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SEIOMM recommendations on the prevention and treatment of vitamin D deficiency

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Summary

Objetive: Provide evidence-based recommendations for preventing and treating vitamin D deficiency .
Methods: A multidisciplinary working group made up of 10 members of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM), formulated the clinical questions of interest. Subsequently, a systematic review of the literature was carried out in MEDLINE (PubMed), EMBASE and Cochrane on the available evidence for each of the questions posed. Articles published in English or Spanish between July 15, 2016 and December 31, 2020 were included. To establish the strength of the recommendations and the degree of evidence, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used. After the formulation of the recommendations, these were discussed jointly in the working group and ratified by all SEIOMM members.
Results and conclusions: This document establishes a series of recommendations on optimal concentrations and screening for 25-hydroxyvitamin D deficiency, vitamin D requirements in different populations, sun exposure and supplementation strategies in patients with deficiency.

Key words: vitamin D, nutrition, 25-hydroxyvitamin D, osteoporosis, fracture, cholecalciferol, calcifediol.

1. Introduction

Since its discovery, a century ago, we have advanced in the knowledge of what was erroneously called "vitamin" D. We now know that it is not a vitamin, but we continue to call it that out of custom and tacit consensus. In fact, it is an endocrine system, the vitamin D endocrine system (VDES), similar to that of other steroid hormones. Cholecalciferol or "vitamin" D3, is the threshold (physiological) nutrient of the system, synthesized from 7-dehydrocholesterol in the skin, by the action of ultraviolet B (UVB) solar radiation. This route represents about 80-90% of the contribution to the body, the rest is obtained from the diet (10-20%)[1]. There is another isoform, of nutritional contribution, called ergocalciferol or "vitamin" D2 that is found in small quantities in foods of vegetable origin, yeasts and fungi, not commonly used in Spain[2,3].

Both cholecalciferol and ergocalciferol are biologically inactive precursors, requiring metabolic modifications to activate the hormonal function of the system. Through the action of the liver enzyme 25-hydroxylase (CYP2R1/CYP27A1 and others), the hydroxylation of cholecalciferol and ergocalciferol occurs to form 25-hydroxyvitamin D_3 (caldidiol or calcifediol) and 25-hydroxyvitamin D_2 (ercalcidiol), respectively. 25-hydroxyvitamin D (sum of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3) has a long half-life (2-3 weeks) and it is the prohormone. It is the prohormone of VDES. It's measurement is used as a marker of the nutritional status of the system.

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1,25-dihydroxyvitamin D_3 is the substrate for the synthesis of 1,25 (OH) $_2D_3$ or calcitriol by the action of 1-α-hydroxylase (CYP27B1) in the kidney for its endocrine actions, and in cells of multiple tissues, organs and systems, such as skin, parathyroid gland, breast, colon, prostate, lung, as well as cells of the immune system and bone, for their auto/paracrine actions. Calcitriol is the hormone of the system and has a very short half-life (5-8 hours).

1-α-hydroxylase in the kidney is regulated, through a feedback mechanism, by parathyroid hormone (PTH), the increase of which leads to an increase in the production of calcitriol, which, in turn, inhibits the production of PTH. Hypophosphatemia and fibroblast growth factor 23 (FGF23) also regulate 1-α-hydroxylase, increasing and decreasing the production of calcitriol, respectively.

The binding of calcitriol to the vitamin D receptor (VDR), a nuclear transcription factor present in cells of multiple organs, determines the systemic and auto/paracrine endocrine action of VDES (Figures 1 and 2).

The system uses the enzyme 24-α-hydroxylase (CYP24A1), both in the kidney (through endocrine control) and in other cells and tissues, to form the inactive metabolites 24,25-dihydroxyvitamin D and 1,24,25-trihydroxyvitamin D, from 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D respectively, which are derived after several oxidations in calcitroic acid, and other glucuronic or sulfate metabolites that are eliminated mainly by the bile, constituting an important catabolic regulation system of the metabolism of VDS.

In the blood, the metabolites of VDES are transported 88% by the transporter protein of vitamin D (DBP), and 10% by albumin, circulating only 1-2% in free form[4].

The main action of VDES, through calcitriol, is the regulation of calcium and phosphorus homeostasis and skeletal mineralization, and it does so in 4 organs: mainly in the intestine, facilitating the absorption of calcium and phosphorus; kidney, increasing the tubular reabsorption of both; parathyroids, inhibiting PTH secretion; and bone, regulating the differentiation of osteoclasts and osteoblasts and the production of mineralization regulating proteins such as osteopontin and osteocalcin[5].

Sustained vitamin D deficiency has been associated with growth retardation and rickets in children, and osteomalacia and osteoporosis in adults[6].

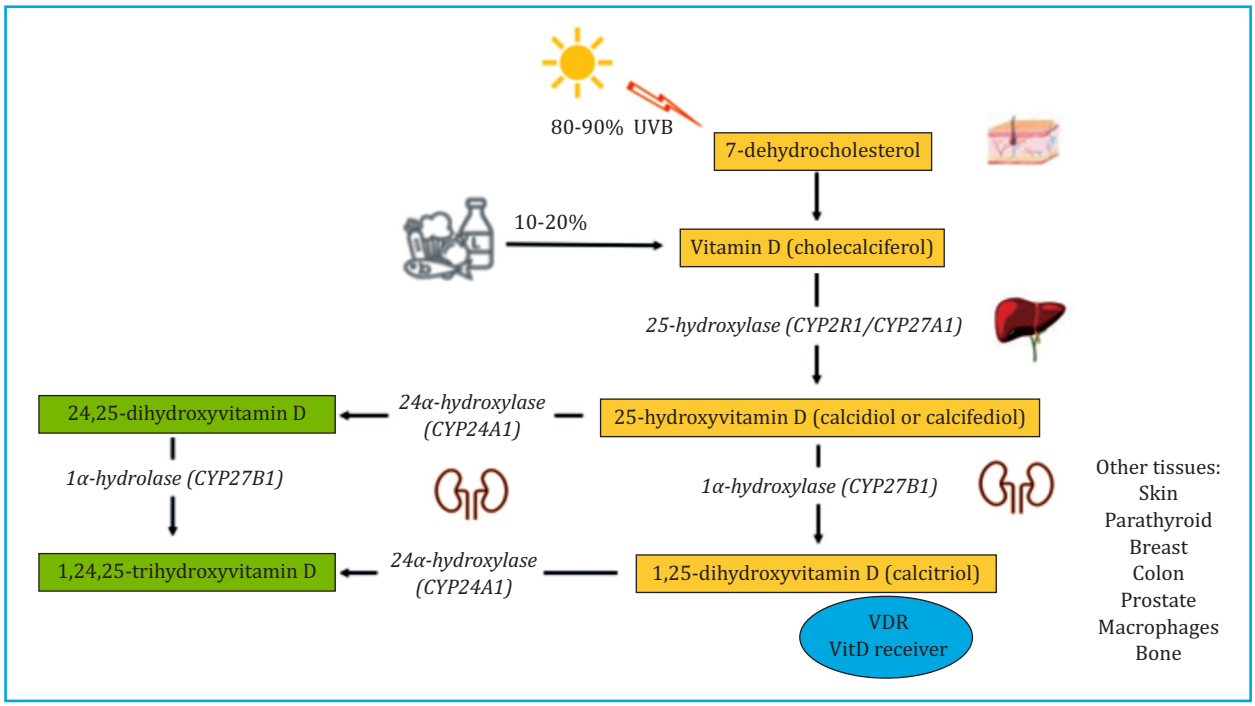
VDES modulates the expression of more than 3% of all the genes in the body, thus regulating different physiological processes in other organs and systems, such as muscle, the innate and adaptive immune system, the cardiovascular system or the pancreas, and regulates cell growth and hormone secretion throughout the body (Figure 2).

