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Vitamin D: Mechanisms and Challenges of a Pandemic

Vitamina D: Mecanismos e Desafios de uma Pandemia

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Abstract
Vitamin D is an essential pro-hormone that plays a critical role in human health, aiding the immune response through the absorption of essential minerals such as calcium, phosphate and magnesium. It also contributes to the inhibition of TH1 and stimulation of T cells, key components in the body's defense. The objective is to explain mechanisms, in addition to listing the impact that this vitamin has not only on the development of the human body, but also against various diseases, avoiding a pandemic of vitamin D deficiency and its consequences. This study reviewed articles published between 2010 and 2023, selecting those which provided the most significant contributions. Evidence indicates that adequate vitamin D supplementation can reduce the risk of type 2 diabetes by up to 76% and the risk of developing certain types of cancer by 66%, as well as being beneficial in cases of severe covid-19 and other diseases. Obese people often have lower levels of vitamin D, complicated by polymorphisms in receptors that can affect the absorption of the vitamin. This study aims to highlight the effectiveness of vitamin D in disease prevention and warns of the global deficiency of this vitamin. We conclude that awareness strategies and targeted interventions are essential, especially for those in at-risk groups, to reduce the persistent pandemic of vitamin D deficiency worldwide.
Keywords: Vitamin D; Cancer; Exercise; Infections; Obesity; Physical activity.

Resumo
A vitamina D é um pró-hormônio essencial que desempenha um papel crítico na saúde humana, auxiliando na resposta imunológica através da absorção de minerais essenciais como cálcio, fosfato e magnésio. Também contribui para a inibição de TH1 e estimulação de células T, componentes chave na defesa do organismo. O objetivo é explicar os mecanismos, além de listar o impacto que essa vitamina tem não apenas no desenvolvimento do corpo humano, mas também contra diversas doenças, evitando uma pandemia de deficiência de vitamina D e suas consequências. Este estudo revisou artigos publicados entre 2010 e 2023, selecionando aqueles que forneceram as contribuições mais significativas. Evidências indicam que uma suplementação adequada de vitamina D pode reduzir o risco de diabetes tipo 2 em até 76% e o risco de desenvolvimento de certos tipos de câncer em 66%, além de ser benéfica em casos de covid-19 grave e outras doenças. Pessoas obesas frequentemente apresentam níveis mais baixos de vitamina D, complicados por polimorfismos em receptores que podem afetar a absorção da vitamina. O estudo objetiva destacar a eficácia da vitamina D na prevenção de doenças e alerta para a deficiência global dessa vitamina. Concluímos que estratégias de conscientização e intervenções direcionadas são essenciais, especialmente para aqueles em grupos de risco, para reduzir a pandemia persistente de deficiência de vitamina D em nível mundial.
Palavras-chave: Vitamina D; Câncer; Exercício; Infecções; Obesidade; Atividade física.

Resumen
La vitamina D es una prohormona esencial que desempeña un papel fundamental en la salud humana, ayudando a la respuesta inmunitaria mediante la absorción de minerales esenciales como el calcio, el fosfato y el magnesio. También contribuye a la inhibición de TH1 y la estimulación de las células T, componentes clave en la defensa del organismo. El objetivo es explicar los mecanismos, además de enumerar el impacto que esta vitamina tiene no solo en el desarrollo

