

Vitamin D as a drug: new therapeutic approaches

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Abstract

Vitamin D is one of the essential vitamins and has recently been demonstrated to be much more important for the appropriate functioning of the human body and well-being than initially believed. Although vitamin D is mainly known for its link with bone fractures and bone diseases, recent studies revealed that vitamin D and its analogues have revealed many pharmacological actions covering the regulation of cell growth, inhibition of inflammation, and improvement of neuromuscular function and immune function. Moreover, vitamin D and its analogues are reported to have role in different types of cancers, skin diseases, diabetes mellitus and infections caused by different bacterial and viral pathogens including SARS-CoV-2. The goal of this study is to evaluate the scientific literature on therapeutic uses of vitamin D and its analogues against different diseases and health condition. Special attention has been given to COVID-19 infection, cancer, skin diseases, and diabetes. The molecular mechanisms involved are also explored.

Keywords

calcidiol, calcitriol, vitamin D3, SARS-CoV-2

Introduction

Vitamin D comprises a collection of fat-soluble secosteroid organic compounds that have anti-rickets properties. The key D vitamins are vitamin D2 (ergocalciferol) and D3 (cholecalciferol) (Raposo et al. 2017; Melguizo-Rodríguez et al. 2021), in which the name “calciferol” comes from the words “calcium” and “ferro.” This name is intended to illustrate the fact that this vitamin is necessary for maintaining healthy bones and calcium levels. Currently, vitamin D deficiency is believed to be one of the most persistent health complications. It

seriously disturbs the body’s homeostasis and increases the threat of certain cancers, type 2 diabetes, and cardiovascular diseases (Melguizo-Rodríguez et al. 2021). It is obvious that the administration of vitamin D to a person suffering from hypovitaminosis D compensates for this deficiency and removes the symptoms of the disease. But in the case of people who are not suffering from deficiency, vitamin D administration may exert certain pharmacological effects that can be used for therapeutic purposes, such as preventing infection and alleviating the effects of COVID-19 (Ali 2020; Meltzer et al. 2020).

Occurrence

It is estimated that 90–95% of the vitamin D required is generated through skin synthesis, while diet is the secondary source of this vitamin in the human body (Aydin et al. 2019). The cholecalciferol form of vitamin D is found in animal products, while ergocalciferol is found in plant-based products. Vitamin D₂ is produced from the provitamin ergosterol, which is found in yeast (Hnokaew and Yammuen-Art SYA 2021), milk, butter, and especially fish oil. Under the influence of ultraviolet radiation, the provitamin dehydrocholesterol is formed in the skin.

Several years ago, it was found that actual vitamin D₃ is calcitriol, while cholecalciferol is a provitamin that is converted to calcitriol in the kidneys (Whiting et al. 2021). Alfacalcid is derived from vitamin D₃ as a very strong metabolite that is used in conditions when the body is unable to convert cholecalciferol into calcifediol due to kidney dysfunction. Thus, it is used for patients with liver and kidney injury who have symptoms of hypovitaminosis D (Galassi et al. 2021).

Pharmacokinetics

Absorption; vitamin D₃ is a lipid-soluble molecule that is absorbed into the lacteals in the gastrointestinal tract through chylomicrons. It is then transported via the lymphatic system and subsequently into the blood stream (Charoenngam et al. 2021). **Distribution;** the bound phase of circulating vitamin D₃ is around 60%, and the free phase is quickly eliminated into the muscle, and adipose tissue due to the action of lipoprotein lipase (Haddad et al. 1993). **Metabolism;** metabolism of this vitamin takes place in the liver to (25(OH)D) (Haddad et al. 1993). Next, 25(OH)D is metabolized by 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) in the kidneys into the active metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D) (Holick 2007). **Excretion;** vitamin D₃ is mainly excreted through the bile into the feces. As part of the absorbed vitamin D is diluted in the adipose tissue, obese individuals have high risk of vitamin D deficiency (Lespessailles and Toumi 2017; Wortsman 2000).

Pharmacodynamics

The role of the vitamin D receptor in the functioning of vitamin D₃ in the body

Vitamin D receptor (VDR) mediates the hormonal function of calcitriol in several physiological processes in the human body (Uberty 2016; Shang and Sun 2017). VDR is a representative of the steroid-thyroid – retinoid superfamily of nuclear transcription factors, which are directly activated via small lipophilic molecules that are responsible for the regulation of gene transcription (Saksa et al. 2015). This receptor is expressed in more than 38 types of human cells and in almost all organs, including the hair follicles, muscles, bone marrow, ducts of the gastrointestinal tract, and the brain (Guo et al. 2013; Bakke and Sun 2018; Lee et al. 2018).