Thus, we now know that the functional deficiency of the VDES is associated not only with rickets, osteomalacia and osteoporosis, but also with an increased risk of suffering from cardiovascular, immunological, dermatological, metabolic diseases, depression, infections, infertility both male and female, pre-eclampsia and other effects on fetal development in pregnant women, and even cancer[8-16]. In this sense, in the last year it has been suggested that supplementation with cholecalciferol or calcifediol could have a beneficial effect in patients with COVID-19, an aspect that is extensively discussed in the SEIOMM position paper on COVID-19 and vitamin D[17].

Measurement of the total circulating 25-hydroxyvitamin D concentration constitutes a robust and reliable biomarker of the nutritional status of VDES. It is used by health authorities and Scientific Societies in Europe and America to establish the status of normality, which today continues to be the subject of debate.

Despite the high prevalence of "vitamin D" deficiency, even in developed countries, with high solar radiation or with easy access to supplementation, as is the case in Spain[18-20], there is no universal consensus to establish recommendations in the prevention and treatment of it.

Figure 1. Synthesis and metabolism of vitamin D



Our aim then is to update the position paper on the needs and optimal levels of 25-hydroxyvitamin D developed by the SEIOMM in 2011[21], based on the scientific evidence accumulated in recent years, and develop a series of recommendations agreed upon by experts from different disciplines on the prevention and treatment of vitamin D deficiency, focusing solely on musculoskeletal health.

2. Methodology

These recommendations have been developed in different stages, as defined below:

1) **Clinical question:** A multidisciplinary working group, composed of 10 physicians and researchers with experience in the management of vitamin D deficiency, formulated the relevant clinical questions regarding the aspects related to vitamin D treated in this document.

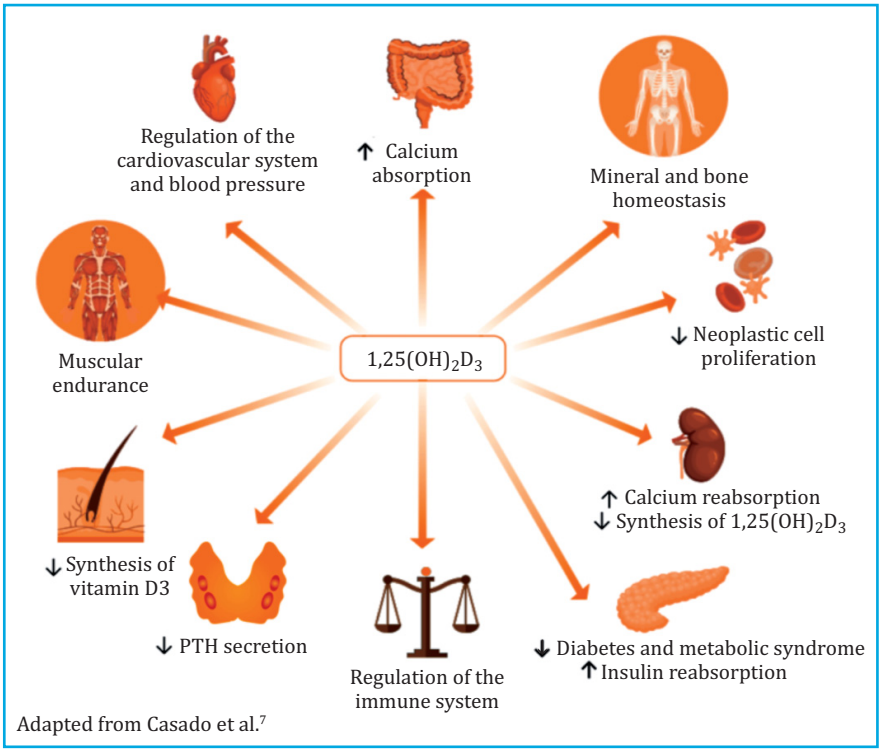
2) **Systematic literature review:** An independent team, made up of 1 doctor and 1 researcher, carried out a systematic review of the literature on studies related to the prevention and management of vitamin D deficiency. The search was carried out by consulting international databases. MEDLINE (via PubMed), EMBASE and Cochrane (Supplementary Table 1). Meta-analysis, systematic reviews, randomized controlled trials and observational studies were selected, conducted in humans and published in English or Spanish between July 15, 2016 and December 31, 2020. In addition, the potentially relevant citations of the identified articles, as well as as suggested by the working group were included.

Studies with antiresorptive or bone-forming drugs where vitamin D was not the comparator and studies conducted in Africa or Asia (except Japan) were excluded.

3) **Formulation of recommendations:** The working group established the recommendations according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to establish the degree of evidence and the strength of the recommendations[22]. The quality of the evidence is classified as very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, or high ⊕⊕⊕⊕. The recommendations are based on evidence, and other factors such as, for example, the risk-benefit balance or the estimation of the consumption of resources or costs. They differentiate between strong recommendations (expressed as "we recommend" and number 1) and weak recommendations (expressed as "we suggest" and number 2), either in favor or against. All the recommendations were debated and agreed unanimously.

4) Finally, the working group prepared a draft of this document that was distributed to all SEIOMM associates for their **ratification**, having a period of 15 calendar days to make any allegation.

Figure 2. Main target tissues and actions of vitamin D



Adapted from Casado et al.[7]

3. Relationship between vitamin D and musculoskeletal health

25-hydroxyvitamin D deficiency and/or mutations in both the VDR and the activating enzyme (CYP27B1) cause alterations in muscle and bone[23]. The relationship between 25-hydroxyvitamin D deficiency and certain bone diseases such as osteomalacia and osteoporosis has long been well known[24].

3.1. Optimal 25-hydroxyvitamin D concentrations

Recommendation

- To attain the bone health benefits provided by vitamin D, it is recommended to maintain serum concentrations of 25-hydroxyvitamin D between 25 and 50 ng/mL (62.5-125 nmol/L) [1 ⊕⊕⊕◯].

- In patients with osteoporosis or at risk of fracture, it is suggested to maintain serum concentrations of 25-hydroxyvitamin D between 30 and 50 ng/mL [2 ⊕◯◯◯].

Evidence

There is some controversy about the levels of 25-hydroxyvitamin D necessary for optimal musculoskeletal health. In general, the minimum levels established in different clinical practice guidelines are between 20 and 30 ng/mL. For healthy populations, the European Food Safety Authority (EFSA) considers sufficient levels above 20 ng/mL, while the Spanish Society of Endocrinology and Nutrition (SEEN) considers that they should be above 30 ng/mL[25]. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends levels above 20 ng/mL for postmenopausal women and above 30 ng/mL for frail elderly[26]. For its part, the Spanish Society of Rheumatology (SER) recommends maintaining 25-hydroxyvitamin D levels above 30 ng/mL for the population with osteoporosis[27].

An association between serum levels of 25-hydroxyvitamin D and bone mineral density (BMD) and muscle

strength has been described[28], and some studies suggest that levels of 25-hydroxyvitamin D equal to or greater than 24 ng/mL are associated with a reduction in the risk of falls[29] and fractures in the general population[30]. However, higher levels may be necessary to obtain other benefits beyond musculoskeletal health, taking into account that concentrations of 31 ng/mL are those that would be associated with a lower risk of mortality[31].

