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REVIEW

Vitamin D and musculoskeletal health

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ABSTRACT

Vitamin D is a steroid pro-hormone, with effects that are not limited to the metabolism of calcium and phosphorus, but are pleiotropic and involve cellular differentiation, the immune response, intermediate metabolism and the cardiovascular system. This fat-soluble vitamin plays a significant role in musculoskeletal homeostasis and its deficiency or mal-regulatory function leads to several bone metabolic disorders.

KEYWORDS: Vitamin D ; Metabolic bone disorders ; Musculoskeletal health

Introduction

Vitamin D belongs to the category of fat-soluble vitamins. There are two forms, vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol), of animal and plant origin respectively, which differ in chemical structure and pharmacokinetic properties. It is actually a steroid pro-hormone, with effects that are not limited to the metabolism of calcium and phosphorus, but are pleiotropic and involve cellular differentiation, the immune response, intermediate metabolism and the cardiovascular system.

Resources – Composition - Vitamin D Effects

Vitamin D3 is produced in the skin under the influence of ultraviolet radiation (UVB 290-315nm). Specifically, 7-dehydrocholesterol, upon exposure to ultraviolet radiation, is converted to provitamin D3 and then into its isomer, vitamin D3. Vitamin D then enters circulation, where it binds to its carrier protein, vitamin-D binding protein (VDBP). Other sources of vitamin D are foods (vitamin D2 - plant origin and D3 - animal origin). In this case Vitamin D is absorbed through the intestine and is transferred to systemic circulation through the lymph by chylomicrons. The two types differ in a methyl group at the C24 position and a double bond between C22-23. Despite they are equally absorbed from the digestive system, they differ in pharmacokinetics, with vitamin D2 due to less binding to VDBP, being eliminated faster. Therefore, vitamin D2, in equivalent intermittent doses, has only 30-40% of the bioavailability of vitamin D3. On the contrary, in daily administration of equivalent doses appear to have similar bioavailability.

The production of vitamin D in the skin, which constitutes at least 80% of the total daily produc-

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tion - the rest comes from food - is affected by multiple factors, among which are sun exposure, the use of sunscreens (sunscreen with an SPF > 8 limits up to 90% the synthesis of vitamin D), clothing, the amount of melanin (black people show lower levels), the time of year (significant decrease during winter), the latitude (increase in latitude is accompanied by a significant limitation of the ability to synthesis), age (decreased ability to produce vitamin D in the elderly), obesity (reduced mobilization of vitamin D from adipose tissue)[1,2,3,4], as well as genetic factors (enzyme polymorphisms involved in the conversion of 7-dehydrocholesterol to provitamin D3 and mainly VDBP polymorphisms). Studies in monozygotic twins show that genes are involved in the synthesis, metabolism and transport of vitamin D thus, interpreting 5-10% of the variability of its levels[4]. A series of studies report that the daily vitamin D intake from food is less than 5 μg (200 IU) per day in most European countries except for the Scandinavian countries, while in North America it is less than 10 μg (400 IU)[4].

After the initial synthesis of vitamin D in the skin and its binding to VDBP, it is transported to the liver where it is hydroxylated at the 25-position to form 25(OH)D. The enzyme responsible is called CYP2R1, it is expressed in the liver and the testis, it belongs to the group of cytochrome p450 oxidases, and besides vitamin D it hydroxylates cholesterol and bile acids. Its activity decreases in severe liver failure.

Then 25(OH)D is transferred to the kidney where, under the influence of CYP27A1 (1-a hydroxylase), it is converted into the active form of vitamin D, $1,25(OH)_2$ vitamin D. The "entry" of 25(OH)D into the epithelial cells of the renal tubule occurs both initial filtration from the glomerulus via the protein megalin, which is expressed on the tubular surface of the cell and the basolateral surface of renal tubular cells. Then 25(OH)D enters the cytoplasm, and with the intracellular binding protein of vitamin D it is brought to the mitochondria where it is hydroxylated by 1-a-hydroxylase to $1,25(OH)_2D$.

CYP27A1 (1-a hydroxylase) is a mitochondrial enzyme. The responsible gene is located on of chromosome 12. Alternatively, 25(OH)D is converted to $24,25(OH)_2D$ by CYP 24A1 (24-hydroxylase) and then to calcitroic acid, which is excreted in the bile. Inactivating mutation of the 1-a hydroxylase gene causes vitamin D-resistant rickets type 1, while inactivating mutations of 24-hydroxylase causes idiopathic hypercalcemia of infancy, as well as PTH-independent hypercalcemia in adults.

