Chapter 10

Skeletal and Extraskeletal Benefits of Vitamin D

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Abstract

Vitamin D exerts its principal actions on bone metabolism, so it has important benefits on the skeleton. Serum 25(OH)D is directly related to bone mineral density (BMD), so subjects with lower levels have lower BMD and higher prevalence of osteoporosis and fractures, mainly hip and non-vertebral fractures. But, vitamin D has also many other beneficial effects, and its deficit has been associated with a great variety of diseases, such as asthma, cancer, diabetes, hypertension and other cardiovascular diseases, some inflammatory and autoimmune diseases, infections and some liver diseases. It is also remarkable its direct effect on muscle strength, so patients with vitamin D deficiency have higher risk of falls. Supplementation with vitamin D in patients with low 25(OH)D levels has shown a favourable effect not only on bone and muscle, reducing the risk of fracture, but also on inflammation, cell proliferation or immune system, reducing the risk of other diseases and complications. However, observational studies are needed with larger numbers of patients and well-designed randomized clinical trials, with baseline vitamin D determination and accurate monitoring to establish a cause-effect relationship between vitamin D deficiency and some diseases.

Keywords: vitamin D, benefits, skeletal, extraskeletal, osteoporosis

1. Introduction

The main vitamin D metabolite (1,25-dihydroxyvitamin D or 1,25$(OH)_2$D) exerts its biological actions through binding to Vitamin D receptor (VDR). VDR is a ligand-induced nuclear receptor that regulates the expression of over 900 genes throughout the genome. 1,25$(OH)_2$D dissociates from serum vitamin D-binding protein (VDBP) and enters the cell and binds to and activates the VDR, leading to the promotion and modulation of the expression of the targeted genes [1].

VDR is found not only in the organs responsible for calcium homeostasis (bone, kidney, intestine and parathyroid) but also in many other tissues such as immune system cells, muscle and myocardium, which explains the extraskeletal effects of this vitamin (**Figure 1**) [1].

