)	18(34.6)	52(100.0)	p-0.032
RITONAVIR	15(68.1)	7(31.9)	22(100.0)	

Table 6: Correlation between serum Vitamin D and age

Variable	Pearson correlation
Vitamin D	rp= -0.010
Age	p-0.894

Table 7: Correlation between serum Vitamin D and CD4 count

Variable	Pearson correlation
Vitamin D	rp= 0.198
Duration of ART in years	p- 0.04

DISCUSSION

This study documents high prevalence of vitamin D insufficiency and deficiency of HIV – infected persons on ART. Out of the total 175 cases, 130 (74.3%) was found to have low serum Vitamin D level while the remaining 45 (25.7%) have sufficient serum vitamin D level. Mean serum vitamin D level was 25.4 ng/ml with a standard deviation of 9.54 ng/ml. It ranges from 9 to 75 ng/ml as shown in [Table 3].

Previous study of NHANES assessments in general US population of vitamin D insufficiency or deficiency as well as other reviews of the optimal 25(OH)D level in preventing several skeletal and nonskeletal health outcomes were found to be similar with our study defining vitamin D insufficiency or deficiency as levels, 30 ng/ml.[14] Based on these definitions, our findings corroborate other estimates of vitamin D levels among HIV-infected adults.[15]

Similar findings to our studies is in a large US prospective cohort study (SUN study) which assessed the prevalence of hypovitaminosis D in 672 HIV-positive subjects, demonstrating that 70.3% of them had 25(OH)D levels below 30 ng/ml.[16] In a cross-sectional study evaluating vitamin D status in HIV-infected postmenopausal women living in New York, Stein et al found that 74% out of 89 HIV-positive women had 25(OH)D levels < 30 ng/ml; the prevalence rate was similar, however, in HIV-negative controls also.[17] They also found no differences in $1,25(OH)_2D$ levels, which were normal in both groups. The data found in the prospective, observational EuroSIDA study on a large cohort of HIV positive subjects across 31 European countries, Israel and Argentina shows hypovitaminosis D as very common among HIV-positive individuals.[18] Out of 1985 patients, 23.7% had indeed 25OHD below 10 ng/ml, 65.3 % between 10 and 30 ng/ml and only 11% above 30 ng/ml.

Kuehn et al in his study among HIV-infected patients suffering with advanced AIDS as well as hypocalcemia found a prevalence of 50% vitamin D deficiency.[19] In contrast to our study which was

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shown in [Table 5], Coodly et al found only 17% vitamin D deficiency [average 25(OH)D-2SD] among adult HIV-infected patients.[20]

The variation on Vitamin D deficiency rates reflects the differences in selected cut off points for deficiency and also vast geographic location, seasonal variation as well as demographics changes of the study population.[21]

The most important aspect of this study is exploration of the possible effect of ARTs on 25OHD levels in HIV patients. Both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI s) have been associated with the impairment of vitamin D metabolic pathways. Analysis of ART effects on vitamin D status revealed that use of efavirenz and nevirapine (NNRTI) and ritonavir (protease inhibitors) was associated with greater odds of vitamin D insufficiency / deficiency in our study.

Four different regimen each containing Efavirenz, Nevirapine, Tenofovir and Ritonavir were studied.The regimen are TLE (Tenofovir, Lamivudine, Efavirenz), ZLE (Zidovudine, Lamivudine, Efavirenz), ZLN (Zidovudine, Lamivudine, Nevirapine), and Ritonavir containing regimen were studied and insufficient vitamin D was seen in more than 50% in all the regimes . And also,insufficient vitamin D was more among nevirapine containing regimen followed by efavirenz, ritonavir and tenofovir as shown in [Table 5] and the finding was statistically significant ($p< 0.05$).

Previous small cohorts studies have reported associations between vitamin D deficiency and nonnucleoside reverse transcriptase inhibitors, and case studies have described low vitamin D levels among HIV-infected persons receiving efavirenz.[22]

As regards NNRTIs, there is an increasing amount of data associating efavirenz (EFV) with compromised vitamin D homeostasis. EFV increases 25OHD catabolism by inducing CYP24 thereby reducing transcription of CYP2R1, α 25-hydroxylase.[23] Our study highlights higher rates of vitamin D deficiency and insufficiency when both EFV and NVP are used rather than taking EFV alone and it is possibly a NNRTI class effect.