Beyond the renal tubule, 1-a hydroxylase is present in many tissues, such as osteoblasts, intestine, monocytes, pancreas, prostate, breast, etc. where it participates in the local production of active vitamin D. Regarding the factors that increase the activity of 1-a hydroxylase in the kidney, the main ones are PTH, hypocalcemia, and hypophosphatemia, while it is reduced in hypoparathyroidism, hypercalcemia, hyperphosphatemia, as well as by FGF23 and $1,25\ (OH)_2D3$. The differences between $25\ (OH)D_3$ and $1.25\ (OH)_2D_3$ are shown in table 1.

Vitamin D exerts genomic and rapid non-genomic actions, which mainly involve ion transport[5]. Regarding the genomic actions, vitamin D, as a steroid hormone, acts through its receptor, the VDR. In particular, $1,25\ (OH)_2$ vitamin D after entering the cytoplasm or produced locally binds to its receptor, which forms a heterodimer with the retinoic acid receptor. The complex binds to a special region of DNA called VDRE (Vitamin D Response Element), near the promoter of the corresponding gene, which is regulated by vitamin D. Then by activating co-activators or co-repressors it causes the activation or suppression of genes with consequent modification of the levels of the corresponding protein. It is estimated that 3000 genes respond to vitamin D.

It should be noted that even 25(OH)D at very high levels can exert endocrine effects, as it binds to VDR, but with a much lower affinity than calcitriol. Such action occurs in the context of hypervitaminosis D as well as when administering cholecalciferol or ergocalciferol to patients with hypoparathyroidism, where the doses used are of the order of 50,000 IU daily or more.

The positive effects of vitamin D mainly target the intestine, bone, kidney and parathyroid. Particularly:

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TABLE 1.

Vitamin D metabolite characteristics

	25 (OH)D	1,25 $(OH)_2D$
Concentration	20-150 nmol/L (8-60 ng/ml)	50-150 pmol/L (20-60 pg/ml)
Half-life time	25 days	7 hours
External effects	Sunlight, season, nutrition	immobilization, calcium intake
Hormonal adjustment	T3	PTH, cortisol, estradiol, calcium, phosphorus, FGF23
Binding to VDR	1/100 of 1,25 $(OH)_2D$	Kd 10^{-10} to 10^{-11}M

– In the intestine it causes an increase in the intestinal absorption of Ca and P, through the induction of TRVP6 channels, calbindin D9k, PMCA1 and the NaP cotransporter IIb.

– In the bones, it causes an increase in osteoblastic and osteoclastic activity, through an increase in the production of RANKL by the osteoblasts, resulting in an increase in the release of calcium and phosphorus from the bones, while it also increases the production of FGF23 by the osteocytes.

– In the kidney, it suppresses 1-hydroxylase, induces 24-hydroxylase, and increases calcium reabsorption in the distal tubule.

– In parathyroids it inhibits the synthesis of PTH and the proliferation of parathyroid cells.

In addition to the above effects, vitamin D affects multiple functions of the human body which are related to inflammation, blood pressure and tumorigenesis.

Vitamin D is associated with suppression of cell growth, increase in cell differentiation, regulation of apoptosis, immune response, differentiation of skin and hair, regulation of blood pressure (reduction of renin), increase in insulin secretion, improvement of muscle function and effect on CNS function.

Vitamin D and musculoskeletal health

As early as the 17th century due to poor socioeconomic conditions of the industrial revolution, the characteristic skeletal disorders of rickets were described, while at the beginning of the 19th century the importance of exposure to solar radiation for the prevention and treatment of rickets was highlighted. At the beginning of the 20th century, exposure of the body and milk to ultraviolet radiation was used therapeutically. In the last decade the recognition of the importance of vitamin D for both optimal musculoskeletal health and its possible extra-skeletal role has led to the need to redefine its place in clinical practice. At the same time, a series of epidemiological studies confirmed the increased frequency of hypovitaminosis D in the general population. A particular study in Germany in a pediatric population reports that levels of 25 (OH)D < 12 ng/ml and < 20 ng/ml are found in 12.5% and 45.6%, while corresponding data in adults especially from northern countries (UK) describe percentages of the order of 22% and 55% [4,6].

