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Effect of vitamin D3 (cholecalciferol) supplementation in patients with HIV

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ABSTRACT. Human immunodeficiency virus (HIV) infection remains a global public health problem that affects thousands of people annually. One of the main comorbidities identified in HIV-positive patients undergoing antiretroviral treatment is insufficiency of vitamin D, a key hormone involved in physiological and metabolic processes in the human body. This review aimed to evaluate the importance of vitamin D3 supplementation in HIV-positive patients with serum concentrations below the recommended limits. The literature search included indexed articles published from 2015 to 2023. The article search strategy included the databases of the National Library of Medicine (PUBMED) and Scientific Electronic Library Online (SCIELO). Non-acquired immunodeficiency syndrome (AIDS)-related opportunistic pathologies are the main causes of morbidity and mortality despite the efficacy of antiretroviral therapy. Several studies have shown that hypovitaminosis D is diagnosed during HIV progression and may be associated with reduced survival rates, highlighting the importance of measuring vitamin D serum levels and providing exogenous vitamin D3 supplementationif needed for these patients. Several studies have pointed out the benefits of vitamin D3 supplementation in HIV-infected patients, independent of antiretroviral treatment, such as the reduction of inflammatory processes and mediators related to bone renewal, increase in CD4 + T lymphocyte count, and increase in antibacterial response against invading microorganisms. Given the importance of this disease worldwide, which is associated with a high number of deaths, there is justification for intensifying and deepening research on the potential and significant role of vitamin D3 supplementation.

Keywords: HIV/AIDS; hypovitaminosis D; metabolic homeostasis; vitamin D3 supplementation.

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Introduction

Global statistics from the Joint United Nations Programme on HIV/AIDS - UNAIDS (2020) indicate that approximately 38 million people are carriers of human immunodeficiency virus (HIV) which causes acquired immunodeficiency syndrome (AIDS); 36.2 million are adults and 1.8 million are children. Among them, 79% were aware of their positive HIV status. An estimated 1.7 million people are infected annually, with an average of 690,000 recorded deaths from AIDS-related diseases in 2020. In Brazil, in 2019, 920,000 people of all ages living with HIV were diagnosed, with an incidence of 0.23 people infected per 1000 inhabitants, showing an important increase in the number of new infections in the Brazilian territory (Brasil, Ministério da Saúde [MS], 2019; Brasil, Ministério da Saúde [MS], 2020; World Health Organization [WHO], 2020; Dybul et al., 2021).

HIV integrates itself into the genome mainly of cells such as CD4 + T lymphocytes and macrophages, causing central problems related to immunosuppression, where the host becomes more vulnerable and susceptible, favoring the development of opportunistic infections, increasing the risk factors, and consequently the mortality rates. In general, this pathology has no cure and requires medical monitoring associated with the pharmacological prescription of antiretroviral cocktails to control viral multiplication and stabilize changes in the immune system (Paulique et al., 2017; Errante et al., 2018; Lins et al., 2019).

Vitamin Dis a pre-hormone synthesized endogenously when the skin is exposed to ultraviolet B radiation (UVB), or acquired through food intake, or vitamin supplementation (Silva et al., 2022). This micronutrient has several beneficial effects on the body, especially in the maintenance of bone and calcium homeostasis in conjunction with parathyroid hormone (PTH). However, patients with HIV who are treated with certain antiretroviral drugs may have reduced serum levels of vitamin D, which may cause injuries to the body and contribute to the development of other diseases related to low serum concentrations of this vitamin. Thus, it is essential to conduct a literature survey on the benefits of vitamin D3 supplementation in patients with HIV, with a focus on the prevention and/or reduction of risks of contracting diseases, HIV progression, and mortality associated with low vitamin D concentrations (Havens et al., 2012; Coelho et al., 2015; Jiménez-Sousa et al., 2018; Adams and Hewison, 2020; Legarth et al., 2020). Thus, the present study aimed to evaluate the importance of vitamin D3 supplementationin patients with HIV who may have serum concentrations below the recommended limits.