It has also been described that below 31 ng/mL of 25-hydroxyvitamin D, PTH levels begin to increase in certain populations[32] and the prevalence of secondary hyperparathyroidism is higher than 10%[33], a relevant aspect in patients with osteoporosis or at high risk of fracture.

In the general population, the panel considers it advisable to maintain serum levels of 25-hydroxyvitamin D above 25 ng/mL to ensure proper bone health. The analytical variability[34], the non-negligible proportion of patients with levels between 20 and 25 ng/mL who present secondary hyperparathyroidism and the increase in the intestinal absorption rate of calcium in some populations when going from 20 ng/ml to higher serum levels are reasons enough for this recommendation[35].

The recommended maximum serum level of 25-hydroxyvitamin D is also controversial, generally settling between 50 and 88 ng/mL[25,26,36]. A recent meta-analysis would support that the maximum concentrations should be in the low range, observing that the risk of mortality, although very slightly, tends to increase from 25-hydroxyvitamin D levels above 50 ng/mL[31]. In any case, it does not seem physiological to exceed 60 ng/mL, which are the maximum levels of 25-hydroxyvitamin D that are usually reached after intense sun exposure [37].

The panel considers that 25-hydroxyvitamin D values between 25 and 50 ng/mL would ensure a benefit in bone health while maintaining a good safety profile in the general population. However, and until there are more studies to corroborate these data, the panel suggests maintaining 25-hydroxyvitamin D levels between 30 and 50 ng/mL in patients with osteoporosis or at high risk of fracture.

It is not clear if the optimal values of 25-hydroxyvitamin D in the Caucasian population can be extrapolated to other types of races or ethnicities[38].

To minimize analytical variability, the panel considers it essential that the laboratory that performs the serum determination of 25-hydroxyvitamin D has the certification of a quality control program for the determinations, such as DEQAS[39] and the standardization of the determinations[40].

3.2. Screening for 25-hydroxyvitamin deficiency

Recommendation

Screening for 25-hydroxyvitamin deficiency is recommended in people with risk factors for hypovitaminosis D [1 ⊕⊕◯◯], and in people with muscle weakness and/or risk of falls [1 ⊕◯◯◯].

Evidence

Various risk factors (intrinsic and extrinsic) are related to 25-hydroxyvitamin deficiency (Table 1). Race is one of the most studied risk factors, observing that people with greater skin pigmentation have a greater risk of suffering from 25-hydroxyvitamin deficiency because UV radiation has less penetration[41]. Age is another classic risk factor due to changes in lifestyle habits (sedentary lifestyle, less sun exposure, less vitamin D synthesis capacity and less absorption capacity, etc.) and other physiological changes such as decreased blood pressure. hydroxylating capacity of vitamin D[42]. Obesity, especially related to the amount of abdominal fat, is another risk factor[43]. In addition, there are numerous risk factors that act synergistically. For this reason, screening for deficits is recommended in risk groups[25,31,41,44-49] (Table 1).

Recent studies have shown the correlation between 25-hydroxyvitamin D levels and muscle strength, mobility, and ultimately, the risk of fracture. An observational study carried out in 101 postmenopausal women suggested that low levels of 25-hydroxyvitamin D were significantly correlated with a decrease in muscle strength[44]. In a study carried out in a population over 70 years of age, it was observed how those men and women with 25-hydroxyvitamin D levels <20 ng/mL had poorer physical function and a slower gait speed than those with 25-hydroxyvitamin levels D ≥30 ng/mL ($p<0.01$)[50]. Loss of muscle strength/sarcopenia, along with other age-specific factors, could increase the risk of falls in people with bone loss, who are already at increased risk of fracture. In this sense, two recent meta-analysis carried out in more than 50,000 adults show that low levels of 25-hydroxyvitamin D are associated with significant increases in the risk of global fracture and hip fracture[30,51].

In addition, due to the risk of fracture in people with hypovitaminosis D, after a fall, screening is considered appropriate in subjects with muscle weakness and at risk of falls.

3.3. Vitamin D requirements

3.3.1. Feeding

Recommendations

- A daily intake (diet and/or supplements) of at least 600 IU of vitamin D_3 is suggested in children and adolescents[2 ⊕⊕◯◯].
- A daily intake (diet and/or supplements) of at least 800 IU of vitamin D_3 is suggested in the general adult population, and 800-1,000 IU in postmenopausal women and men over 50 years of age [2 ⊕⊕◯◯].
- A daily intake (diet and/or supplements) of 800-2,000 IU of vitamin D_3 is suggested in patients with osteoporosis, fractured patients and/or institutionalized elderly. [2 ⊕⊕◯◯].

Table 1. Risk factors and/or diseases associated with hypovitaminosis D

- Non-Caucasian race
- Old age and/or institutionalized people
- Restricted sun exposure
- Smoking
- Cognitive impairment
- Obesity (particularly abdominal)
- Malnutrition or risk of malnutrition
- Malabsorption syndrome or bariatric surgery
- Kidney or liver failure
- Hypo and hyperparathyroidism
- Rickets and/or osteomalacia
- Osteoporosis and/or fragility fractures
- Paget's disease of bone
- History of fracture
- Pregnancy and breastfeeding
- Use of drugs that interfere with cytochrome P450, such as:
  - Glucocorticoids
  - Antiepileptics
  - Antiretrovirals
  - Antifungals
  - Rifampicin

Table 2. Estimated vitamin D content according to food

	Vitamin D per 100 gr
Milk and derivatives	
Cheese	0.17 - 1.2 µg (6.8 - 48 UI)
Yoghurt	0.2- 1 µg (8 - 40 UI)
Whole milk	0.3 µg (12 UI)
Skimmed milk	0.1 µg (4 UI)
Milk curd	0.21 µg (8.4 UI)
Eggs and derivatives	
Hens eggs	2 - 11.4 µg (80 - 456 UI)
Meat products and derivatives	
Lung (lamb-veal)	11 - 12 µg (440 - 480 UI)
Duck	1 µg (40 UI)
Boiled ham	0.7 - 0.9 µg (28 - 36 UI)
Chicken, rabbit	0.2 - 0.4 µg (8 - 16 UI)
Fish, mollusks, crustaceans and derivatives	
Elver (raw)	110 µg (4,400 UI)
Salted herring	40 µg (1,600 UI)
Caviar	35 µg (1,400 UI)
Tuna, bonito, smoked herring and conge	3.5 - 34 µg (140 - 1,360 UI)
Smoked salmon and prawn	18-19 µg (720 - 760 UI)
Pomfret, horse mackerel, bream, and salema	14-16 µg (560 - 640 UI)
Anchovies (in vegetable oil)	11.8 µg (472 UI)
Sardine, salmon, perch, anchovies, swordfish, cod	7 - 8 µg (280 - 320 UI)
Oyster (raw)	3 µg (120 UI)
Fats and oils	
Cod liver oil	210 µg (8,400 UI)
Butter (low calorie)	12 µg (480 UI)
Margarine	2.5- 3.8 µg (100 - 152 UI)
Cereals and derivatives	
Cereals (wheat, rice, corn, muesli)	4 - 8 µg (160 - 320 UI)
Legumes, seeds, nuts and derivatives	
Almond milk	5 µg (200 UI)
Vegetables, vegetable derivatives	
Borage	13 µg (520 UI)

UI: international units BEDCA network[65]. https://www.bedca.net/bdpub/.