Vitamin D pathophysiology deficiency

Although the exact sequence of pathophysiological changes in vitamin D deficiency has not been fully elucidated in humans, a common denominator regardless of the cause (Table 2) is a decrease in intestinal absorption of calcium and phosphorus and the development of secondary hyperparathyroidism. Studies in dogs[7] under 2 years of low calcium and vitamin D intake suggest a progressive decrease in calcium levels with a concomitant increase in PTH.

PTH increases the rate of bone remodeling, resulting in an increase in the release of calcium and phosphorus from bone, a decrease in renal calcium excretion and an increase in phosphorus excretion, and a concomitant increase in calcitriol production, at least in the early stages. The increase in calcitriol partially compensates for the decrease of calcium

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TABLE 2.

Causes of Vitamin D Deficiency
• Decreased skin complexion – Use of sunscreen – age (older) – Burns
• Decreased bioavailability – Malabsorption syndrome – Obesity
• Increased catabolism – Antiepileptic, glucocorticoids, HAART, isoniazid
• 25-hydroxylase deficiency – Liver failure
• Increased loss(es) – Nephrotic syndrome
• Decreased composition of 1,25 (OH)2 D – Chronic Kidney Disease
• Genetic Causes of Rickets – Resilient to Vitamin D Type 1,2,3 – XLHR – ADHR – ARHR
• Acquired hypophosphatemia disorders – TIO

TABLE 3.

Risk factors for rickets and osteomalacia
Maternal factors
Vitamin D deficiency
Skin colour
Full coverage of the body with clothing
Stay in high altitude in winter / spring
Other causes for low sun exposure (stay outside the house, restricted mobility, pollution)
Decreased dietary Vitamin D intake
Neonatal- infant factors
Infant vitamin D deficiency due to maternal Vitamin D deficiency
Lack of complementary nutrition or substitute
Skin colour
Full coverage of the body with clothing
Stay in high altitude in winter / spring
Other causes for low sun exposure (stay outside the house, restricted mobility, pollution)
Decreased dietary Vitamin D intake
Low calcium intake
Low income, malnutrition, special dietary habits.

and phosphorus, increases their intestinal absorption and bone release. Late, further depletion of vitamin D due to consumption leads to a decrease in calcitriol levels, resulting in an even greater decrease in calcium and phosphorus levels.

Vitamin D deficiency during puberty - childhood

Rickets is a disease of the developing skeleton and is characterized by disruption of chondrocyte apoptosis, delay or failure of the mineralization of connective cartilage and osteoid, resulting in its enlargement and the appearance of characteristic skeletal deformities[8,9]. The most common cause is the lack of vitamin D or the reduced intake / absorption of calcium, which leads to a decrease in the intestinal absorption of calcium and phosphorus, secondary hyperparathyroidism with consequent further worsening of phosphorus deficiency.

Hypophosphatemia leads to a decrease in the normal apoptosis of hypertrophic chondrocytes, a phenomenon that is necessary for the development of vascularization in the connective cartilage and its subsequent mineralization. The incidence of rickets increases significantly at 25(OH)D levels < 30 nmol/L (12 ng/ml), while in full clinical expression the levels are less than 12.5 nmol/L (5 ng/ml). As a rule, it manifests itself between the 6th-24th month of life in infants with reduced exposure to the sun or under exclusive breastfeeding.

The higher frequency in the neonatal age is attributed to the limited vitamin D pool in the neonate (it is estimated that 25(OH)D levels in the umbilical cord are 50-60% of maternal levels, due to low VDBP), to the low amount of vitamin D in breast milk and in the significant dependence of the intestinal absorption of calcium on vitamin D

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TABLE 4.