Methods

The literature search included indexed articles published from 2015 to 2023, in English and other languages. The focus was on studies reporting the influence of low serum levels of vitamin D in patients with HIV infection, or its contribution to the development of other diseases, and which considered the supplementation of vitamin D3 as an alternative for the prevention or control of such pathologies.

Electronic databases of the National Library of Medicine (PUBMED) and Scientific Electronic Library Online (SCIELO) were searched using the following search terms: "25-hydroxycholecalciferol," "Cholecalciferol," "Vitamin D," "Vitamin D supplementation$_3$," "Serum dosage," "HIV-infected," "HIV/AIDS", "Antiretrovirals," "Hypovitaminosis D," and "Diseases".

Articles were analyzed based on the quality of the description of the hypothesis/objectives, priority of the description of the outcome to be studied, characterization of the sample included, peculiarity of the description, and discussion of the subjects of interest for the development of this study.

Literature review

General aspects about HIV/AIDS

HIV is the cause of AIDS, which was identified in the 1980s in the United States, initially in several adult homosexual men, with varied clinical manifestations resulting from an immune deficiency through the involvement of white blood lineage cells such as CD4 + T lymphocytes (Brasil, Ministério da Saúde, 2021; Dybul et al, 2021; Silva et al., 2021; Wang et al., 2021).

HIV is a retrovirus of the retroviridae family, measuring approximately 100 nm in diameter, and has an envelope with a lipid membrane, encapsulating the protein matrix and viral capsid. Inside the capsid is the viral genetic material, as well as the RNA transporter and enzymes responsible for viral multiplication (Sabino, et al., 2015).

Among the main forms of HIV transmission, sexual contact without a condom is the most significant, but contamination can also occur through exposure to contaminated blood, reuse or sharing of syringes, occupational accidents involving needles or other contaminated sharp materials, vertical transmission from mother to child during pregnancy or delivery or breastfeeding, and organ or tissue transplants without proper viral detection (Dias, 2017; Angelim et al., 2017; Brasil, Ministério da Saúde, 2021; Feitoza et al., 2021).

HIV is divided into two types, HIV-1 and HIV-2, which differ in their genomic variants. HIV-1 has two groups, major (M) and outlier (O), while HIV-2 is divided into five groups, namely, A, B, C, D, and E. HIV-1 has greater virulence and is associated with malignancy, while type 2 is milder and is less frequently associated with malignant change. There are different prevalences of the virus types and groups of the virus globally (Sabino et al., 2015).

HIV infection occurs through the binding of the glycoprotein to CD4 + T lymphocyte receptors, leading to entry into the cell. In the cell cytoplasm, the virus converts its RNA into DNA by the action of the reverse transcriptase enzyme, and the DNA formed integrates into the host genome, with the regulation of viral gene expression and subsequent production of structural proteins responsible for the formation of new viruses, which exit the cell in the plasma and thus can invade new lymphocytes (Sabino, et al., 2015; Brasil, 2018).

From a clinical perspective, HIV infection is divided into three main phases: 1) acute infection; 2) the chronic asymptomatic phase; and 3) the chronic symptomatic phase. In acute infections, the clinical presentation resembles flu-like symptoms, in which the patient may present with fever, fatigue, headache, lymphadenopathy, pharyngitis, myalgia, nausea, vomiting, and diarrhea (Brasil, 2018).

The chronic asymptomatic phase is characterized by the mild presence or absence of clinical manifestations. The chronic symptomatic phase can be divided into two stages: HIV infection (not AIDS), and AIDS. Symptoms usually include night sweats, fever, fatigue, weight loss, diarrhea, and various opportunistic diseases associated with immune fragility (Brasil, 2018).