Calcitriol interacts with the receptors via two pathways: the classical genomic associated pathway, where calcitriol interacts with the nuclear VDR, and the non-genomic pathway, where this vitamin interacts with the membrane VDR (Venter et al. 2001). It has been proven that 1,25-dihydroxycholecalciferol can regulate about 3–5% of genes in the human genome by activating VDRs (Chen et al. 2016). Genes that are controlled by VDRs are responsible for regulating the metabolism of calcium and its absorption from the gut, as well as cell proliferation and differentiation, the hair growth cycle, and function of the immune system, among others (Guo et al. 2013). One of the target genes for VDR is *CYP24A1*, which controls the level of calcitriol (Chen et al. 2016).

Role in the body

Vitamin D is vital for the appropriate functioning of the whole body, particularly through its effects on metabolic processes (Wisniewska and Szybowska 2021). This vitamin is an essential and basic factor that determines proper calcium management in the body (together with calcitonin and para-thyroid hormones, which are also secreted in the thyroid gland) (Prentice et al. 2013). Vitamin D principally augments the absorption of calcium and phosphate from the gastrointestinal tract and prevents their excretion in the urine, thus elevating the blood-calcium concentration and enhancing the deposition of calcium phosphate in the bones. Therefore, proper bone mineralization depends on the presence of adequate levels of these vitamins, and without them, calcium does not accumulate in the bones (Prentice et al. 2013). Vitamin D also has important roles in many extra-skeletal targets (Fig. 1), including the immune system, central nervous system and cardiovascular system (Bouillon 2017; Bouillon et al. 2019).

Potential therapeutic uses

SARS-CoV-2 virus infection

Vitamin D₃ has been suggested as a possible adjunct therapy for COVID-19 due to the in vitro observations of antiviral and protective effects against respiratory tract infections (including rhinovirus and respiratory syncytial virus infections), as well as its immunomodulation effects (Ling et al. 2020; Tan et al. 2020). It has been suggested that vitamin D₃ can decrease the intensity of viral infection by inducing antimicrobial peptides and enhancing cellular immunity. This occurs by decreasing the concentration of pro-inflammatory cytokines and increasing the concentration of anti-inflammatory cytokines (Wang et al. 2021a). It is also generally accepted that vitamin D₃ may prevent complications of COVID-19 by regulating the renin-angiotensin system (RAS) (Figs 2, 3), innate and adaptive cellular immunity, and the integrity of physical barriers, as well as supporting the control of comorbidities, such as hypertension and diabetes (Annweiler et al. 2020).

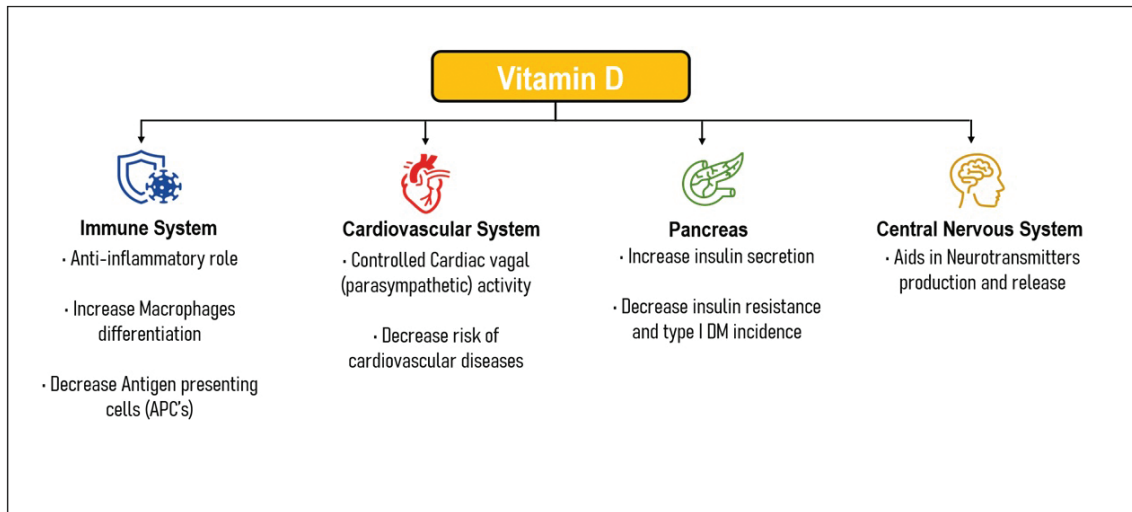


Figure 1. Extra-skeletal importance of vitamin D in different body systems.