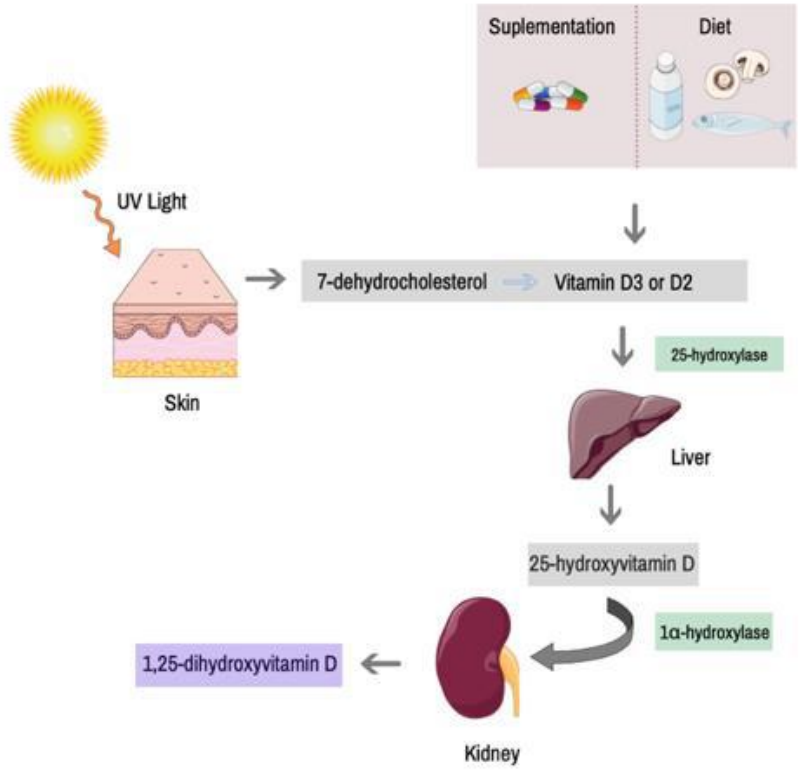
del cuerpo humano, sino también contra diversas enfermedades, evitando una pandemia de deficiencia de vitamina D y sus consecuencias. En este estudio se revisaron los artículos publicados entre 2010 y 2023, seleccionando aquellos que aportaban las contribuciones más significativas. Las pruebas indican que una suplementación adecuada de vitamina D puede reducir el riesgo de diabetes tipo 2 hasta en un 76% y el riesgo de desarrollar ciertos tipos de cáncer en un 66%, además de ser beneficiosa en casos de covid-19 grave y otras enfermedades. Las personas obesas suelen tener niveles más bajos de vitamina D, lo que se complica por polimorfismos en los receptores que pueden afectar a la absorción de la vitamina. El estudio pretende destacar la eficacia de la vitamina D en la prevención de enfermedades y alerta de la deficiencia mundial de esta vitamina. Se concluye que las estrategias de concienciación y las intervenciones específicas son esenciales, especialmente para los grupos de riesgo, para reducir la persistente pandemia de deficiencia de vitamina D en todo el mundo.
Palabras clave: Vitamina D; Cáncer; Ejercicio; Infecciones; Obesidad; Actividad física.

1. Introduction

Vitamin D is a steroid-based prohormone that enhances intestinal absorption of minerals such as calcium, phosphate, and magnesium. Such activity prevents the development of rickets in children and osteoporosis in elder people, but also helps against inflammatory processes, diabetes, infections, cancer, and other diseases (Koo & Walyat, 2013).

Vitamin D, a term used to ergocalciferol (D2) cholecalciferol (D3), can be obtained in three ways: sun exposure, diet, or supplementation. The 7-dehydrocholesterol (7-DHC), present in the skin, when exposed to sunlight forms vitamin D3 (Fletcher et al., 2022). After that, vitamin D in the liver undergoes an enzymatic reaction, through 25-hydroxylase (P450 group), into 25-hydroxyvitamin D (25OHD). Soon after, the next enzymatic reaction in the kidneys follows, with the help of 1α-hydroxylase, which converts 25OHD (CYP27B1) into the biologically active hormone, also called calcitriol or 1,25-dihydroxyvitamin D. As for food, vitamin D, whether D2 or D3, arises from its absorption in the intestine with the help of fats and bile, the origin of this compound can be given by some plants, fungi (D2), animal food sources (D3), or fortified foods, and it then follows the reactions in the liver and kidneys to arrive at its active form. However, it is also possible to directly supplement, mainly, D2, D3 or 25OHD. Both D2 or D3 follow two steps of hydroxylation process, but with different metabolization (Wilson et al., 2017). Vitamin D3 binds more easily to vitamin D protein and is degraded more slowly than vitamin D2, being a better option for supplementation than vitamin D2 (Figure 1) (Tripkovic et al., 2012).