Antiretroviral therapy

Antiretrovirals (ARVs) are drugs used to treat patients with HIV, and their pharmacological effects are related to the reduction of morbidity and mortality, increasing quality and life expectancy. The mechanism of action of these drugs makes it possible to inhibit replication and reduce the viral load to undetectable levels in the bloodstream (Foresto et al., 2017; Garbin et al., 2017; Coutinho et al., 2018).

Antiretroviral treatment consists of a combination of two or more drugs of the same or different pharmacological classes that potentiate antiretroviral activity, consequently increasing the number of CD4 + T lymphocytes and reducing the plasma concentration of HIV-RNA (Foresto et al., 2017; Garbin et al., 2017; Brasil, 2018; Coutinho et al., 2018).

The importance and benefits of treatment with antiretroviral drugs are widely known, but they are not free of adverse effects, which can include poor distribution of body fat and accentuated inflammatory processes. In addition, viral strains with potential resistance to treatment can arise. Long-term use of antiretroviral drugs can lead to serious side effects such as aging of organs such as the liver, kidneys, bones, and central nervous system, and cardiovascular and nutritional deficiencies, especially vitamin D (Nogueira, 2018; Abreu, 2022).

Vitamin D: Physiological aspects, metabolism, function and sources

Vitamin D is a steroid hormone, a fat-soluble molecule derived from 7-dehydrocholesterol (7-DHC), and is present in virtually all tissues, especially the dermis and epidermis, which participate in photolytic and enzymatic reactions upon exposure to UVB. The 7-DHC is converted into pre-cholecalciferol D3, which undergoes further enzymatic reactions until it forms vitamin D3(Hsieh and Yin, 2018).

After its formation, vitamin D3 is transported in the blood by vitamin D-binding protein to the liver, where it is hydroxylated by cytochrome P450 to produce 25-hydroxyvitamin D (25(OH)D), which is a more stable and abundant metabolite of vitamin D. The 25(OH)D is the predominant circulating form of vitamin D, and its levels are best indicator of vitamin D status, because it is related to skin synthesis and intake (Hsieh and Yin, 2018).

The 25(OH)D is further metabolized in the proximal renal tubules of the kidney by 1-α-hydroxylase, which catalyzes the hydroxylation of 25(OH)D into the hormonally active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), also called calcitriol. This is the most biologically active form of vitamin D, with a high degree of affinity for receptors present in almost all human cells, except for mature striated muscle cells, RBCs, and some differentiated cells of the central nervous system (Hsieh and Yin, 2018).

Vitamin D is characterized by important biological activities such as regulating osteomineral physiology, homeostasis of several cellular processes, such as autoimmune modulation mainly in the autocrine immunoregulation of CD4 + , CD8 + T lymphocytes and antigen-presenting cells, synthesis of inflammatory interleukins, and control of blood pressure. It also acts as an antioncogene due to its action in the regulation of cell multiplication and differentiation processes. The vitamin also regulates calcium and phosphorus metabolism, controls intestinal absorption processes, and influences the renal reabsorption of ions. Vitamin D participates in a wide range of physiological functions to maintain the body's homeostasis (De Carvalho et al., 2020).

In addition to sun exposure, which represents the main source of vitamin D (between 80 and 90%), diet is also a source of vitamin D; however, the quantities obtained are not sufficient to maintain the body's daily demand. The main food sources of vitamin D3cholecalciferol of animal origin are fish liver oils, particularly cod and tuna, mammalian livers, eggs, and dairy products. Vitamin D2, ergocalciferol of plant origin, is present in edible fungi. Oral intake of vitamin D supplements is another common source of the vitamin (Figure 1) (Melo, 2019; Câmara et al., 2021).