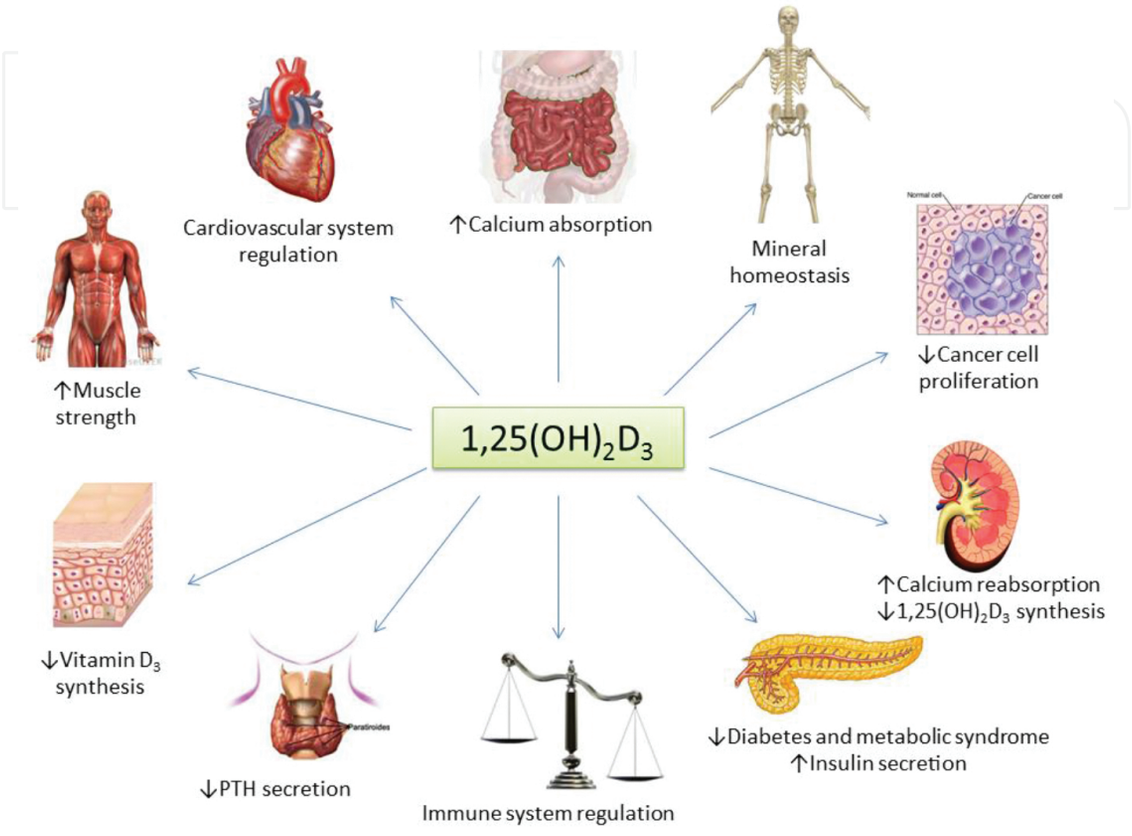

Figure 1. Principal targets and actions of vitamin D.

Serum determination of $1,25(OH)_2D$ does not have much interest, as it has a very short half-life and its levels are highly regulated by some hormones such as parathyroid hormone (PTH), so subjects with vitamin D deficiency can have normal $1,25(OH)_2D$ levels. Therefore, the best assessment of vitamin D status is provided by serum 25(OH)D levels and thus should be the only vitamin D assay typically performed, since its half-life is about 2 weeks.

2. Skeletal benefits of vitamin D

Vitamin D exerts its principal action on bone metabolism regulating the intestinal absorption of calcium and bone remodeling [2]. This vitamin is essential for the normal development of the skeleton in utero and during childhood and adolescence and also to maintain bone health in adults. Optimal levels of vitamin D are needed to achieve a proper balance of calcium and phosphorus for a normal bone mineralization. A longstanding vitamin D deficiency has been associated with growth retardation and rickets in children, and osteoporosis or, in the most severe cases, osteomalacia in adults [3].

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Serum 25(OH)D in both sexes and in all races is directly related to bone mineral density (BMD), so that people with lower levels have lower BMD and higher prevalence of osteoporosis and fractures [4]. This is, in part, because a sustained decrease in 25(OH)D induces a higher secretion of PTH (secondary hyperparathyroidism), with an increase in osteoclast differentiation and bone resorption over bone formation.

Levels of 25(OH)D are inversely associated with the risk of non-vertebral and hip fracture [5] (**Figure 2**), so patients with lower levels of vitamin D have higher risk of fracture.

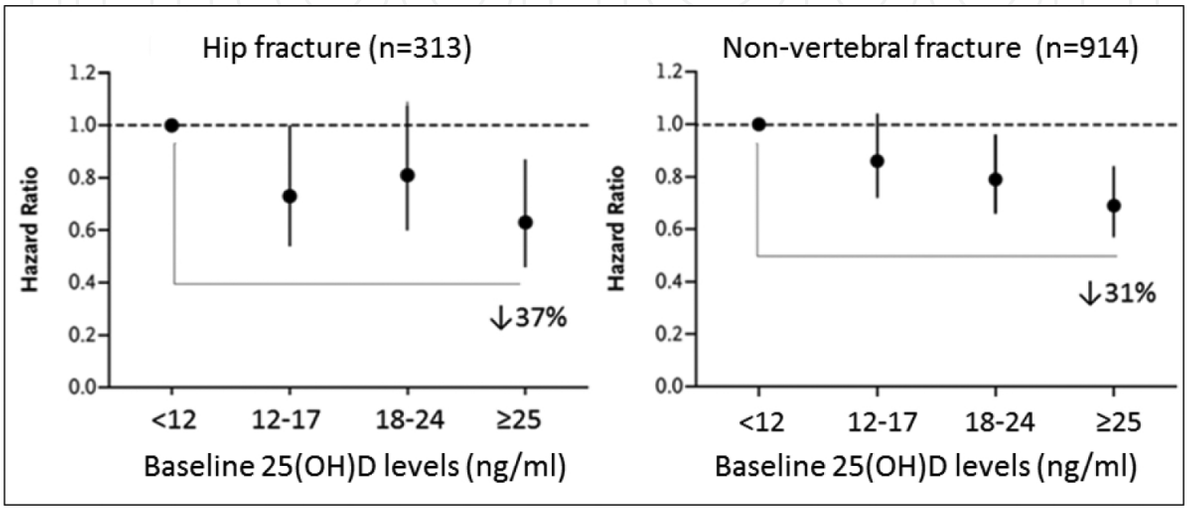

Figure 2. Risk of fracture, according to quartile of baseline 25-hydroxyvitamin D level [5].