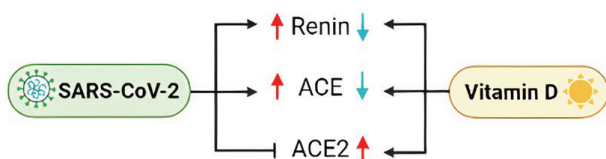


Figure 2. Potential therapeutic role of vitamin D for COVID-19.

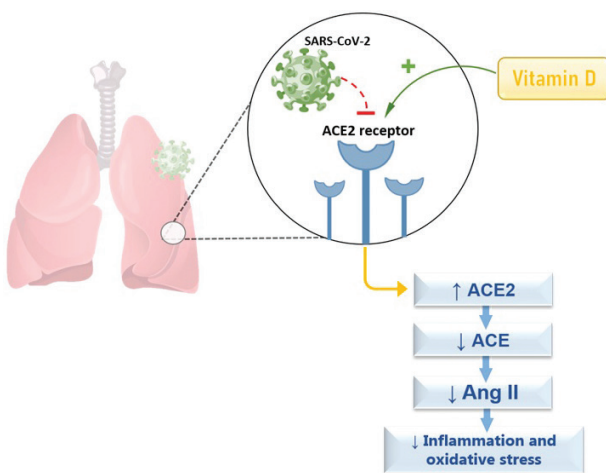


Figure 3. Mechanism of action of vitamin D supplementations in treatment of COVID-19.

A number of clinical studies have examined or are currently exploring the relationship of vitamin D3 with SARS-CoV-2 infection. A retrospective cohort study showed that people infected with the SARS-CoV-2 virus had more than two-times lower serum concentrations of calcidiol on average than those in the control group (11.1 ng/ml and 24.6 ng/ml, respectively, $P = 0.004$) (D’Avolio et al. 2020). Another observational study examined data from 20 different European countries and showed a negative correlation between the mean serum concentration of calcidiol and the morbidity and mortality caused by COVID-19 (Ilie et al. 2020). This result is also supported by retrospective observational studies conducted on a group of 130 people aged 76 ± 13 years, half of which were the control group. The authors postulate that vitamin D3

deficiency in patients was associated with a more severe course of COVID-19, longer duration of the disease, and the risk of death in the elderly (Sulli et al. 2021). All of these studies show the effectiveness of vitamin D3 supplementation as an adjunctive therapy in the treatment of COVID-19. However, further studies on much larger, representative groups of people are necessary.

Vitamin D is reported to have a protective effect against SARS-CoV-2 infection, which prompted its inclusion in both preventive and treatment regimens for COVID-19. Serum vitamin D concentration is reported to serve as predictor of SARS-CoV-2 infection, which is independent of age, sex, race and attitude (Ilie et al. 2020). In comparison to placebo, a single high dose of vitamin D is reported to have an immediate beneficial effect on hospitalized COVID-19 patients in terms of shortening the duration of hospitalization and reducing the need for mechanical ventilation (Jaun et al. 2022)

Although some progresses have been made in understanding the molecular basis of action of vitamin D, the total picture is not clear. However, enhanced expression of antimicrobial proteins, defensin and cathelicidin which are reported to play important role in the infection outcome process of various bacterial and viral agent (Kearns et al. 2015; Fiske et al. 2019; Tomaszewska et al. 2022) is speculated to have an important role in vitamin D induced protective functions in SARS = CoV-2 infection. Additionally, vitamin D is also speculated to have a protective effect in alleviating COVID-19 infection especially in patients with severe symptoms and lung damage as it is reported to have a similar role in enhancing lung immunity in respiratory diseases (Hansdottir and Monick. 2011).