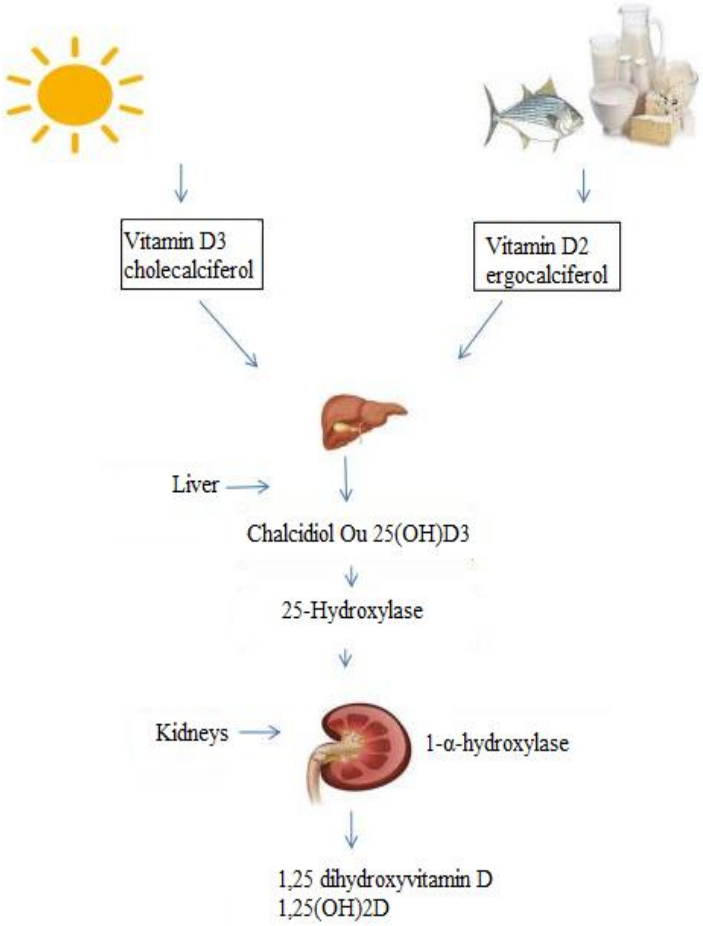

Figure 1. Schematic Diagram of Vitamin D Metabolism
Adapted de Pereira (2019).

Hypovitaminosis D

Hypovitaminosis D is characterized by insufficiency or deficiency of vitamin D and is considered a social and worldwide problem. The main causes of hypovitaminosis D are associated with low cutaneous exposure to sunlight due to environmental factors, such as season, latitude, exposure time, age, skin type, and sunscreen use. The dietary intake of rich sources of this vitamin may also be low. It is worth noting that the use of some medications, such as the antiretroviral drugs, glucocorticoids, and anticonvulsants, increases the metabolism of 25(OH)D, contributing to the deficiency of this vitamin (Elizondo-Montemayoret al., 2017; Duránet al., 2019).

Serum vitamin D levels can be determined through laboratory tests measuring 25(OH)D. This metabolite represents vitamin D obtained from food and that obtained via skin synthesis (Dutra et al., 2020; Almeida-Afonso et al., 2021).

There is no internationally accepted guideline for optimal serum vitamin D levels and satisfactory daily intake values, and there are variations in physiological or pathological needs among individuals (Poiana et al., 2019; Ayelign et al., 2020; Almeida-Afonso et al., 2021).

Vitamin D deficiency is characterized by a serum vitamin D concentration < 20 ng mL^{-1}, insufficiency is indicated by serum levels < 30 ng mL^{-1}, and ideal/sufficient serum concentrations are defined as between 30 and 100 ng mL^{-1}. Monitoring serum vitamin D levels is important and recommended for individuals at risk of hypovitaminosis D, such as in older and institutionalized patients, and those with HIV/AIDS, as it is associated with faster disease progression and an increased risk of acquiring opportunistic infections, such as tuberculosis, (Bouillon and Carmeliet, 2018; Jorge et al., 2018; Poiana et al., 2019; Ayelign et al., 2020).