Figure 1 - Metabolism of Vitamin D.



Source: Authors.

During sun exposure, when in contact with the skin, stimulates the transformation of 7-dehydrocholesterol into vitamin D3. Otherwise, whether vitamin D3 or vitamin D2 can be given by food sources. Furthermore, in the liver, the reaction will occur to transform vitamin D3 or D2 into 25-hydroxyvitamin D by means of the 1α-hydroxylase enzyme. Thus reach the bioactive form, 1,25-dihydroxyvitamin D (Figure 1).

This study highlights the importance of vitamin D, and our objective is to explain mechanisms, in addition to listing the impact that this vitamin has not only on the development of the human body, but also against various diseases, avoiding a pandemic of vitamin D deficiency and its consequences (Holick, 2017).

2. Methodology

The methodology used in this study is qualitative (Pereira et al., 2018) and it describes an approach for a narrative literature review (Casarin et al., 2020), with a descriptive and exploratory character. The focus is on its implications for immune response, cancer combat, obesity, infections, and physical activity. With a qualitative nature, the research seeks to synthesize and understand the available evidence regarding the interactions of vitamin D in the human body.

The chosen databases for the search were PubMed, SciELO, and Google Scholar, recognized for their wealth of scientific productions in the fields of health and biomedicine. The descriptors employed included terms such as "vitamin D," "cancer," "exercise," "infections," "obesity," and "physical activity," using AND for cross-referencing information and refining results. This procedure aimed to identify articles that articulate multiple aspects of vitamin D's impact in different clinical contexts.

In the inclusion criteria, we selected peer-reviewed articles published between January 2010 and Dezember 2023, in

Portuguese, English, and Spanish, focusing on studies that addressed the effects of vitamin D on public and clinical health, with quantitative and qualitative data regarding absorption, active metabolites, and impacts on various population groups. For the exclusion criteria, we disregarded articles that did not discuss direct physiological or therapeutic effects of vitamin D, as well as duplicate or irrelevant content to the central objective, along with abstracts from congresses, theses, or dissertations without peer review.

Data collection and synthesis involved extracting information from selected articles, organized into themes to facilitate analysis. An analytical-synthetic approach was employed to integrate findings and discuss their implications in clinical practice and public health, confirming the reliability of results through the inclusion of various studies from diverse regions and demographic groups. The main objective of this methodology is to provide a comprehensive understanding of the benefits and limitations of vitamin D, as well as to indicate areas that could benefit from further research, contributing to improved health practices and disease prevention.

3. Results and Discussion

3.1 Ideal status of vitamin D

An ideal level of vitamin D may vary in each region, but, in general, values below 50 nmol/L or 20 ng/ml of 25(OH)D are considered deficient (Amrein et al., 2020). Despite the fact that the status of vitamin D has increased in the world in recent years, the world is still experiencing a pandemic period of vitamin D deficiency, with very low levels in countries in the Middle East and some countries in Asia, but almost 50% of people in developed countries like the USA (Forrest & Stuhldreher, 2011).

Among the factors that explain vitamin D deficiency are lack of sun exposure, use of sunscreen, diet, little physical activity, increased body mass index and socioeconomic status (Lips et al., 2021).

In addition, even with sun exposure, supplementation and food rich in vitamin D sources, some people may be deficient in this vitamin due to polymorphisms in the gene of its receptor, impairing its absorption (Abdollahzadeh et al., 2021). Over 1000 genes somehow regulate the active compound of vitamin D: 1,25-dihydroxyvitamin D (Dhanapal & Vimaleswaran, 2022). But, for those who do not have a level of vitamin D deficiency, the benefits can be many in immunity, whether against cancer, infections, obesity, and other diseases with suppression of molecules or process like prostaglandin, NF-κB signaling, p38 protein stress, IL-6, IL-8, IL-10, and TGF-Beta (Liu et al., 2018).

3.2 Vitamin D and cancer

Vitamin D plays a role in DNA repair, antioxidant, and immunomodulation, which may be extremely important against cancer (Fleet et al., 2012). A recent prospective study showed that those who consumed the most vitamin D (≥450 IU/day vs <300 IU/day) had a 51% lower risk of developing early colorectal cancer. This association was stronger for those who ate vitamin D-rich foods compared to those who supplemented (66% lower risk versus 23% lower risk) (Kim et al., 2021).