Larrosa et al. described an association between vitamin D deficiency and the severity of hip fracture [6]. Patients with more severe femoral neck or intertrochanteric fractures (Garden III–IV and Kyle III–IV) have higher prevalence of vitamin D deficiency (74%) and lower levels of 25(OH)D (20 ± 15 ng/ml) than patients with less severe fractures (57% and 26 ± 21 ng/ml).

The supplementation with vitamin D has shown to improve the skeletal health reducing the risk of fracture.

A meta-analysis conducted by Bischoff-Ferrari et al. [7] revealed that supplementation with 700–800 IU/day of vitamin D reduced up to 23% the risk of non-vertebral fractures and 26% the risk of hip fracture, while doses <400 IU had no effect. The minimum levels of 25(OH)D to reduce the risk of hip fracture are 29.6 ng/ml. These data have served as the basis for the International Osteoporosis Foundation (IOF) to set as "optimal" 25(OH)D ≥ 30 ng/ml.

More recently, the same group conducted another meta-analysis involving more than 30,000 subjects and showing that only supplementation with high doses of vitamin D (800–2000 IU/day) had an effect in the reduction in the risk of fracture (30% for hip and 14% for non-vertebral) [5], in population over 65 years regardless of whether they were institutionalized or not.

It is controversial whether the association of calcium with vitamin D contributes to a more efficacy. In fact, in the last meta-analysis [5], patients supplemented with less calcium (<1000

mg/day) had lower fracture risk than those receiving higher doses (≥1000 mg/day). Furthermore, in another meta-analysis, the authors found that supplementation with calcium alone (without vitamin D) could even increase the risk of hip fracture. However, they recommend taking this data with caution as participants included in some trials had been receiving more dietary calcium than usual in the normal population. So, it cannot be ruled out that supplementation with calcium is most beneficial in patients with poor dietary intake.

Despite this controversy, there is sufficient evidence of benefit of calcium supplementation (preferably from diet) and vitamin D in osteoporosis patients, especially when receiving antiresorptive treatment, so that clinical practice guidelines recommend the use of combined calcium (1000–1200 mg/day) and vitamin D (800–1000 IU/day), and if not are achieved with diet should be in the form of supplements [8].

3. Extraskeletal benefits of vitamin D

In addition to its main benefits on bone health, vitamin D has many other beneficial effects and its deficit has been associated with a great variety of diseases.

3.1. Vitamin D and asthma

Vitamin D regulates certain key genes for lung growth during embryonic development, and a deficiency can lead to a change in the structure and lung function.

It has been reported that the forced vital capacity in children of both sexes is strongly associated with maternal 25(OH)D and that vitamin D deficiency in mothers is associated with an increased incidence of asthma in children [9].

The anti-inflammatory effect of vitamin D (inhibits interleukin-6 and Tumor Necrosis Factor), its immunomodulation of both the innate and adaptive immune systems and its potential antimicrobial action also contribute to explain the protective effect of vitamin D in asthma [10].

Vitamin D also enhances the response of asthmatic patients to treatment and could have a synergistic effect with steroids [11].

Some authors have even been suggested that vitamin D deficiency may be responsible in part for the increased prevalence of asthma worldwide and that 25(OH)D levels could be a potentially modifiable marker of severe asthma [12].

3.2. Vitamin D and cancer

The antitumour activity of vitamin D has been shown in a variety of malignancies, and these seem to be the main mechanisms by which this action is exerted:

– Inhibition of cell proliferation. Vitamin D inhibits the phosphorylation of some proteins, leading to inhibition of a series of genes responsible for the progression of cellular cycle [13].

