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Scientific Research

Vitamin D and Secondary Hyperparathyroidism in HIV Infected Patients Taking Antiretroviral Therapy

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Abstract

Objective: Due to the lack of studies assessing hypovitaminosis D and secondary hyperparathyroidism in Brazilian HIV-infected population, especially in the northeastern population, this study aimed to determine the profile of these conditions in patients infected with HIV and its correlation with immuno-virological, sociodemographic data and associated comorbidities. Methods: Comparison studies were obtained from routine clinical samples of HIV infected patients submitted for 25-OH Vitamin D, PTH and alkaline phosphatase determination. Results: A total of 78 patients were included, 42 (53.8%) males, mean age 45.7 years. Antiretroviral regimens most used in this study were Zidovudine/Lamivudine/Efavirenz 17.9%, Tenofovir/Lamivudine/Efavirenz 17.9%, Tenofovir/Lamivudine/Atazanavir-r 15.4%. The mean value CD4 count was 592.1 ± 247.2 cells/mm^3, CD8 cell count was 1026.5 ± 467.3 cells/mm^3, mean detectable viral load was 2220 ± 15703 copies and CD4/CD8 ratio was 0.63 ± 0.33. A total of 34 vitamin D dosages were collected with 41.2% representing sufficient amount and 58.8% insufficient. Alkaline Phosphatase (ALP) dosage was elevated in 49.3% (N=35) of the patients. Parathormone (PTH) was elevated in 18% (N = 11). Among patients with elevated PTH levels, 81.9% had elevated levels of ALP (p = 0.01). In the group of patients with high levels of ALP, 45.7% had a CD4 count < 500 cels/mm^3 (p = 0.02). There was no significant difference in vitamin D related to gender (p = 0.21), age (p = 0.23), CD4 count (p = 0.26), suppressed viral load (p = 0.44) or blood glucose (p = 0.45). Conclusions: This study evi-

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denced a high prevalence of Vitamin D insufficiency in Northeast Brazil, which suggests HIV infection correlation. A high prevalence of Hyperparathyroidism was detected and related with inflammatory condition persistence and low CD4 count. We suggest improve vitamin D follow up and measurements in this population with better CD4 count control to avoid future osteoarticular complications of HIV treatment.

Keywords

HIV, Hyperparathyroidism, Vitamin D, Antiretroviral Therapy

1. Introduction

According to the United Nations Program on HIV/AIDS (UNAIDS), around 35 million people were living with HIV, 2.1 million have been infected by the virus and 1.5 million died in 2013 [1]. Brazil estimates 718,000 people living with HIV, which represents a prevalence of 0.4% in general population, but just 574,000 are diagnosed. In 2012, around 313,000 people were on antiretroviral therapy, only 44% of people living with HIV infection [2].

Under the advent of antiretroviral therapy (ART), the number of new infected persons, the onset of opportunistic infections and mortality in HIV patients had a large reduction [3]. This view attended to new health problems in the population living with HIV, such as higher prevalence of cardiovascular diseases, diabetes mellitus [4], acute myocardial infarction [5] [6] and heart failure [7]. Besides those, disturbances such as hypovitaminosis D had been related [8] [9].

As ultraviolet B exposure varies with the latitude of regions and during the year, mean vitamin D concentrations in general populations can change. Furthermore, women and elderly people are generally more prone to low 25(OH)D concentrations, because of testosterone, less sun exposure and limited capacity of the skin to produce vitamin D metabolites. In a meta-analysis of eight prospective cohort studies, the lowest vitamin D quintile was associated with increased all-cause mortality, cardiovascular mortality, and cancer mortality [10].

Vitamin D is a steroid-derived, fat-soluble vitamin related to the modulation of immune response [11] [12]. This was demonstrated with *in vitro* studies in which there was maturation of monocytes, reduction in viral replication and infection of macrophages after pre-treatment with vitamin D [13].

The deficiency of vitamin D is markedly more frequent in patients diagnosed with HIV, especially at advanced stages, than in the general population. Studies have already showed a high prevalence of this condition among general population, as even 86.7% in Iranian one [14] [15].