Evidence

Vitamin D requirements are those that ensure that 25-hydroxyvitamin D levels are maintained within the optimal range (25-50 ng/mL). The recommended intake of vitamin D has varied considerably over the past decades[21] and is still the subject of debate. In large part, the difference in existing criteria between different societies is due to the population to which they are directed: general population or patients with special needs[52,53].

The recommendations contained in this document are based on previous evidence, and especially on that published in recent years. To determine the amount of vitamin D that ensures optimal 25-hydroxyvitamin D values, we have compiled clinical trials and meta-analysis in which different cohorts (placebo versus vitamin D; or different doses of vitamin D) are compared by analyzing the levels of 25 -hydroxyvitamin D achieved. It is important to note the heterogeneity observed between the studies in relation to the results obtained, the levels considered adequate, and the baseline characteristics of the populations analyzed. Similarly, not in all the studies the vitamin D provided by the diet is strictly collected (Table 2), or adequate controls or adherence monitoring to the intervention are carried out, which makes the interpretation of the results difficult.

Until new studies supply more conclusive data, the panel is inclined to make conservative recommendations.

Premature infants: A recent study suggests that doses of 1,000 IU/day (diet plus supplement) of vitamin D achieve significantly higher values of 25-hydroxyvitamin D at 4 weeks than doses of 600 IU/day. However, at 8 weeks these differences would not be significant, and it is also observed that calcium levels reach a steady state at 4 weeks[54]. Given the lack of recommendations in preterm infants from the main guidelines, the panel considers a minimum intake of 600 IU/day advisable in premature infants.

Children and adolescents: The Institute of Medicine (IOM) recommends a dietary allowance of 400 IU/day in children under 1 year and 600 IU/day from 1 to 7 years[55]. In a recent meta-analysis that included a total of 5,403 children between the ages of 2 and 18, it was observed that age or sex would not affect vitamin D requirements[56]. In children under one year of age, no significant differences have been observed in the percentage of children

reaching values> 20 ng/mL between doses of 600 IU/day (supplement plus diet) and doses of 1,000 to 1,800 IU/day. These results would suggest that intakes of 600 IU/day would be as adequate to achieve optimal levels of 25-hydroxyvitamin D as higher doses. On the other hand, in a clinical trial carried out in Canadian children (2-8 years old) that compared the diet with dairy products fortified in vitamin D and without fortification (in a period of minimum UVB), the levels of 25-hydroxyvitamin D were higher than the 20 ng/mL in 85% of the subjects who consumed fortified dairy compared to 70% of the subjects in the control group[57].

Postmenopausal women: The daily intake of vitamin D recommended by the National Osteoporosis Foundation and the Institute of Medicine, for the prevention of hypovitaminosis D in women over 50 years of age is 800 to 1,000 IU/day[58,59]. In this sense, two randomized clinical trials[42,58] would suggest that intakes of 800 IU/day might not be sufficient, while doses of 1,000 IU/day would allow the majority of women (≥75%) to achieve 25-hydroxyvitamin D levels >20 ng/mL. For this reason, the panel recommends a daily intake (diet and/or supplements) of at least 800 IU of vitamin D in the general adult population (including pregnant or lactating women), and 800-1,000 IU in postmenopausal women. and men over 50 years of age.

Patients with osteoporosis or at high risk of vitamin D deficiency: The vitamin D requirements necessary for the population at risk of deficiency could vary considerably taking into account the special needs of each population. A randomized clinical trial carried out in 297 postmenopausal women with osteopenia or osteoporosis, suggests that supplementation with 800 IU/day (regardless of the contribution by diet), could be sufficient to maintain or moderately increase (~7 ng/mL) the 25-hydroxyvitamin D levels[60]. It should be noted that in this study, conducted in Norway, women ingested more than 8 µ/day (320 IU/day) of vitamin D in their diet and had baseline 25-hydroxyvitamin D levels >30 ng/ml, so these results cannot be extrapolated to other populations. Another study carried out in fractured elderly suggests that 85% would reach 25-hydroxyvitamin D levels above 20 ng/mL at 4 weeks with doses of 800 IU/day[61]. In the case of institutionalized elderly, a recent study suggests that 2,000 IU/daily of vitamin D are necessary to achieve optimal levels of 25-hydroxyvitamin D in plasma in the long term[62], while other studies suggest that lower daily intakes (1,000 IU/day) might be enough[63,64].

3.3.2. Sun exposure

Recommendation

- A 15-minute daily sun exposure on the face and arms is recommended in the Caucasian population between the months of March and October, with a protection factor between 15 and 30, depending on the latitude and intensity of the radiation. In the elderly population and in patients with osteoporosis, the recommended daily sun exposure would be 30 minutes [1 ⊕⊕◯◯].

Evidence

It is difficult to ascertain exactly the amount of vitamin D produced with sun exposure since it depends on factors such as age, skin phototype, season, time of day or geographical latitude[66].

Several studies have addressed this issue, such as one carried out in Japan that indicates that, in the afternoon hours during the summer months, 3.5 minutes of sun exposure would produce 5.5 µg of vitamin D3 (approximately 220 IU). However, in the winter months it could take between 22 minutes and 271 minutes depending on the time and weather conditions[67]. Other authors suggest that exposing 20% of the body surface to a minimum erythema dose of 0.5 would be equivalent to ingesting 1,400-2,000 IU of vitamin D[68]. Finally, in a recent meta-analysis, a mathematical formula has been postulated that would allow determining the increase in 25-hydroxyvitamin D based on the radiation received, the basal level of 25-hydroxyvitamin D and the area of the body exposed[69]. According to this formula, on a day with a moderate radiation index, a 12-minute sun exposure on the face and hands would be sufficient to increase the 25-hydroxyvitamin D level by 6.3 ng/mL. However, it does not take into account the differences that exist according to skin type.

The Australian Society for Endocrinology and Osteoporosis establishes specific recommendations such as sunbathing for 6 to 40 minutes a day on the face and arms depending on latitude, time of day, season and skin type[70].

However, the increased risk of developing melanoma due to excessive sun exposure has meant that dermatological societies such as the American Academy of Dermatology recommend that the source of vitamin D be through nutrition and not by sun exposure (outdoors or in UVB cabinets)[71]. The European Academy of Dermatology and Venereology notes the risk of using sun booths to ensure adequate 25-hydroxyvitamin D levels, but does not specifically restrict limited sun exposure[72,73]. Other societies, however, do state that adequate sun exposure is an appropriate source of vitamin D. Thus, the Spanish Society of Dermatology and Venereology considers it healthy to combine limited sun exposure and adequate nutrition.

A group of experts, based on a review of the literature, showed that the use of sun creams, even with a high protection factor (30 or more), does not interfere with the skin synthesis of vitamin[74].

To maintain skin synthesis of vitamin D, the panel recommends a 15-minute daily sun exposure on the face and arms in the Caucasian population during the months of March and October. In the elderly population and patients with osteoporosis, the panel recommends a daily sun exposure, between the months of March and October, of about 30 minutes, provided there are no contraindications, and also advising the use of a protection factor between 15 and 30, depending on latitude and intensity of UVB radiation[74].

3.4. Vitamin D supplementation

3.4.1. General recommendations

Recommendation

- It is recommended to use cholecalciferol or calcifediol to supplement or treat patients with 25-hydroxyvitamin D deficiency, reserving calcitriol and alfacalcidol for populations with special diseases [1 ⊕⊕◯◯].

- It is suggested to assess the dose and type of metabolite required based on the baseline levels of 25-hydroxyvitamin D, associated pathology and characteristics of the individual [2 ⊕◯◯◯].