Vitamin Din HIV Infection

Epidemiological data point to several HIV-related factors that can lead to hypovitaminosis D, such as the HIV infection itself leading to chronic inflammation and immune activation increasing IL6 and TNFα levels, as well as activated monocyte phenotypes and a reduced CD4 + T cell count. Chronic inflammation can also

alter the enzymatic activity of 1α-hydroxylase at the renal level, reducing the production of $1,25(OH)_2D$ by blocking the conversion by PTH of 25(OH)D to $1,25(OH)_2D$ (Jiménez-Souza et al., 2018; Poiana et al., 2019; Ayelign et al., 2020).

Other situations, such as comorbidities, infectious complications, and frequent and prolonged hospitalization of patients with HIV lead to reduced exposure to solar radiation, malnutrition, reduced consumption of foods rich in vitamin D, and medications such as antiretroviral drugs, can directly impact on the vitamin D metabolic pathways (Jiménez-Souza et al., 2018).

Effects of vitamin D3(Cholecalciferol) supplementation on HIV infection

Despite most HIV-infected patients having hypovitaminosis D, no safe optimal supplementation dose has been established for these patients. Normally, a healthy person consumes between 400 and 600 IU of vitamin D daily to maintain optimal levels. Recently, the Institute of Medicine has recommended a standard dose of 600 IU to meet the daily needs of 97.5% of the population. The American Society of Endocrinology, on the other hand, recommends three times the standard dose for patients with HIV and who are on antiretroviral treatment (Jiménez-Souza et al., 2018; Alvarez et al., 2019; Hauger et al., 2020).

Several studies have demonstrated a range of benefits from adequate vitamin D3 supplementation for patients with HIV infection receiving antiretroviral treatment. These include increased CD4 + and CD8 + T lymphocyte counts favoring immune recovery and viral load control, reduction in the percentage of activated cytotoxic T cells (CD8 + CD38 + HLA DR +), maintenance of bone mass, reduction in biomarkers associated with bone turnover, increase in osteocalcin, a biomarker associated with bone formation, reduction in PTH levels, and stimulation of the expression of antimicrobial peptides such as cathelicidins and human beta-defensins which have antimicrobial properties and assist in the elimination of *Mycobacterium tuberculosis* and antiviral responses contributing to the inhibition of HIV replication. Given these benefits, there is support for vitamin D3 supplementationas an adjuvant for the treatment of these patients (Alvarez et al., 2019; Hauger et al., 2020; da Silva Monaco et al., 2021).

Vitamin D supplementation must follow clinical follow-up protocols, because it may pose risks when patients have serum 25(OH)D levels > 100 ng mL^{-1} or when serum calcium levels are > 2.70 mmol L^{-1}. Under these conditions, the skeletal system, cell membrane permeability, and nerve impulses can be affected, leading to muscle weakness, spasms, fatigue, kidney problems, and digestive symptoms, among others (Pereira, 2019; Alvarez et al., 2019).

Conclusion

Hypovitaminosis D may potentiate the pathogenesis of HIV infection, negatively impacting innate and adaptive immune responses, allowing inflammatory processes through the activation of the immune system, and may increase the risks of comorbidity and mortality not directly related to AIDS in this population group with HIV infection. Adjuvant exogenous supplementation with vitamin D3 may contribute in a prophylactic manner because, according to recent studies, it may beneficially alter the immune system by reducing or even preventing the development of inflammatory cascades. There is controversy, however, as several other studies have indicated that variation in the serum level of this vitamin does not positively influence the pathogenesis of HIV infection.

Given the great importance of this theme and the lack of clear data, it is essential to conduct more studies on vitamin D and HIV infection as this important issue affects millions of people worldwide. Defining diagnosis, standard serum concentration, and establishing adequate supplementation protocols is still a challenge to overcome; currently, the literature and responsible bodies do not guidelines, leaving clinicians without reliable tools to guide their patients in clinical practice.

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