Recommended Vitamin D intake from the American Institute of Health and the Endocrine Society. (AI: adequate intake, EAR: estimated average requirements, RDA: recommended daily allowance, DR: daily requirement, UL: tolerable upper intake level) [10, 11]

	IOM recommendations				Endocrine Society	
	AI	EAR	RDA	UL	DR	UL
Infants						
0-6 months	400			1000	400-1000	2000
6-12 months	400			1500	400-1000	2000
Children						
1-3 years		400	600	2500	600-1000	4000
4-8 years		400	600	3000	600-1000	4000
Men						
9-18 years		400	600	4000	600-1000	4000
19-70 years		400	600	4000	1500-2000	10000
> 70 years		400	800	4000	1500-2000	10000
Women						
9-18 years		400	600	4000	600-1000	4000
19-70 years		400	600	4000	1500-2000	10000
> 70 years		400	800	4000	1500-2000	10000
Pregnancy - lactation						
14-18 years		400	600	4000	600-1000	4000
19-50 years		400	600	4000	1500-2000	10000

at this age[4,8,9]. The diagnosis is made on the basis of history, clinical picture, biochemical control and is confirmed by radiological control. International clinical guidelines for the prevention of nutritional rickets (Nutritional Rickets) have recently been published which briefly state[9]:

1. Vitamin D levels

a. Adequate: > 20 ng/ml (50 nmol/L)

b. Insufficiency: 12-20 ng/ml (30-50 nmol/L)

c. Deficiency: < 12 ng/ml (<30 nmol/L)

d. Toxicity: > 100 ng/ml (>250 nmol/L)

2. Calcium nutrients to prevent rickets

a. Neonates- infants: 0-6 months of age : 200 mg & 6-12: 260 mg

b. Children > 12 months calcium intake < 300 mg increases rickets risk.

c. Classification of nutrition calcium intake for children > 12 months of age

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TABLE 5.

Indications for testing for of vitamin D Deficiency [11,14]
• Rickets, osteomalacia
• Osteoporosis
• Adults with a medical history of falls, low energy fractures
• Chronic Kidney Disease
• Liver failure
• Malabsorption syndrome – Fibrocystic disease – Inflammatory Bowel Disease – Bariatric surgery – Radiation enteritis
• Hyperparathyroidism
• Medication
• Pregnancy - lactation
• Athletes (indoor sports)
• Obesity
• Granulomatous diseases
• Certain lymphoma

i. Adequacy: > 500 mg/day
ii. Insufficiency: 300-500 mg/ day
iii. Deficiency: < 300 mg/ day

3. Vitamin D administration to prevent rickets / osteomalacia

a. Neonates-infants 0-12 months: 400 IU (10 μg) day

b. children > 12 months: 600 IU (15μg) day via supplements or diet

4. Areas of population (Table 3)

a. Healthy children do not need Vitamin D preventive check up

b. Candidates for Vitamin D supplements after the age of 12 months old lacking in Vitamin D nutrition

i. Children with symptomatic Vitamin D Deficiency
ii. High risk Vitamin D Deficiency Children and Adults
iii. Pregnancy

5. Rickets treatment

a. Minimum dose of vitamin D 2000 IU/day and 500 mg calcium for 3 months

b. Oral administration of vitamin D is the most effective

c. Vitamin D2 and D3 in daily administration are equally effective

d. On intermittent administration D3 is more effective

a. Universal vitamin D supplements in all newborns and infants up to 12 months of age. After this age vitamin D supplements only in high-risk individuals and in pregnancy.

b. Monitoring the implementation of intervention strategies

c. Detection and intervention in high-risk populations

d. Implementation of informational programs at the population level

e. Evaluating the effectiveness and cost/benefit ratio of food fortification programs at the population level.

Corresponding to the above are the guidelines from the US Institute of Health for the prevention of rickets[10], while the American Endocrinology Society recommends an intake of 400-1000 IU up to 1 year and 600-1000 IU up to 18 years[11] (Table 4). Regarding the relationship between vitamin D levels and musculoskeletal health during childhood, a series of studies describe a positive association between higher levels of vitamin D and bone density, bone mineralization, intestinal calcium absorption and muscle function.

However, there are not clear data, for now, regarding children / teenagers.

Vitamin D Deficiency in adults

Osteomalacia

Osteomalacia is a disease of adults and is usually caused by long-term vitamin D deficiency. Histomorphometrically, it is characterized by an in-

crease in volume and a decrease in osteoid mineralization[12]. Osteomalacia leads to significant bone loss in the cortical bone with an accompanying increase in the risk of falls and fractures. At a clinical level, it manifests itself with a series of symptoms and signs (osteomalacia syndrome) such as bone tenderness and bone sensitivity to palpation, muscle weakness and difficulty walking, which usually go unnoticed.