- It is recommended long-term supplementation in the population at risk of 25-hydroxyvitamin D deficiency (<25 ng/mL) [1 ⊕⊕◯◯].

- Low-dose vitamin D supplementation is recommended, except when rapid normalization of 25-hydroxyvitamin D concentrations is necessary [1 ⊕⊕◯◯].

- Monitoring serum concentrations of 25-hydroxyvitamin D is suggested to assess the response to supplementation every 3-4 months until adequate concentrations are reached, and then every 6 or 12 months [2 ⊕◯◯◯].

- In patients treated with calcifediol at a dose of 266 µg, it is suggested that 25-hydroxyvitamin D levels not be determined until at least 7 days after the last intake [2 ⊕◯◯◯].

- In patients with insufficient response after supplementation, it is suggested to increase the frequency or dose, or to consider a change in the type of supplement/treatment [2◯◯◯◯].

- For good bone health, it is recommended to accompany supplementation or treatment with an adequate intake of calcium (1,000-1,200 mg/day preferably from food), and moderate intensity physical exercise, especially in patients with osteoporosis or at risk of suffering falls or fractures [1⊕⊕⊕◯].

Evidence

Effect of vitamin D on musculoskeletal health

The results on the effect of vitamin D supplementation identified in the literature are heterogeneous due to the difference between the studied populations (postmenopause, osteoporosis, the elderly or the general population), the evaluated strategies (combination or not with calcium and/or exercise), and the outcome variables analyzed (strength, mobility, stability, falls, fractures and/or BMD).

In relation to strength, a meta-analysis performed in postmenopausal women[75] and a randomized trial in institutionalized elderly[63] suggest that vitamin D supplementation and exercise increase muscle strength. However, in 4 other studies conducted in the elderly, no significant increase in strength was observed without exercise[61,76,77] or in combination with exercise[78]. Regarding mobility, in 3 studies conducted in the elderly receiving vitamin D supplements[61] in combination with exercise[63,78], a significant increase was observed. On the contrary, a meta-analysis suggests that vitamin D supplementation could even cause a slight (albeit significant) decrease in mobility in institutionalized elderly[76]. As for stability, a recent study suggests that supplementation with vitamin D improves stability in postmenopausal women[79]. For its part, a meta-analysis carried out in the general adult population found a marginally significant improvement in BMD in the population treated with vitamin D compared to the untreated population[80].

One of the purposes of vitamin D supplementation is to reduce falls, and ultimately fractures. In this sense, 2 meta-analysis and 3 randomized trials carried out in the elderly and postmenopausal women suggest that vitamin D supplementation reduces the risk of falls. However, in the general population this benefit would not be demonstrated[80,81]. Interestingly, although various previous meta-analysis had found a correlation between calcium and vitamin D supplementation and a reduction in the risk of fracture[82,83], subsequent studies identified in the present review would not corroborate a statistically significant risk reduction[61,80,84].

The effect of vitamin D supplementation depends on the baseline values of 25-hydroxyvitamin D, and it has been shown that supplementation causes a better response the greater the deficiency[85]. In this sense, it is important to note that in many studies the effect of vitamin D supplementation is evaluated, including people who do not have 25-hydroxyvitamin D deficiency, and who, therefore, would not need to be supplemented. Specifically, in the review carried out for this document, only 8% of the studies identified had 25-hydroxyvitamin D levels lower than 20 or 30 ng/mL as inclusion criteria. In fact, combined analysis support that vitamin D supplements only prevent fractures and falls in people with 25-hydroxyvitamin D deficiency[80]. Therefore, in line with what has been argued by many authors[13,86-88], we consider that it cannot be concluded that vitamin D supplementation is not effective in people with hypovitaminosis, in terms of reducing fractures or falls.

Vitamin D derivates

Currently, for the treatment of 25-hydroxyvitamin D deficiency there are different metabolites of the SEVD marketed in Spain: cholecalciferol and calcifediol for deficiency diseases, in addition to calcitriol and alfacalcidol for populations with special conditions, such as chronic kidney disease, rickets/osteomalacia hypophosphatemic linked to the X chromosome, hypophosphatemic autosomal and oncogenic among others.

Available vitamin D metabolites have different half-life, potency and speed of action. Thus, calcifediol has a shorter half-life, is 3-6 times more potent, and has a faster action than cholecalciferol in the treatment of vitamin D deficiency[89].

In general, both cholecalciferol and calcifediol are effective and safe forms for the prevention and treatment of vitamin D deficiency in all populations. However, in some specific situations one metabolite may be preferable over the other.

In patients with chronic liver disease, treatment with drugs that compete with the synthesis of 25-hydroxyvitamin D or that are severely deficient and require rapid replacement, treatment with calcifediol may be preferable.

In patients with primary hyperparathyroidism or in those in whom 25-hydroxyvitamin D levels cannot be monitored, supplementation with cholecalciferol may be preferable[90].

The dose, frequency, and duration of supplementation/treatment are factors that are independently associated with 25-hydroxyvitamin D levels[91]. The dose and frequency will depend on the severity of the deficit, its causes and the formulation of the metabolite used. In general, for vitamin D it has been observed that different dosing regimens have similar results[92]. On the other hand, various studies comparing cohorts treated with different doses suggest that in the medium term, moderate doses would have a similar effect to that of higher doses[54,57,62,93], even too high doses (mega doses) could increase the risk of falls, fractures, and even lower BMD[94-96].

However, it is important to mention that certain groups of patients may require higher doses and/or administered parenterally, such as, for example, malabsorptive symptoms, morbid obesity or undergoing bariatric surgery. Therefore, we recommend calculating the dose in each case, generally opting for low doses, and increasing it or changing the supplement in the event of an inadequate response.

There is no single supplementation regimen in patients with 25-hydroxyvitamin D deficiency. Table 4 shows the regimen recommended by the panel for both the general population and for patients with osteoporosis or other populations at risk of 25-hydroxyvitamin D deficiency, whether opting for cholecalciferol or calcifediol.

Follow-up monitoring

Another key point is the follow-up of patients with 25-hydroxyvitamin D deficiency or insufficiency. It is estimated that plasma levels of 25-hydroxyvitamin D stabilize after 2 or 3 months of starting supplementation[56,61,62, 78.97].

In line with the Endocrine Society[55] and SEEN[25], we recommend monitoring patients initially every 3-4 months, and once the appropriate concentrations are reached, every 6-12 months.

In a pharmacokinetic study, the administration of a single 140 µg dose of calcifediol produced an initial peak in the plasma concentration of 25-hydroxyvitamin D, which normalize after 7 days. However, this same dose of cholecalciferol achieved progressive increases in 25-hydroxyvitamin D levels, which did not reach the maximum peak until after 3 months[98]. For this reason, in patients treated with calcifediol, the determination of 25-hydroxyvitamin D should preferably be performed at least 7 days after the last administration, while with the supplementation with cholecalciferol, the time of determination does not matter.

Calcium intake

For a suitable effect of the anti-osteoporotic drugs, it is advisable, it is advisable to ensure an optimal daily intake of calcium (approximately between 1 and 1.2 grams), being preferable to do so through food whenever possible[25,59,82,99-102].

3.5. Prevention of 25-hydroxyvitamin D deficiency and maintenance

Recommendation

- In the general population, optimal sun exposure and adequate nutrition are recommended, and if this is not enough, it should be supplemented with 800 IU/day (20 µg/day) of cholecalciferol (or 25,000 IU/month; 625 µg/month) [1 ⊕⊕⊕◯].