– Apoptosis. Vitamin D induces cell death in some tumours through inhibition of antiapoptotic factors and/or stimulation of proapoptotic factors, depending on the cell type [14].

– Inhibition of angiogenesis. Vitamin D inhibits proliferation of endothelial cells and some angiogenic factors, such as transforming growth factor alpha (TGFα), the epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) [15]. Vitamin D also reduces the migration and invasiveness of tumour cells.

3.2.1. Breast cancer

Breast cancer is probably the most studied cancer in regard to vitamin D status. In a cohort of American women with breast cancer, authors found that women with optimal levels of 25(OH)D were up to 63% lower risk to present a breast cancer [16]. However, in prospective studies, it has not succeeded in showing any relationship between 25(OH)D and breast cancer [17]. Peppone et al. [18] in a retrospective study of 224 women with non-metastatic breast cancer concluded that vitamin D deficiency is associated with poor prognosis and quality of life. With these data, it seems reasonable to determine 25(OH)D levels in women with breast cancer and supplement those with vitamin D deficiency.

3.2.2. Prostate cancer

When we analyse the association between vitamin D and prostate cancer, the literature is more controversial. A meta-analysis published in 2014 that included 21 studies concluded that higher concentrations of 25(OH)D were associated with an increased risk of developing prostate cancer [19]. However, a more recent study has described a 30% higher risk in patients with 25(OH)D in the lowest quartile than patients in the highest quartile [20].

The use of calcitriol combined with conventional treatment in patients with prostate cancer has been proved to be effective, both in vitro and in vivo, so vitamin D enhances the antitumour effect of the conventional treatment [21]. A clinical trial of 63 patients showed that patients with prostate cancer treated with 4000 IU of vitamin D3 for one year had a lower tumour progression than controls (38 versus 63%) [22]. However, to date, there is no such randomized clinical trial with a greater number of patients that can confirm these results.

3.2.3. Colon and rectal cancer

Colon and rectal cancer have also been associated with vitamin D deficiency, especially rectal cancer. Several meta-analysis have described an inverse association between 25(OH)D and the incidence of colorectal cancer [23]. Patients with 25(OH)D in the highest quartile have 33% lower risk of developing this cancer than patients with 25(OH)D in the lowest quartile [24].

At the moment, there is no evidence that vitamin D influences in the progression of colorectal cancer, although it seems to have a protective effect on mortality [25].

3.3. Vitamin D and cardiovascular disease

Vitamin D deficiency has been associated with inflammation and endothelial and platelet dysfunction, which favours the risk of cardiovascular complications [26].

$1,25(OH)_2D$ has a direct action on myocardial cells, smooth muscle fibres and vascular endothelial cells stimulating the calcium ATPase activity, promoting the calcium transfer to the intracellular space [1]. Vitamin D also regulates blood pressure by decreasing gene expression of renin and aldosterone synthesis. All these explain why vitamin D deficiency has been associated with cardiovascular disease, including hypertension, ischemic heart disease and heart failure [27].

Patients with hypertension and vitamin D deficiency have two-fold increased risk of cardiovascular complications [28] and up to 52% more risk of stroke [29]. In these patients, supplementation with vitamin D could reduce blood pressure by decreasing the activity of renin and angiotensin II values, although this effect has not been demonstrated in all studies.

A multicenter study [30] showed that 96% of patients with myocardial infarction (MI) had 25(OH)D < 30 ng/ml. On the other hand, it is reported that 25(OH)D is an independent predictor of cardiovascular complications in patients with MI and that the risk is 40% higher in patients with levels <7.3 ng/ml [31].

However, one of the effects of vitamin D is the increase in phosphate levels and a high amount of phosphorus increases vascular calcification and, consequently, may increase morbidity and mortalidad [32]. It is, therefore, important to keep vitamin D levels in a safe threshold, where the benefits outweigh the risks.

3.4. Vitamin D and diabetes

Vitamin D also has receptors in pancreatic cells and exerts a regulatory action on glucose metabolism.