Some risk factors have been established, such as nonwhite race [16], low sun exposure, use of efavirenz, metabolic syndrome [17], lactose intolerance [18], physical inactivity [19], use of ART for more than three years, low CD4 + T cells [20], high body mass index (BMI) [21] and unsuccessful viral suppression of HIV [22]. The deficiency of this compound is also related to disease progression to more advanced stages, but also association with levels of CD4 [23].

HIV is associated with a reduction in bone mineral density by generating hypovitaminosis D, through mechanisms such as induction of consumption of 25-hydroxyvitamin D by immune cells, inhibition of hydroxylation of this molecule in the kidneys and increase of TNF-α levels [24]. Consequently, patients with HIV are at higher risk of falls and fractures [25] [26].

As already known, it is not only the virus that causes changes in the patient. The use of ART is also related to major changes in the metabolism of calcium. Among these changes, we observed a greater tendency to osteoporosis, reduction of calcium levels, reduction of 1,25-dihydroxyvitamin D and the increase of levels of parathyroid hormone [14]. The drugs more relevant are protease inhibitors [8], reverse transcriptase inhibitor tenofovir [27] and Zidovudine, related to hypovitaminosis D [28].

Based on the risks proposed by the deficiency of vitamin D, it has been given greater attention to the use of cholecalciferol and calcium supplementation for patients with HIV, objecting a reduction in bone reabsorption and maintenance in bone mineral density [29].

In the last years we observed the increased survival of patients with HIV after the introduction of HAART, and therefore more attention has been given to long-term complications. Due to the lack of studies assessing the

complications of hypovitaminosis D and secondary hyperparathyroidism in Brazilian HIV-infected population, especially in the northeastern population, this study aimed to determine the profile of hypovitaminosis D and secondary hyperparathyroidism in patients infected with HIV and its correlation with immuno-virological, sociodemographic data and patients comorbidities.

2. Materials and Methods

This was a retrospective, observational, analytical study, which included patients who are followed at the clinic in Hospital Geral de Fortaleza, Brazil. A files review of the patients diagnosed with HIV infection was conducted. Data were collected through a form containing sociodemographic, immuno-virological, antiretroviral therapy, blood glucose, vitamin D, parathyroid hormone (PTH), alkaline phosphatase (ALP), and comorbidities related, as osteoarticular diseases and tuberculosis.

Vitamin D and parathormone were detected by automated direct chemiluminescent assays. Alkaline Phosphatase Assay Kit, Kinetic Determination, was designed to measure ALP activity in biological samples. Reference values for Vitamin D were considered as hipervitaminose (>100 ng/mL), sufficiency (30 - 100 ng/mL), insufficiency (30 - 10 ng/mL) and deficiency (<10 ng/mL). Alkaline phosphatase normal values considered normal between 50 - 250 units per liter, and Parathormone between 16 - 87 picograms per milliliter (pg/mL).

Data were collected only after the Ethics Committee of Hospital Geral de Fortaleza has approved the study.

All results are expressed as mean and standard deviation, and submitted to D'Agostino-Pearson normality test. Comparing the groups using Student's t test complemented statistical analysis. The test is considered statistically significant if $p < 0.05$. Sample size (N) is for convenience, by adding the maximum possible number of components.

3. Results

A total of 78 patients were included, 42 (53.8%) males with a mean age of 45.7 ± 11.03 years (variance 25 - 81). The mean period of HIV diagnosis was 100.1 ± 49.8 months and the mean period of the last ART in use was 49.5 ± 30 months. Most of the patients were asymptomatic during clinical evaluation (69.2%), and some had complained about articular pain (17.9%) or lumbar pain (12.8%).

Antiretroviral regimens most used by patients in this study were Zidovudine/Lamivudine/Efavirenz 17.9%, Tenofovir/Lamivudine/Efavirenz 17.9%, Tenofovir/Lamivudine/Atazanavir-r 15.4% and Zidovudine/Lamivudine/Atazanavir without booster 10.3%, which represented 61.5% of all regimens. Just two patients were using integrase inhibitor; the others had schemes of transcriptase inhibitors and protease inhibitors associations. Patients had a diagnosis of tuberculosis associated with HIV in 10.3%. The mean value of blood glucose levels was 104 ± 25 mg/dL, and 46.2% of patients had blood glucose levels above 100 mg/dL.