Another randomized study of more than 25,000 people showed that supplementers had a 17% lower risk of advanced cancers (metastatic or fatal) compared with the placebo group, but for people with a BMI < 25 who supplemented, the risk of cancer metastatic or fatal was 38% lower (Chandler et al., 2020).

A pooled analysis with two randomized studies and another prospective study showed that, comparing breast cancer incidence rates, there was an 82% lower incidence rate of breast cancer for women with vitamin D concentrations greater than or equal to 60 ng/mL, compared with women with levels below 20 ng/mL (McDonnell et al., 2018).

Additionally, a randomized study with more than 2,000 elderly people tried to evaluate the effects of omega-3, vitamin D (2,000 IU/day) and exercises at home against invasive cancer. Vitamin D supplementation reduced the risk of invasive cancer by 24%, but when combined with vitamin D supplementation, omega-3 and physical exercise, the risk was 61% lower (Bischoff-

Ferrari et al., 2022).

Therefore, some studies show the benefits of vitamin D against cancer, while others do not, but in the uncertainty of the results, vitamin D brings much more benefits than risks for patients who do not have contraindications (Manson et al., 2019).

3.3 Vitamin D and infections

Several studies show the benefits of vitamin D against infections, acting as an immunomodulator, preventing the cytokine storm, regulating adaptive immunity through th1 inhibition, and stimulating T cells, being very important in the fight against Covid-19 (Ali, 2020; Dhanapal & Vimaleswaran, 2022; Jolliffe et al., 2013; Mangin et al., 2014).

A lower vitamin D status (<20 ng/ml) was more common in patients with severe or critical Covid-19 illness, with up to 14x higher risk (Dror et al., 2022).Vitamin D supplementation in Covid-19, in a randomized study, reduced the length of hospital stay by 50% (De Niet et al., 2022).

In another randomized study, patients taking 10,000 IU of vitamin D per day spent less time in the hospital, required less oxygen, and improved other clinical patterns (Cervero et al., 2022). But other studies have also shown that the benefits may be related to reduced inflammation (Karonova et al., 2022).

Meta-analyses have also shown the benefits of vitamin D in Covid. Vitamin D was associated with a 59% reduction in the odds of ICU admission or mortality from Covid-19. Vitamin D was also associated with a 73% reduction in the odds of unwanted Covid-19 events (Pal et al., 2022).

Elderly patients are a risk group for Covid-19, but with vitamin D deficiency this risk may worsen furthermore by increasing d-dimer level and oxygen support (Cheung & Cheung, 2021).

Therefore, although at the beginning of the Covid-19 pandemic there was not much evidence about vitamin D and Covid-19, today there is a lot of evidence that shows benefits outweighing the risks, especially for groups with comorbidities and worse prognosis for the disease. Moreover, the same was observed for other infections such as influenza (Zhu et al., 2022).

3.4 Vitamin D and obesity

Obesity is a chronic disease that affects more than 650 million people around the world and is considered a risk factor for several diseases. Obese people have a lower level of vitamin D (Karampela et al., 2021). A recent study showed that vitamin D supplementation worked best in people who are not overweight. This explains why, even when supplementing, overweight people still have little health benefit from vitamin D (Tobias et al., 2023).

A meta-analysis showed a 41% higher risk of vitamin D deficiency in obese children and adolescents (Fiamenghi & Mello, 2021). This data is quite alarming for overweight people and should serve as a basis for supplementation (Pittas et al., 2023). In addition, obese people may have a higher glycemic index, a factor that is reduced by up to 30% with vitamin D supplementation. Obesity can be a risk for several diseases that the risk can be reduced with an optimal vitamin D status. Therefore, vitamin D for the obese public can be extremely beneficial.