Imaging show osteopenia, an increase cortical porosity, a rarely fibrous cystic osteitis due to secondary hyperparathyroidism, while Looser zones are characteristic which appear on the pelvis, scapula or less frequently on the medial surface of the femoral neck or medial surface of the diaphysis of the long bones. Laboratory findings include low 25(OH)D levels, elevated alkaline phosphatase and secondary hyperparathyroidism. Regarding 25(OH)D levels below which osteomalacia occurs, most agree that 25(OH)D levels ≥ 20 ng/ml rule out osteomalacia.

Nevertheless, a recent study of bone biopsies in more than 600 subjects, who passed away of violent death, showed that a percentage of patients (» 20%) with 25(OH)D levels between 20-30 ng/ml have static histomorphometric findings of osteomalacia, while all patients with levels above 30 ng/ml had a normal biopsy. The treatment is recommended to correct hypovitaminosis D.

Osteoporosis

In recent decades the undisputed role of vitamin D in the musculoskeletal system has made both its determination and its use as a therapeutic agent a prerequisite in the evaluation and treatment of osteoporosis. Nevertheless, even today there is a dichotomy[10,11] regarding the ideal levels of vitamin D for optimal musculoskeletal health, due to the lack of consensus on the ideal endpoint (intestinal calcium absorption, PTH levels, bone density, rate of bone loss, fractures, falls) and, on the other hand, the conflicting results of several clinical trials. .

The definition of ideal levels of vitamin D and consequently the recommended daily intake varies according to the population being tested. Consequently, the US Institute of Health sets ideal levels of 25(OH)D ≥ 20 ng/ml (50 nmol/L)[10] in the general population, while the IOF[13] and the American Society of Endocrinology[11] set a goal of ≥ 30 ng/ml (75 nmol/L) in patients with metabolic bone diseases.

ESCEO[14] characterizes levels of 25(OH)D < 10 ng/ml as vitamin D deficiency, levels of 10-20 ng/ml as vitamin D deficiency, while levels > 20 ng/ml are considered sufficient, with the exception of some elderly individuals where values > 30 ng/ml probably lead to a better outcome regarding falls and fractures. 25(OH)D values > 50 ng/ml are likely to be associated with adverse effects.

The lack of unanimity regarding ideal vitamin D levels, therapeutic targets, and corresponding replacement doses is attributed to a lack of adequate data in the general healthy population regarding the effects of vitamin D deficiency, the absence of well-designed intervention studies with clear endpoints in specific populations, and in the lack of reliability of measuring the levels of 25(OH)D in daily clinical practice. For example, regarding intestinal calcium absorption, a study by Heaney[15] in postmenopausal women showed that an increase in 25(OH)D from 20 ng/ml to 34 ng/ml is associated with an increase in intestinal calcium absorption by 40-60%, while a recent, better-designed study found that increasing 25(OH)D levels from 20 to 66 ng/ml results in only a 6% increase in intestinal calcium absorption, which is significantly reduced at levels below 10 ng/ml[16].

The relationship between PTH levels and 25(OH)D is not linear, with PTH levels increasing exponentially at lower levels of vitamin D. At the same time, there appear to be significant differences depending on race (blacks show an increase in PTH at levels of 25(OH)D < 16 ng/ml vs. white 24 ng/ml), the duration of hypovitaminosis, the presence of pathological conditions (functional hypoparathyroidism in diabetes mellitus, smoking, hypomagnesemia, etc.).

Conversely, studies addressing the restoration of PTH levels by correcting hypovitaminosis have conflicting results, with some showing further PTH reduction at 25(OH)D values > 30 ng/ml and others not. It is possible that the differentiation of

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the results is related, among other things, to the duration of the maintenance of ideal 25(OH)D levels as sufficient time (more than 6 months) is required for the correction of secondary hyperparathyroidism[17].

Studies concerning the relationship between 25(OH)D and other endpoints, more characteristic of osteoporosis, show an almost linear association between vitamin D levels and bone density as well as the rate of bone loss. In addition, a series of studies (generally case-control) show a significant increase in fracture risk in the context of hypovitaminosis D (clinical fractures, hip fractures, non-vertebral fractures) in the white race and in both sexes[18]. However, a recent WHI analysis does not confirm the association of low 25(OH)D levels and fractures in postmenopausal black women[19].