- In patients with osteoporosis or a population at risk of vitamin D deficiency, supplementation with cholecalciferol at doses of 1,000-2,000 IU/day (25-50 µg/day) or calcifediol at doses of 8-12 µg/day (480 -720 IU/day). If a regimen with a lower frequency of administration is preferred, the administration of 25,000-30.000 IU of cholecalciferol/15 days (50,000-60,000 IU/month) or 266 µg of calcifediol every 3-4 weeks is recommended [1 ⊕⊕⊕◯].

- Obese patients, with malabsorption syndromes, bariatric surgery or treated with drugs that affect the metabolism of vitamin D (eg antiepileptics, glucocorticoids, rifampicin or antiretrovirals) may require doses 2-3 times higher than usual (3,000-6,000 IU/day of cholecalciferol), being preferable the administration of calcifediol (up to 12 µg/day or more) or, in cases of severe malabsorption, as in some cases of bariatric surgery "bypass type", the administration of parenteral vitamin D could be needed [1 ⊕⊕◯◯].

Evidence

As previously mentioned, and based on the vitamin D requirements in each population, the panel recommends a daily intake (diet and/or supplements) of at least 800 IU (20 µg/day) of vitamin D in the general population. Adult, and 800-1,000 IU (20-25 µg/day) in postmenopausal women and men over 50 years.

In studies carried out in the elderly and institutionalized population in which an improvement in musculoskeletal health is observed with vitamin D supplementation (alone or in combination with calcium and exercise), this improvement is achieved with doses greater than 700 IU/day[29], and generally between 800 and 1,000 IU/day[61,63,64,78].

In patients with osteoporosis, especially if they receive powerful antiresorptive treatments, it is necessary to ensure an adequate supply of calcium and vitamin D. In this way, the risk of hypocalcemia is minimized, and a better therapeutic response is ensured[103,104].

As we have discussed previously, the association between 25-hydroxyvitamin D deficiency and obesity is well established, although its causes are still under study[105]. Although obesity has traditionally been considered a protective factor against fragility fractures and some studies suggest this[106], others question the cause-effect relationship[107-109]. Obese individuals are estimated to require higher doses of vitamin D (2 to 3 times higher) than the non-obese population[110]. Likewise, in cases of severe malabsorption, such as "bypass-type" bariatric surgery, parenteral administration may be needed[111].

Various medications (such as antiepileptic agents, glucocorticoids, rifampin, or antiretroviral drugs) can interfere with vitamin D and bone metabolism by various mechanisms, such as modifying 24-hydroxylase activity[112].

In the same way, in patients treated with drugs that can affect the metabolism of vitamin D, higher doses are recommended. Thus, for example, the sustained use of glucocorticoids induces bone loss by reducing intestinal calcium absorption and increasing renal excretion, suggesting minimum doses of 1,800 IU/day for this type of patients[113]. In the same way that glucocorticoid therapy is associated with bone loss, chronic antiretroviral therapies are associated with a decrease in BMD in HIV-infected people[114]. The European AIDS Clinical Society recommends the administration of between 800 and 2,000 IU/day in HIV patients to achieve 25-hydroxyvitamin D levels above 20 ng/mL[115]. Likewise, it has been observed that antiepileptic therapies are associated with a decrease in the levels of 25-hydroxyvitamin D[49,116], which could be prevented, at least in part, with high doses of vitamin D (equivalent to 2,000 IU/day)[117].

Bariatric surgery also causes a reduction in BMD, the deterioration of bone structure and an increase in bone resorption, due to the malabsorptive process triggered by the surgery, increasing the risk of fragility fracture[118-120]. Bariatric surgery patients receiving cholecalciferol before surgery (28,000 IU...) (28,000 IU/week for 8 weeks) and after surgery (16,000 IU/week), along with calcium and exercise, experience significantly less decline in bone health[121]. However, more studies are necessary to determine the effect and the necessary doses in these patients. In any case, some guidelines such as the American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic & Bariatric Surgery, have recommended supplementation with high doses of vitamin D (3,000 to 7,000 IU/day) for several years. in these patients, and in some cases parenteral administration may be necessary[122,123]. In these cases, it must be requested as a foreign medication as it is not available in Spain.

Calcifediol, due to its pharmacokinetic characteristics, may be preferable in patients with interference in the synthesis of 25-hydroxyvitamin D (eg treatment with anti-epileptic drugs), with a lower bio-availability of vitamin D3 (eg obesity) or with severe malabsorption (eg bariatric surgery)[124].

4. Conclusions

This document includes a set of recommendations for the prevention and treatment of 25-hydroxyvitamin D deficiency prepared by a multidisciplinary group of experts, based on the most recent scientific evidence, and ratified by the SEIOMM.

Table 3. Recommended supplementation regimen with cholecalciferol or calcifediol in patients with 25-hydroxyvitamin D deficiency

Population (desirable levels of 25-hydroxyvitamin D)	Serum 25-hydroxyvitamin D levels	Treatment (any of the suggested regimens)
General population (>25 ng/mL)	<10 ng/mL (severe deficiency)	Calcifediol: 266 µg/week *(16,000 IU/week *)* for 5 weeks . Cholecalciferol: 50,000 IU/week for 4-6 weeks. Then continue with the insufficiency regimen.
	10-25 ng/mL (insufficiency)	Colecalciferol: 25.000 UI/month or 800 UI/day. Calcifediol: 266 µg/month *(16.000 UI/month*)*.
Osteoporosis and other population groups at risk of vitamin D deficiency (>30 ng/mL)	<10 ng/mL (severe deficiency)	Calcifediol 266 µg/week *(16.000 UI/week*)* for 5 weeks. Colecalciferol: 50.000 UI/week for 6-8 weeks. Then continue with the insufficiency regimen.
	10-30 ng/mL (insufficiency)	Colecalciferol: 50.000 UI/month or 1.000-2.000 UI/day. Calcifediol: 266 µg/3-4 weeks *(16.000 UI/3-4 weeks*).*

*: equivalence according to technical data sheet. Actually, this equivalence cannot be established, and it is preferable to use µg for the doses of calcifediol.

These recommendations are an update of those made in the SEIOMM Position Paper on Optimal 25-Hydroxyvitamin D Needs and Levels. The optimal 25-hydroxyvitamin D levels currently recommended are slightly lower (25-50 ng/mL) than those recommended in 2011 (30-75 ng/mL), while the 25-hydroxyvitamin D levels required by different populations as patients with osteoporosis (30-50 ng/mL), they would be, in general, similar to those previously recommended, including premature infants. In addition, it delves into aspects such as, for example, sun exposure, the populations in which it is necessary to supplement with vitamin D or treat, with what dose to do it, and the frequency of patient monitoring.

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Supplemental Table 1. Search terms: vitamin D and musculoskeletal health

VITAMIN D
Vitamin D [MeSH]
Vitamin D Deficiency [MeSH]
"hypovitaminosis D" [ti]
250HD [tiab]
"Vitamin D*" [tiab]
Cholecalciferol [MeSH]
Cholecalciferol [tiab]
Calcifediol [tiab]
Ergocalciferols [MeSH]
Ergocalciferol [tiab]
QUESTION 1: WHAT ARE THE ADEQUATE VALUES OF VITAMIN D?
"Level" [tiab]
"Concentration" [tiab]
QUESTION 2: WHAT TYPE OF PATIENT SHOULD BE SCREENED FOR POSSIBLE HYPOVITAMINOSIS?
Diagnosis [MeSH]
"Diagnostic Screening Programs" [MeSH]
Screening [ti]
"Population-based screening" [tiab]
"Risk Factors" [MeSH]
"Risk factors" [ti]
QUESTION 3: WHAT ARE THE REQUIREMENTS FOR VITAMIN D?
"Diet, Food, and Nutrition" [MeSH]
"Nutritional requirement" [tiab]
QUESTION 4: WHAT ARE THE SOURCES OF VITAMIN D?
Sunlight [MesH]
"light exposure" [ti]
Daylight [ti]
"source" [ti]
"nutrition*" [ti]
"food" [ti]

Supplemental Table 1. Search terms: vitamin D and musculoskeletal health (cont.)