3.5 Vitamin D and physical activity

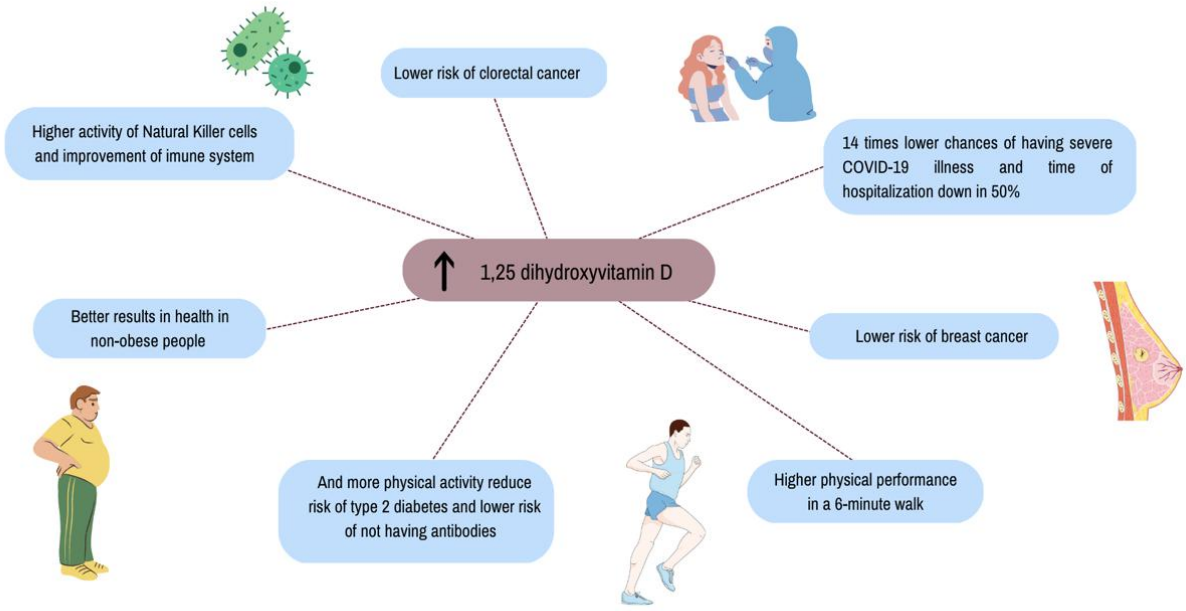
Previous studies have already shown that the level of vitamin D can increase with physical activity (Fernandes & Barreto, 2017). When they assessed whether vitamin D status was correlated with the physical performance of those people who survived Covid-19, vitamin D deficiency was detected in 35% of people, with a percentage of 40% in people aged 65 and over, risk group for covid.

This vitamin D deficiency was associated with 176% higher risk in another study, higher BMI, severity of Covid and lower physical performance in a 6-minute walk (Figure 2) (Galluzzo et al., 2022; Pittas et al., 2023).\

The activity of Natural Killer (NKA) cells in more than 2000 people with an average age of 48 years was evaluated in another study. NKA cells are part of the innate system and help fight various diseases Figure 2.

Compared with men with low serum 25(OH)D (<20 ng/mL), men with better vitamin D levels (30-39.9 ng/mL) had a 65% lower risk of very low NKA. In women, little exercise or moderate/high exercise had a 48% lower risk of low NKA compared with no exercise (Figure 2).

Figure 2 - The increase of the bioactive form of vitamin D (1,25 dihydroxy vitamin D) generates a series of reactions in the body that interfere with the immune system, which results in lower chances of cancer, lower risk of developing severe Covid, better performance in physical activities and lower risk of type 2 diabetes.



Source: Authors.

Furthermore, in men and women over 60 years of age, physical exercise significantly decreased the risk of low NKA (Oh et al., 2021). These data show that vitamin D, along with physical activity, can help to have a better immune response, reduce the severity of Covid and reduce the risk of type 2 diabetes.

3.6 Vitamin D and vaccine

Reinfections of diseases are common in vaccinated or recovered people. Since the emergence of omicron, Covid vaccines have had their effectiveness greatly impaired, which can cause more deaths due to Covid-19 (Offit, 2023).