Regarding the intervention studies with the endpoint reduction of fractures and falls, the data are conflicting due to the different controlled populations (community, institutional patients, with or without osteoporosis), the different doses [400 to and above 800 IU daily, intermittent administration (weekly, monthly, yearly)], in the parallel administration of calcium as well as in the degree of compliance. Nevertheless, most meta-analyses conclude that the administration of vitamin D with calcium in doses between 480-770 IU/day and the achievement of 25(OH)D levels around 30 ng/ml are associated with a reduction in the risk of non-vertebral fractures by average 20%[13,20], while there is a reduction in the risk of falls by 18%[21]. In addition, in all clinical studies of approved osteoporosis drugs (calcitonin, bisphosphonates, SERMS, strontium ranelate, denosumab, teriparatide-complete parathyroid hormone) calcium and vitamin D were co-administered at doses of 400-800 IU daily.

Special conditions

Pregnancy – Lactation

The past few years, vitamin D deficiency in pregnancy and lactation is closely related to multiple endpoints for both the mother and the fetus – newborn baby[22]. During pregnancy, significant amounts of calcium are transferred from the mother to the fetus, especially during the 3rd trimester, where it is estimated that the daily transfer approaches 300 mg. Adaptation occurs through an increase in intestinal absorption of calcium. In contrast during lactation, where approximately 300 mg of calcium is transported per day, the adaptation occurs through an increase in bone mobilization of calcium through PTHrp.

It is noted that during pregnancy, 25(OH)D passes through the placenta, a transfer which determines the levels of vitamin D in the newborn, while in breast milk, in addition to calcium, calciferols (D2 and D3) are transferred and not 25 (OH)D. The prevalence of hypovitaminosis D is particularly high worldwide (18% to 80%) and has been associated with a higher incidence of preeclampsia, gestational diabetes mellitus, preterm delivery, caesarean section, low birth weight and reduced BMC/BMD of the newborn. Additionally, the effect of vitamin D deficiency on the intrauterine programming of the fetus is discussed given the pleiotropic actions of vitamin D.

However, Vitamin D Intervention studies have basically failed to prove effectiveness. Two recent studies, conducted in the EU[23]and the USA[24] describe a marginal benefit in infant wheezing and asthma with cholecalciferol administration during pregnancy at doses of 2800 IU/day vs. 400 IU/day and 4400 IU/day vs. 400 IU/day respectively.

Based on the above data, von Mutius E & Martinez FD in the editorial[25] that followed suggest that the administration of higher doses of cholecalciferol than recommended (≈ 2800 IU) to women at high risk for giving birth to children with asthma (e.g. history of asthma, eczema, allergic rhinitis) to be a trial strategy, subject to confirmation by new studies with sufficient sample size. Finally, the MAVIDOS[26] study was recently published, which concerns the administration of 1000 IU of vitamin D3 versus placebo during pregnancy, with the primary endpoint being the newborn's bone mass.

Vitamin D administration was not associated with a significant benefit in terms of bone mineral density, with the possible exception of neonates born in winter. It was also found that risk factors

for 25(OH)D levels < 20 ng/ml at the 34th week of pregnancy are: 1. Delivery in winter, 2. Weight gain during pregnancy, 3. Reduced 25(OH) levels during the 14th week, 4. non-white race and 5. Low compliance. The IOM recommends an intake of 600 IU/day in pregnancy and lactation, while the American Endocrinological Society 600-1000 IU for ages 14-18 and 1500-2000 IU for over 18.

Chronic Kidney Disease

Disorders of bone and mineral metabolism (CKD-BMD) occur early in the course of CKD and are characterized by secondary hyperparathyroidism, bone disease, and vascular calcifications. The main causes are related to phosphorus retention and disturbances in vitamin D metabolism.

The progressive decrease in calcitriol levels during the progression of renal disease is attributed to the decrease in 1-a hydroxylase activity due to a decrease in renal mass, increase in FGF23 due to hyperphosphatemia, to a decrease in the supply of 25(OH)D to the kidney due to a decrease in the expression megalin (protein which is responsible for endocytosis of 25(OH)D). Due to the high frequency of hypovitaminosis D in the context of CKD and its association even with mortality, the control of 25(OH)D levels is recommended in all patients with impaired renal function, with ideal values of 30 ng/ml[27]. Although there is not much intervention data, it seems that restoring ideal levels of vitamin D is safe, leading to a decrease in PTH levels up to stage 3 CKD, after which you usually require the administration of vitamin D analogues. Nevertheless, restoring vitamin D deficiency even stage 5 CKD is advocated due to its pleiotropic actions.