During immuno-virological evaluation the mean CD4 count was 592.1 ± 247.2 cells/mm^3, CD8 cell count 1026.5 ± 467.3 cells/mm^3, and mean detectable viral load was 2220 ± 15,703 copies. Analyzing CD4/CD8 ratio in the same period was 0.63 ± 0.33.

A total of 34 vitamin D dosages were collected with 41.2% representing sufficient amount and 58.8% insufficient. Alkaline Phosphatase (ALP) dosage was elevated 49.3% (N = 35) and normal in 50.7% (N = 36) of the patients. Parathormone (PTH) was elevated in 18% (N = 11) and normal in 82% (N = 50) patients (**Table 1**).

Among patients with elevated PTH levels, 81.9% had elevated levels of ALP, while in the group of patients with normal PTH levels, only 41.3% showed increased ALP values ($p = 0.01$, 95%, CI 1.27 - 3.08, RR 1.98), (**Table 2**).

In the group of patients with high levels of ALP, 45.7% had a CD4 count < 500 cels/mm^3, while in the group with normal ALP, only 22.2% had CD4 counts < 500 cels/mm^3 ($p = 0.02$, 95%, CI 1.01 - 4.18, RR 2.05), (**Table 3**).

There was no significant difference in vitamin D related to gender ($p = 0.21$), age ($p = 0.23$), CD4 count ($p = 0.26$), suppressed viral load ($p = 0.44$) or blood glucose ($p = 0.45$).

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There was no significant difference in vitamin D related to gender ($p = 0.21$), age ($p = 0.23$), CD4 count ($p = 0.26$), suppressed viral load ($p = 0.44$) or blood glucose ($p = 0.45$).

Table 1. Dosage of Vitamin D in patients taking antiretroviral therapy related eith epidemiology and immune-virologic parameters.

Vitamin D	Deficient	Insufficient	Sufficient	Hypervitamin	p value
Female	0	10	9	0	0.21
Male	0	10	5	0	
Age (years)					
<50	0	13	12	0	0.23
≥50	0	6	2	0	
Blood glucose (mg/dL)					
≤100	0	11	8	0	0.45
>100	0	9	6	0	
CD4 count (cels/mm^3)					
<500	0	4	5	0	0.26
≥500	0	16	9	0	
Viral load suppression (copies)					
<50	0	17	13	0	0.44
≥50	0	3	1	0	
Alkaline phosphatase (UI/L)					
50 - 250	0	9	9	0	0.41
>350	0	6	5	0	
Parathormone (pg/ml)					
Normal (16 - 87)	0	13	10	0	0.42
Elevated (>87)	0	2	3	0	

Table 2. Parathormone in patients taking antiretroviral therapy related eith epidemiology and immune-virologic parameters.

Parathormone (pg/ml)	Normal (16 - 87)	Elevated (>87)	p value
Female	23	5	0.48
Male	27	6	
Age (years)			
<50	37	8	0.59
≥50	13	3	
Blood glucose (mg/dL)			
≤100	29	6	0.41
>100	21	5	
CD4 count (cels/mm^3)			
<500	16	5	0.2
≥500	34	6	
Viral load suppression (copies)			
<50	44	10	0.62
≥50	6	1	
Alkaline phosphatase (UI/L)			
50 - 250	27	2	0.017
>350	19	9	

Table 3. Alkaline phosphatase in patients taking antiretroviral therapy related eith epidemiology and immune-virologic parameters.