A study evaluating serology data from over 5,000 people vaccinated with AstraZeneca or Pfizer showed the relation between antibodies and vitamin D levels. Those who ingested vitamin D had a 27% lower risk of not having more antibodies after vaccination (Jolliffe et al., 2022).

The explanation for this fact may be: antiviral activity of vitamin; regulation of the innate immune response, helping in a more robust immune response; regulation of adaptive immunity, aiding in a more specific immune response; modulation of the ACE2 receptor and the renin-angiotensin system, acting against the entry of the virus into cells; Interaction of vitamin D with the most potent natural antiviral (interferon-I), helping in a good immune response; and other specific mechanisms (Chiu et al.,

2021).

3.7 Risks and Misuse of Vitamin D Supplementation

Vitamin D supplementation is widely recognized for its health benefits, including improving bone density and strengthening the immune system (Ruscalleda, 2023). However, inappropriate and excessive use can lead to significant health risks, highlighting the importance of clear guidelines and public education on its safe use (Silva Pantoja et al., 2023).

The main risk associated with excessive use of vitamin D is toxicity, more specifically hypercalcemia, a condition in which there is a harmful accumulation of calcium in the blood(Silva Pantoja et al., 2023; Ruscalleda, 2023). This excess calcium can cause a variety of adverse effects, including gastrointestinal symptoms such as nausea and vomiting, muscle weakness, fatigue, calcification of organs and soft tissues, and kidney complications that can lead to kidney failure (Silva Pantoja et al., 2023). In more serious cases, it can result in heart problems and even coma(Silva Pantoja et al., 2023). Studies indicate that toxic levels can be reached with a daily intake of more than 10,000 IU of vitamin D, the risk of hypercalcemia increases significantly (Ruscalleda, 2023)Studies indicate that toxic levels can be reached with a daily intake of more than 10,000 IU of vitamin D, when the risk of hypercalcemia increases significantly (Ruscalleda, 2023).

Several factors contribute to the misuse of vitamin D. Firstly, easy and unrestricted access to supplements, often sold as over-the-counter medicines (OTCs), promotes self-medication without proper medical advice (Silva Pantoja et al., 2023). In addition, widespread misinformation, which reinforces the perception that “the more, the better”, encourages excessive use (Ruscalleda, 2023). Another aggravating factor includes prescription errors, in which inappropriate doses are recommended without the need for confirmation through preliminary tests, such as those for serum 25(OH)D levels (Silva Pantoja et al., 2023).

It is crucial that healthcare professionals exercise caution when prescribing vitamin D, ensuring that adequate doses are administered based on clinical data (Ruscalleda, 2023). It is recommended that dosages are carefully adjusted to individual needs, considering factors such as age, weight, underlying health conditions and sun exposure received (Ruscalleda, 2023).

4. Conclusion

The data therefore suggests that vitamin D plays an important role in protecting against a variety of diseases, helping to reduce the risk of future complications. This study reinforces its importance, highlighting its ability to strengthen bone health through the absorption of essential minerals such as calcium, phosphate and magnesium, and to act as an effective modulator of the immune system. These benefits are particularly relevant in the fight against serious infections, such as Covid-19, where vitamin D has been associated with a reduction in the severity of symptoms and length of hospital stay.

In addition, there is substantial evidence that adequate levels of vitamin D can help prevent cancers and reduce the adverse effects of obesity. People who maintain good levels of this vitamin often have a lower risk of developing certain types of cancer and see improvements in problematic metabolic factors commonly found among obese patients.

Vitamin D deficiency persists as a significant global public health challenge, affecting diverse regions and highlighting the need for effective strategies to improve its availability and consumption. This includes balanced diets, appropriate supplementation and controlled sun exposure. Although many countries have managed to raise the levels of this vitamin in their populations, we are still facing a “pandemic” of vitamin D deficiency, affecting more than 50% of the population in some areas.

Continued awareness of the benefits of vitamin D impacts on an improved quality of life, however, special attention to correct supplementation practices is needed to help avoid reducing the benefits through adverse effects, emphasizing the need for health education and structural policies that support the safe use of vitamin D.

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