Pleiotropic effects of Vitamin D[28,29]

Apart from the proven bone activity of vitamin D, already at the beginning of the 20th century it was observed that children with rickets presented, in addition to the musculoskeletal disease, an increased frequency of respiratory infections. In 1903 Finsen (Nobel prize in medicine) used ultraviolet radiation to treat cutaneous tuberculosis (lupus vulgaris), while in 1915 Hofman observed that cancer mortality was higher in populations far from the equator.

The recognition in recent decades that calcitriol exerts important actions in multiple tissues beyond the classic ones (bones, intestine) such as in the skin, large intestine, breast, pancreas, brain, T and B lymphocytes, macrophages, where VDR is expressed, as well as that calcitriol can be synthesized locally dueto the local expression of 1-a-hydroxylase in the above tissues, linked the observation of hypovitaminosis D with a series of diseases such as neoplasms (cancer of the breast, colon, esophagus, prostate, pancreas), autoimmune diseases (multiple sclerosis, type 1diabetes mellitus), infections (tuberculosis), skin diseases (psoriasis), intermediate metabolism diseases (type 2 diabetes), CNS diseases (dementia) and cardiovascular diseases.

A series of in vitro studies document that vitamin D improves differentiation and inhibits cell proliferation, inhibits angiogenesis and induces apoptosis, increases insulin secretion, reduces renin, increases the production of cathelicidin, a peptide that facilitates the destruction of Mycobacterium tuberculosis.

To date, numerous epidemiological studies describe an important relationship between hypovitaminosis D and the above disorders, while some intervention studies describe a reduction in the occurrence of the above diseases by restoring vitamin D levels to values above 30 ng/ml.

Despite this, there is a lack of data from well-designed studies with endpoints in the above diseases, except for psoriasis, where topical vitamin D analogues are already used with good results.

Consequently, despite the abundance of basic research data and observational studies regarding the beneficial relationship of higher vitamin D levels with multiple non-skeletal diseases, such as malignancies, reproductive function, infections, cardiovascular diseases, neurological diseases, data from well-designed randomized trials with clearly defined endpoints, well-defined populations of interest, specific vitamin D dosing regimens, specific 25(OH)D target levels to test both the efficacy and safety of achieving higher 25(OH)D levels are lacking or failed to show significant effect.

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Treatment of vitamin D deficiency

The treatment of low vitamin D includes two phases, first the restoration of the lack/insufficiency and second the long-term maintenance of ideal levels. It is estimated that for every 100 IU (2.5 μg) of vitamin D administered, 25(OH)D levels increase by 1 ng/ml (2.5 nmol/L). Even today there are many questions regarding the form of vitamin D (D2 vs. D3) that is more effective, the dose, the route, and the intervals of administration.

From a pharmacokinetic point of view, the absorption from the digestive tract of calciferols (D2 or D3) is similar.

Administering calciferol during hypovitaminosis D leads to a rapid increase in its hydroxylation at the 25- position with a plateau at 25(OH)D levels of approximately 34 ng/ml[30]. Calciferols are then removed from the circulation, either metabolized and eliminated with faster metabolic clearance of D2, due to reduced binding to VDBP, or stored in adipose tissue (probably D3 is better stored than D2).

Regarding the use of vitamin D analogues (calcitriol and alphacalcidol) its use should be limited to patients with impaired renal function, patients with hypoparathyroidism as well as to patients with hereditary or acquired hypophosphatemic disorders. Their use to treat vitamin D deficiency is not indicated, as it does not increase 25(OH)D levels (possibly even reducing them) and it does not provide the necessary substrate for the formation of calcitriol locally in the tissues. Finally, the adequacy of replacement cannot be tested as, as mentioned, it does not restore 25(OH)D levels.

Regarding the effectiveness of the various regimens, it is clear that vitamin D3 in intermittent regimens (weekly, monthly) is superior to D2, due to the faster clearance of D2[31], oral administration is superior to parenteral administration, daily versus intermittent administration and the total dose. Studies concerning the route of administration show that 25(OH)D levels increase rapidly after administration of 300,000 IU D3 per os[32], while at least 2 months are required for 25(OH)D levels to increase after intramuscular administration.