Alkaline phosphatase (UI/L)	Normal (50 - 250)	Elevated (>250)	p value
Female	20	14	0.1
Male	16	21	
Age (years)			
<50	27	24	0.28
≥50	9	11	
Blood glucose (mg/dL)			
≤100	22	16	0.1
>100	14	19	
CD4 count (cels/mm^3)			
<500	8	16	0.02
≥500	28	19	
Viral load suppression (copies)			
<50	28	31	0.25
≥50	7	4	

4. Discussion

Vitamin D is actually considered as immune modulatory substance, after a discovery of specific receptors of this substance on cells of immune system, as lymphocytes and dendritic cells. In addition, a series of studies correlated their deficiency with a higher incidence of diarrhea, tuberculosis and general respiratory infections [30]. Despite a high prevalence of low vitamin D in our study, it was not correlated with symptomatic patients and even tuberculosis coinfection.

Studies conducted in different parts of the world evidenced inadequate levels of vitamin D in most patients with HIV infection, including developed countries as United States, as The Women's Interagency HIV Study (WIHS) study demonstrated a 60% prevalence of hypovitaminosis D [14]. In the present study there was no gender related alterations in vitamin D or hyperparathyroidism, suggesting a stronger association with HIV infection as cause than gender hormone differences.

Conrado *et al.* (2011) [31] showed that vitamin D deficiency is higher among Brazilian population with HIV, with an incidence of approximately 40%. Although vitamin D is obtained from diet and dietary supplements, the main source of vitamin D is its production in skin under the influence of solar ultraviolet B radiation. In this study, the region mean temperature during the year varies from 24˚C to 29˚C. Despite the weather conditions being in favor of the production of vitamin D in northeastern Brazil due to elevated sun exposure, the prevalence of deficiency of this compound in the present study was elevated in patients with HIV surveyed in this region and reaching higher than those seen in other Brazilian studies values.

In a cohort performed by Cervero *et al.* (2012) [22] it was noticed that vitamin D deficiency was 16.4% more prevalent in the group with HIV. Furthermore, several factors were identified as independent risk factors for the onset of this deficiency, such as exposure to efavirenz and higher viral loads. Efavirenz is a first line drug in Brazil, as Tenofovir and Zidovudine, so a great percentage of this study population was under these drugs use, which could be an important contributing factor to vitamin D insufficiency.

The high values of PTH in patients from our study show that there is the development of secondary hyperparathyroidism in this group, being that a response for the maintenance of calcium homeostasis and reduction of the effects of hypovitaminosis D.

Several diseases and organic impairments are related to this vitamin deficiency, the most important are: changes that generate bone fragility [32], progression of Alzheimer's disease [33], diabetes [34], risk of cardiovascular diseases [35], increased risk of cancer [36] and kidney disease [37]. Besides we did not found a large correlation with comorbidities as diabetes mellitus, there is an evidence of high levels of blood glucose above

100 mg/dL in all population studied, suggesting insulin periphery resistance as common find.

High levels of ALP are related to increased risk for fractures and mortality from cardiac and infectious causes. These effects are independent from calcium and PTH [38]. Therefore, patients with HIV are at risk by: inflammatory process of the disease, hypovitaminosis D, elevated PTH values and also have high risk of death due to high prevalence of elevated ALP. In the present study, we observed a prevalence of low CD4 counts in patients with higher ALP values, and low ratio CD4/CD8, suggesting a persistent inflammatory response that could be contributing to vitamin D insufficiency and possible other mortality causes.

Detecting a high prevalence of this vitamin D deficiency in HIV population, organs such as the European AIDS Clinical Society (EACS) indicates following measurements of vitamin D levels in all patients with HIV and recommend replacement in cases of subnormal values [39], 2011.

This study has some limitations as small number of patients included and the lack of exams in all patients, being necessary studies including a larger number of patients to assess the impact of secondary hyperparathyroidism and increased alkaline phosphatase in patients with HIV.

5. Conclusion

This study evidenced a high prevalence of Vitamin D insufficiency in Northeast Brazil, which could be not related with less sun exposure but suggests HIV infection correlation. A high prevalence of Hyperparathyroidism was also detected and related with inflammatory condition persistence and low CD4 count. We suggest improve vitamin D follow up and measurements in this population with better CD4 count control to avoid future osteoarticular complications of HIV treatment.

Conflict of Interest

The authors declare no interest conflicts.

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