QUESTION 5: WHICH PATIENTS CAN BENEFIT FROM VITAMIN D SUPPLEMENTATION? WHAT IS THE RECOMMENDED TYPE OF VITAMIN, DOSE AND DURATION OF TREATMENT? ALONE OR WITH CALCIUM?
Outcome Assessment (Health Care) [MeSH]
"Dose-Response Relationship, Drug" [MeSH]
Dose [ti]
"therapeutic use" [MeSH]
Effectiveness [ti]
Supplement [ti]
QUESTION 6: WHAT IS THE APPROPRIATE MONITORING FREQUENCY?
"Drug Monitoring" [MeSH]
"monitoring" [ti]
"Continuity of Patient Care" [MeSH]
SALUD ÓSEA
"Bone Density" [MeSH]
"Osteoporosis" [MeSH]
"Osteoporosis" [ti]
Bone Demineralization, Pathologic [MeSH]
"Fracture, bone" [MeSH]
Fracture [ti]
"Accidental falls" [MeSH]
Falls [ti]
"Muscle Strength" [MeSH]
"Muscle Strength" [ti]
{OR #1-#10} AND {OR #11-#35} AND {OR #36-#45}

("Vitamin D" [MeSH] OR "Vitamin D Deficiency" [MeSH] OR "hypovitaminosis D" [ti] OR "Vitamin D*" [tiab] OR "250HD" [tiab] OR "Cholecalciferol" [MeSH] OR "Cholecalciferol" [tiab] OR "Calcifediol" [tiab] OR "Ergocalciferols" [MeSH] OR "Ergocalciferol" [tiab]) AND ("Level" [tiab] OR "Concentration" [tiab] OR "Diagnosis" [MeSH] OR "Diagnostic Screening Programs" [MeSH] OR "Screening" [ti] OR "Population-based screening" [tiab] OR "Risk Factors" [MeSH] OR "Risk factors" [ti] OR "Diet, Food, and Nutrition" [MeSH] OR "Nutritional requirement" [tiab] OR "Sunlight" [MesH] OR "light exposure" [ti] OR "Daylight" [ti] OR "source" [ti] OR "nutrition*" [ti] OR "food" [ti] OR "Outcome Assessment (Health Care)" [MeSH] OR "Dose-Response Relationship, Drug" [MeSH] OR "Dose" [ti] OR "therapeutic use" [MeSH] OR "Effectiveness" [ti] OR "supplement" [ti] OR "Drug Monitoring" [MeSH] OR "monitoring" [ti] OR "Continuity of Patient Care" [MeSH]) AND ("Bone Density" [MeSH] OR "Osteoporosis" [MeSH] OR "Osteoporosis" [ti] OR "Bone Demineralization, Pathologic" [MeSH] OR "Fracture, bone" [MeSH] OR "Fracture" [ti] OR "Accidental falls" [MeSH] OR "Falls" [ti] OR "Muscle Strength" [MeSH] OR "Muscle Strength" [ti]).