Regarding the intermittent administration of vitamin D both for the restoration of hypovitaminosis and for the chronic maintenance of ideal levels, it probably excels in terms of compliance compared to daily regimens, nevertheless cumulatively significantly larger doses are required to achieve the same effect. In addition, there is increasing data regarding the safety of administering large doses of vitamin D either intermittently or in large daily doses to elderly patients.

In particular, a study in the elderly with oral administration of 500,000 IU D3 orally once a year[34] showed an increase in the risk of fractures and falls during the first trimester, a phenomenon that was attributed either to the rapid improvement in the mobility of the subjects and consequently an increase in falls, or in the rapid decrease in vitamin D levels after the initial large increase, a phenomenon possibly related to the seasonal distribution of fractures.

Another one-year study[34] in elderly community patients with satisfactory baseline vitamin D levels found that vitamin D3 administration at doses of 60,000 IU/month vs. 60,000 IU/month in combination with calcifediol vs. 24,000 IU/month for one year did not improve muscle function, but was accompanied by an increase in falls compared to the group receiving 25,000 IU/month. In this study achieving 25(OH)D levels between 44.7-98.9 ng/ml vs. 21-30 ng/ml was associated with a 5.5-fold greater risk of falls. Corresponding data were described in a recent study[35] with daily administration of vitamin D where correction of hypovitaminosis was accompanied by a reduction in falls, while achieving high levels was unexpectedly associated with an increase in falls.

These data raise serious questions regarding the safety of large single doses of vitamin D on a long-term basis in elderly subjects (monthly doses > 50,000 IU) and possibly also the target levels of 25(OH)D in these groups (values > 45 ng/ ml probably related to an increase in falls).

In any case, a prerequisite for the safe restoration of vitamin D deficiency is the previous determination of calcium and PTH. In vitamin D[11] deficiency, administration of 50,000 IU vitamin D3/week/8 weeks or 5000-6000 IU vitamin D/day/8 weeks

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(D2/D3) is recommended.

An interval of at least 3 months is required from the start of treatment to assess the efficacy of the regimen by determination of 25(OH)D, while the restoration of PTH levels may be delayed even longer. Regarding the maintenance of ideal vitamin D levels, the recommended daily dosage varies according to the 25(OH)D target that is set.

If we aim for levels > 20 ng/ml, which are recommended by most international organizations, taking 800 IU/day is sufficient in most cases (probably longer doses are required for obesity, ongoing losses, malabsorption syndromes, etc.), while if we aim values above 30 ng/ml, then a higher total daily dosage of 1500-2000 IU/day or more is required, with an upper safe daily dose based on IOM of 4000 IU/day and 10000 IU according to the guidelines of the American Endocrine Society.

Hypervitaminosis D[36]

Hypercalcemia occurs in 0.2% and 4% of the general and hospitalized population, respectively, with the most common causes being primary hyperparathyroidism and hypercalcemia due to malignancy. Classically, hypercalcemia is divided into PTH-dependent and PTH-independent. Hypervitaminosis D refers to PTH-independent hypercalcemia, as PTH levels are low.

The frequency of hypercalcemia due to hypervitaminosis D is low, however, the widespread use of vitamin D supplements, vitamin D analogs as well as the identification of inactivating mutations in the metabolic pathway of vitamin D clearance (24-hydroxylase-CYP24A1) may lead to an increase in the frequency. In general, doses up to 10,000 IU for a short period of time appear to be safe, while hypervitaminosis D has not been described at vitamin D levels < 50 ng/ml (125 nmol/L).

Laboratory tests show an increase in calcium, phosphorus, 25(OH)D (usually > 150 ng/ml), hypercalciuria, suppression of PTH, while the levels of $1,25(OH)_2$ are not particularly elevated. Pathophysiologically, hypercalcemia is due to VDR activation by 25(OH)D, while the involvement of increased endogenous synthesis of 5,6-trans-25(OH)D_3 is also suspected, a derivative that can activate the receptor. In addition, hypercalcemia after administration of vitamin D can occur in the presence of granulomatous disease (sarcoidosis, tuberculosis, leprosy, systemic mycosis, Wegener's disease, Crohn's disease, etc.), inactivating mutations of CYP24A1, Williams-Buren syndrome, hypophosphatasia, etc.

Finally, hypercalcemia can be caused much more often during the administration of vitamin D analogs, especially when they are administered in large doses in combination with calcium. Treatment consists of stopping vitamin D, hydration or administration of furosemide, corticosteroids or, in extreme cases, extrarenal dialysis.

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