A meta-analysis revealed that vitamin D supplementation in children reduces the risk of developing type 1 diabetes (odds ratio: 0.71) [33] and also seems to prevent the development of type 2 diabetes, as evidenced by a meta-analysis published in 2012. In this study, vitamin D deficiency was associated with a 43% higher incidence of diabetes and 62% more progression of prediabetes to diabetes [34].

3.5. Vitamin D in inflammatory and autoimmune diseases

Vitamin D has been linked to many other autoimmune diseases, beyond type 1 diabetes.

Some studies have reported a higher prevalence of some autoimmune diseases at higher latitudes, suggesting that sun exposure and, therefore, the production of vitamin D may play a role in the pathogenesis of some diseases such as type 1 diabetes, multiple sclerosis and Crohn disease [33].

In patients with vitamin D deficiency has been described a higher incidence of Crohn's disease, so, in addition to its immunomodulatory effect, vitamin D promotes the function of the intestinal barrier and stimulates the synthesis of antimicrobial peptides, all of them protective factors for the development of inflammatory bowel disease (IBD) [35]. A prospective study found that vitamin D deficiency could be a risk factor for developing IBD, and higher 25(OH)D

seemed to be associated with a significant reduction in the incidence of Crohn's disease, but not ulcerative colitis [36].

Supplementation with vitamin D does not seem to improve significantly the clinical course of Crohn's disease, but it can decrease relapse in some patients.

The risk of developing multiple sclerosis is also associated with lower levels of 25(OH)D. When we analyse the association between 25(OH)D and flare-up in patients with multiple sclerosis before and after supplementation with 3000 IU/day of vitamin D, a strong negative association was found between the incidence of flares and 25(OH)D levels ($p < 0.0001$) [37].

Vitamin D seems to have a protective role in rheumatoid arthritis (RA). In a prospective cohort of nearly 30,000 women aged 55–69 years, authors found that the incidence of RA was 33% lower in patients receiving more vitamin D [38].

Low vitamin D levels have also been associated with an increased incidence and/or relapses of other autoimmune diseases such as systemic lupus erythematosus, partly due to VDR gene polymorphisms [39].

3.6. Vitamin D and infections

Vitamin D has a protective role against infections by stimulating the production of cathelicidin (antimicrobial peptide) and modulating the production of cytokines and the inflammatory cascade during the infection [40], so vitamin D deficiency has also been associated with an increased risk of infections, especially those of the respiratory tract, including tuberculosis [41].

3.7. Vitamin D and liver disease

It has also been suggested that vitamin D may play a role in the development of some chronic liver diseases such as non-alcoholic fatty liver disease, cholestatic disease and autoimmune liver disease; and that supplementation with vitamin D could improve the patient response to antiviral therapy in hepatitis C [42].

3.8. Vitamin D and falls

Vitamin D has a direct effect on muscle strength through its action on specific receptors on the muscle.

Vitamin D deficiency has been associated with type II muscle fibres atrophy, which leads to impaired muscle function and disability, increasing the risk of falls, especially in the elderly [43].

Supplementation with vitamin D at doses of 700–1000 IU/day reduces the risk of falls up to 34%, contributing to the antifracture effect [44]. This reduction in the risk of falls seems apparent already in the first 6 months of treatment with vitamin D.

Levels of 25(OH)D > 24 ng/ml are needed to achieve a significant reduction in the risk of falls (relative risk [RR]: 0.77; confidence interval [CI]: 95%, 0.65–0.90), while lower values do not seem sufficient (RR: 1.35; 95% CI: 0.98–1.84) [45].

4. Summary and conclusions

Besides the well-known benefits on the skeleton, especially as regards on reducing the risk of non-vertebral and hip fracture, vitamin D also has other favourable effects on many organs. Its immunomodulatory, anti-inflammatory, antitumour and antimicrobial effects, as well as their effects on glucose metabolism, cardiovascular system and muscle, are remarkable.

Although the association of vitamin D deficiency with many diseases, as well as the benefits of supplementation, seems clear, it is not easy to establish a cause-effect relationship. Observational studies with larger numbers of patients and well-designed randomized clinical trials are needed with accurate determination and close monitoring of vitamin D.

Conflict of interests

The author declares no conflict of interest.

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