Our study also shows there is an association between ritonavir exposure and decrease odds of vitamin D insufficiency or deficiency reflecting the underlying mechanism of ritonavir on metabolism of vitamin D. Ritonavir is a potent inhibitor of cytochrome P450 enzymes and blocks in vitro the action of the 1α hydroxylase which converts 25(OH)D to 1,25(OH)2D in the kidney.[24]

Tenofovir (TDF) has been associated with low BMD as it induce proximal renal tubular dysfunction leading to renal phosphate wasting and finally BMD loss.[25]

Our discussions throws light on the difficulties in sorting out the effects of specific ARTs or combinations of ARTs on vitamin D levels in a cross-sectional data. In conclusion, this study contributes to the growing literature that suggests that use of certain ARTs, especially NNRTI and PI, is associated with alterations in 25OHD levels.

The correlation between serum vitamin D concentration and the time of cumulative use of different antiretrovirals (years) was evaluated and was found to have negative correlation as shown in [Figure 2]. Thus, longer the duration of antiretroviral therapy, higher were the chances of having low serum vitamin D concentration. Similar findings were seen in many studies. In some longitudinal studies, there was decreased levels of 25(OH)D levels after 12 months of starting efavirenz containing cART.[23]

There were variation regarding the use with nevirapine as in some studies there were no changes in serum vitamin D level while in other studies there were decreased level similar to those observed with efavirenz.[26] In our study, with increasing age there was chance of decreasing vitamin D level and a negative correlation was seen between age and serum vitamin D level as shown in table 6. Similar findings were seen in study done by Martins D et al and Ginde AA et al where the elderly have lower vitamin D level, which leads to higher rates of vitamin D supplementation in older population due to perceived increased risk of bone disease.[27]

The relationship seen between 25OHD levels and CD4+ T-cell count needs further evaluation. Many studies have described a positive correlation between serum vitamin D and CD4 count.[28] Similarly in our study also, serum vitamin D level was found to have a positive correlation with CD4 count as shown in [Table 7] and the finding was statistically significant ($p< 0.05$). The analysis of the association between vitamin D concentration and CD4 lymphocyte count, that express the degree of immunosuppression, may be affected by the fact that antiretroviral is started irrespective of the CD4 lymphocyte count that makes the assessment of association between vitamin D deficiency and CD4 lymphocyte count a complex task.

CONCLUSION

Our study shows high levels of vitamin D deficiency in patients on antiretroviral therapy. A positive correlation was found between serum vitamin D level and CD4 count and negative correlation between duration of antiretroviral theory and serum vitamin D level. Recently, mortality in HIV-infected individuals has dramatically decreased as a result of all the investment made in diagnosis and management of HIV infection.

This is, partly, a consequence of the implementation of successful interventions, from which ART is a main reference. Despite all the benefits of an anti-retroviral therapy (ART), some evidence suggests that HIV-infected subjects treated with ART have higher risk of vitamin D deficiency and also cancer, cardiovascular disease, diabetes and other

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immunological diseases. Not only vitamin D deficiency is highly prevalent in HIV-positive patients, but also NNRTI therapy further decreases 25(OH)D3 serum levels.

Together with this chain of possible events, vitamin D deficiency may also be included as one more cause of bone loss, the metabolic syndrome, dyslipidemia and an increased risk of CVD. These results are of particular relevance for HIV-positive persons on ART. Not only are they likely to stimulate the progression of the disease through vitamin D deficiency, but also add one more risk factor to the prolonged use of antiretroviral therapy.

Low levels of 25(OH)D is associated with many health related issues among HIV-infected persons emphasizing the need for routine screening for vitamin D. Future studies are needed to verify potential alterations in vitamin D metabolism caused by the exposure to antiretrovirals and their duration of use. Other studies on larger population would be beneficial so as to assess the impact of vitamin D supplementation for preventing many comorbidities like osteoporosis, cardiovascular diseases, osteopenia etc in HIV-infected adults.

Vitamin D supplementation, therefore, will provide additional benefits in terms of reduced HIV transmission and reduced HIV disease progression and also potential skeletal, immunological, cardiovascular and other benefits of vitamin D supplementation in HIV-positive patients. Future studies based on antiretrovirals exposure and their duration of use for potential variation in vitamin D metabolism would be beneficial. It would be prudent to advocate vitamin D supplementation as a global strategy in all HIV positive patients on antiretroviral therapy.

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