SARS-CoV-2 infection is often leads to neurological symptoms such as loss of smell and taste, dizziness and confusion as a result of damages to the neurons caused by the virus. Vitamin D exerts neuroprotective effect by regulating the production of neurophilins, which are key factors modulating survival, differentiation and proliferation of neurons. Studies have shown that vitamin D promotes the migration and proliferation of oligodendrocytes,

enhancing the remyelination of damaged neurons in animal models (Gomez-Pinedo et al. 2020), suggesting a possible mechanism through which it can alleviate neurological symptoms. Taken together, these findings highlight the importance of vitamin D as an adjunct therapeutic agent against infection caused by SARS-CoV-2.

Cancer diseases

Increasing evidence suggests that vitamin D and its derivatives exhibit antitumor effects in mice (Aslam et al. 2021; Li et al. 2021) and humans (Wang et al. 2021b) and decrease the proliferation of cancer cells derived from several tissues (Hassan et al. 2022). Moreover, the expression of VDRs rises with malignant transformation and declines with advanced tumour growth, and activation of these receptors stimulates more than 60 genes, leading to pro-differentiating, anti-proliferative, and anti-metastatic effects on cells (Kim et al. 2012). It is also accepted that vitamin D and its analogues can suppress cancer cell growth by modifying cell-cycle progression and can induce apoptosis in various cancer cells (Schneider et al. 2022). Furthermore, vitamin D can enhance TNF α (Chen et al. 2021) and can act as a pro-oxidant in cancer cells (McConnell et al. 2018).

Nonetheless, the key adverse effects of vitamin D – hypercalcemia and hypercalciuria – restrict its utilization in cancer therapy (Rizzoli 2021). Therefore, more than 3000 vitamin D analogues have been synthesized, and some of them display fewer toxic effects and more effectiveness than vitamin D (Gu et al. 2021). However, large multicentre randomized controlled trials are urgently needed to explore which vitamin D analogues are effective for cancer, either alone or in combination with other anticancer drugs.

Skin diseases

Vitamin D can increase the production of several antimicrobial peptides as well as the effects of cytokine and T helper type 2 cells. Thus, using this vitamin could decrease the risk of skin infection (Umar et al. 2018). Likewise, vitamin D and its analogues are already utilized in the treatment of atopic dermatitis, psoriasis, vitiligo, acne, and rosacea. But the effectiveness of these agents varies from 4 to 53% (Kechichian and Ezzedine 2018) and this is ascribed to the enormously variable nature of psoriasis and its diverse presentations in patients (Ben-Shabat et al. 2005). Additionally, many of these agents have serious adverse effects, such as hypercalciuria and hypercalcemia (Ben-Shabat et al. 2005).

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However, it has been revealed that calcipotriol is a safe and very effective topical drug for the treatment of hyperproliferative skin diseases, such as psoriasis (McCormack 2011).

Although the mechanism of action of vitamin D and its analogues is not fully understood, it is known that this vitamin can augment keratinocyte differentiation and either activate or inhibit keratinocyte growth depending on the dose (Umar et al. 2018). Similarly, vitamin D can also elevate the production of platelet-derived growth factor (PDGF), thus supporting wound healing, as well as TNF α , which supports keratinocyte differentiation (Geilen et al. 1997). Decreased synthesis of IL-1 α , IL-6, and chemokine ligand 5 resulting from vitamin D decrease inflammation in epidermal keratinocytes (Fujita et al. 2007).

Diabetes mellitus

Both type 1 and type 2 diabetes can be prevented or treated with vitamin D and its analogues. This results from normalizing the function of the immune system, promoting B-cell survival and function, facilitating insulin secretion and glucose uptake, and controlling insulin-receptor gene expression (Sintov et al. 2014; Abdel-Rehim et al. 2019). This vitamin has been demonstrated to normalize the action of B cells and can affect the muscle and fat cells. Furthermore, it can elevate insulin action by decreasing insulin resistance as well as inhibiting inflammation, which is usually associated with type 2 diabetes (Sintov et al. 2014).

Conclusion

A growing body of clinical, experimental, and epidemiological studies suggests that vitamin D and its analogues may have therapeutic potential, particularly for the prevention and treatment of COVID-19 infection, various cancers, diabetes, and some skin diseases. Nevertheless, further long-term randomized controlled trials on vitamin D and its analogues are required to better understand their efficiency in the prevention and therapy for diseases, their adverse effects, and their molecular mechanisms of actions.

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