Bibliography

1. Fraser WD, Milan AM. Vitamin D assays: Past and present debates, difficulties, and developments. Calcif Tissue Int. 2013;92:118-27.
2. Navarro-Valverde C, Quesada Gómez JM. Vitamina D, determinante de la salud ósea y extra ósea; Importancia de su suplementación en la leche y derivados. Nutr Hosp. 2015;31:18-25.
3. Charoenngam N, Shirvani A, Holick MF. Vitamin D for skeletal and non-skeletal health: What we should know. J Clin Orthop Trauma. 2019;10:1082-93.
4. Oleröd G, Hultén LM, Hammarsten O, Klingberg E. The variation in free 25-hydroxy vitamin D and vitamin D-binding protein with season and vitamin D status. Endocr Connect. 2017;6:111-20.
5. van Driel M, van Leeuwen JPTM. Vitamin D endocrine system and osteoblasts. Bonekey Rep. 2014;3:1-8.
6. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest. 2006;116:2062-72.
7. Casado Burgos E. Funciones de la vitamina D: beneficios óseos y extraóseos. Med Clin (Barc). 2016;17:7-11.
8. Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of vitamin D in treatment of inflammatory bowel disease. Medicine (Baltimore). 2018;97:e12662.
9. Franco AS, Freitas TQ, Bernardo WM, Pereira RMR. Vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases. Medicine (Baltimore). 2017;96:e7024.
10. Hu Z, Chen J, Sun X, Wang L, Wang A. Efficacy of vitamin D supplementation on glycemic control in type 2 diabetes patients. Medicine (Baltimore). 2019;98: e14970.
11. Khaing W, Vallibhakara SAO, Tantrakul V, Vallibhakara O, Rattanasiri S, McEvoy M, et al. Calcium and vitamin D supplementation for prevention of preeclampsia: A systematic review and network meta-analysis. Nutrients. 2017;9:1-23.
12. Autier P, Mullie P, Macacu A, Dragomir M, Boniol M, Coppens K, et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. Lancet Diabetes Endocrinol. 2017;5: 986-1004.
13. Rejnmark L, Bislev LS, Cashman KD, Eiríksdottir G, Gaksch M, Grübler M, et al. Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data. Slominski AT, editor. PLoS One. 2017;12:e0180512.
14. Navarro-Triviño FJ, Arias-Santiago S, Gilaberte-Calzada Y. Vitamina D y la piel. Una revisión para dermatólogos. Actas Dermosifiliogr. 2019;110:262-72.
15. Arab A, Hadi A, Moosavian SP, Askari G, Nasirian M. The association between serum vitamin D, fertility and semen quality: A systematic review and meta-analysis. Int J Surg. 2019;71:101-9.
16. Chu J, Gallos I, Tobias A, Tan B, Eapen A, Coomarasamy A. Vitamin D and assisted reproductive treatment outcome: A systematic review and meta-analysis. Hum Reprod. 2018;33:65-80.
17. Pérez Castrillón JL, Casado E, Corral Gudino L, Gómez Alonso C, Peris P, Riancho JA.. COVID-19 y vitamina D . Documento de posición y del Metabolismo Mineral (SEIOMM). Rev Osteoporos y Metab Miner. 2020;12:155-9.
18. Holick M. Vitamin D. Phtobiology, metabolism, mechanism of action, and clinical applications. Prim Metab bone Dis Disord Miner Metab. 6a. 2006. p. 129-37.
19. Cashman KD, Dowling KG, Škrabáková Z, Gonzalez-Gross M, Valtueña J, De Henauw S, et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr. 2016; 103:1033-44.
20. Navarro Valverde C, Quesada Gómez JM. Deficiencia de vitamina D en España: ¿realidad o mito? Rev Osteoporos y Metab Miner. 2014;6:5-10.
21. Gómez de Tejada Romero M, Sosa Henríquez M, Del Pino Montes J, Jodar Gimeno E, Quesada Gómez J, Cancelo Hidalgo M, et al. Sociedad Española de Investigación Ósea y del Metabolismo Mineral (SEIOMM) y Sociedades afines. Documento de posición sobre las necesidades y niveles óptimos de vitamina D. Rev Osteoporos Metab Min. 2011;3: 53-64.
22. Schünemann H, Brożek J, Guyatt G, Oxman A. (2013). Manual GRADE para calificar la calidad de la evidencia y la fuerza de la recomendación (1ª Ed. en español). P.A Orrego & M.X. Rojas (Trans.) Mar 2017. Publicación Original: http://gdt.guidelinedevelopment.org/app/handbook/handbook.htm.
23. Girgis CM, Baldock PA, Downes M. Vitamin D, muscle and bone: Integrating effects in development, aging and injury. Mol Cell Endocrinol. 2015;410:3-10.
24. Erem S, Atfi A, Razzaque MS. Anabolic effects of vitamin D and magnesium in aging bone. J Steroid Biochem Mol Biol. 2019;193.
25. Varsavsky M, Rozas Moreno P, Becerra Fernández A, Luque Fernández I, Quesada Gómez JM, Ávila Rubio V, et al. Recomendaciones de vitamina D para la población general. Endocrinol Diabetes y Nutr. 2017;64:7-14.
26. Rizzoli R, Boonen S, Brandi ML, Bruyère O, Cooper C, Kanis JA, et al. Vitamin D supplementation in elderly or postmenopausal women: A 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin. 2013; 29:305-13.
27. Sociedad Española de Reumatología. Grupo de trabajo ESPOGUIA. Guía de Práctica Clínica para el Tratamiento de la Espondiloartritis Axial y la Artritis Psoriásica. [[monografía en internet]]. Madrid: Sociedad Española de Reumatología. 2015.[Internet] Available from: https://espoguia.ser.es/.
28. Wu F, Wills K, Laslett LL, Oldenburg B, Seibel MJ, Jones G, et al. Cut-points for associations between vitamin D status and multiple musculoskeletal outcomes in middle-aged women. Osteoporos Int. 2017;28:505-15.
29. Bischoff-Ferrari HA. Relevance of vitamin D in fall prevention. Gériatrie Psychol Neuropsychiatr du Viellissement. 2017; 5:E1-7.
30. Lv Q-B, Gao X, Liu X, Shao Z-X, Xu Q-H, Tang L, et al. The serum 25-hydroxyvitamin D levels and hip fracture risk: a meta-analysis of prospective cohort studies. Oncotarget. 2017;8:39849-58.
31. Gaksch M, Jorde R, Grimnes G, Joakimsen R, Schirmer H, Wilsgaard T, et al. Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. PLoS One. 2017;12:e0170791.
32. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: Consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001;22:477-501.
33. Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab. 2005;90:3215-24.
34. Altieri B, Cavalier E, Bhattoa HP, Pérez-López FR, López-Baena MT, Pérez-Roncero GR, et al. Vitamin D testing: advantages and limits of the current assays. Eur J Clin Nutr.2020;74:231-47.
35. El-Hajj Fuleihan G, Bouillon R, Clarke B, Chakhtoura M, Cooper C, McClung M, et al. Serum 25-Hydroxyvitamin D Levels: Variability, Knowledge Gaps, and the Concept of a Desirable Range. J Bone Miner Res. 2015;30:1119-33.
36. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) 2016, 'Dietary reference values for vitamin D: (Scientific Opinion)', E F S A Journal, bind 14, nr. 10, 4547. [Internet] Available from: https://doi.org/10.2903/j.efsa.2016.4547.
37. Binkley N, Novotny R, Krueger D, Kawahara T, Daida YG, Lensmeyer G, et al. Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab. 2007;92:2130-5.
38. Bikle DD. Vitamin D: Newer concepts of its metabolism and function at the basic and clinical level. J Endocr Soc. 2020;4: 1-20.
39. Giustina A, Adler RA, Binkley N, Bollerslev J, Bouillon R, Dawson-Hughes B, et al. Consensus statement from 2nd International Conference on Controversies in Vitamin D. Rev Endocr Metab Disord. Reviews in Endocrine and Metabolic Disorders; 2020; 21:89-116.
40. Sempos CT, Vesper HW, Phinney KW, Thienpont LM, Coates PM. Vitamin D status as an international issue: National surveys and the problem of standardization. Scand J Clin Lab Invest. 2012; 72:32-40.
41. Parva NR, Tadepalli S, Singh P, Qian A, Joshi R, Kandala H, et al. Prevalence of Vitamin D Deficiency and Associated Risk Factors in the US Population (2011-2012). Cureus. 2018;10.
42. Valverde NC, Gómez QJ, Manuel J. Deficiencia de vitamina D en España. ¿Realidad o mito? La 25-hidroxivitamina D el marcador del estatus corporal de vitamina D. Rev Osteoporos Metab Min. 2014;6:5-10.
43. Felipe Salech M, Rafael Jara L, Luis Michea A. Cambios fisiológicos asociados al envejecimiento. Rev Médica Clínica Las Condes. 2012;23:19-29.

44. Vuksanovic M, Mihajlovic G, Beljic Zivkovic T, Gavrilovic A, Arsenovic B, Zvekic Svorcan J, et al. Cross-talk between muscle and bone in postmenopausal women with hypovitaminosis D. Climacteric. Informa UK Limited, trading as Taylor 8 Francis Group; 2017;20:31-6.
45. Gorter EA, Oostdijk W, Felius A, Krijnen P, Schipper IB. Vitamin D Deficiency in Pediatric Fracture Patients: Prevalence, Risk Factors, and Vitamin D Supplementation. J Clin Res Pediatr Endocrinol. 2016;8:445-51.
46. Santos A, Amaral TF, Guerra RS, Sousa AS, Álvares L, Moreira P, et al. Vitamin D status and associated factors among Portuguese older adults: Results from the Nutrition UP 65 cross-sectional study. BMJ Open. 2017;22;7(6):e016123.
47. Chetcuti Zammit S, Ellul P, Girardin G, Valpiani D, Nielsen KR, Olsen J, et al. Vitamin D deficiency in a European inflammatory bowel disease inception cohort. Eur J Gastroenterol Hepatol. 2018;30:1297-303.
48. Arias PM, Domeniconi EA, García M, Esquivel CM, Martínez Lascano F, Foscarini JM. Micronutrient Deficiencies After Roux-en-Y Gastric Bypass: Long-Term Results. Obes Surg. 2020 Jan;30(1):169-173.
49. Teagarden DL, Meador KJ, Loring DW. Low vitamin D levels are common in patients with epilepsy. Epilepsy Res. 2014;108:1352-6.
50. Houston DK, Tooze JA, Neiberg RH, Hausman DB, Johnson MA, Cauley JA, et al. 25-hydroxyvitamin D status and change in physical performance and strength in older adults. Am J Epidemiol. 2012;176:1025-34.
51. Feng Y, Cheng G, Wang H, Chen B. The associations between serum 25-hydroxyvitamin D level and the risk of total fracture and hip fracture. Osteoporos Int. 2017;28:1641-52.
52. Rosen CJ, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, et al. IOM Committee Members Respond to Endocrine Society Vitamin D Guideline. J Clin Endocrinol Metab. 2012;97:1146-52.
53. Vieth R, Holick MF. The IOM-Endocrine Society Controversy on Recommended Vitamin D Targets. Vitam D. 2018. p. 1091-107.
54. Anderson-Berry A, Thoene M, Wagner J, Lyden E, Jones G, Kaufmann M, et al. Randomized trial of two doses of vitamin D3 in preterm infants <32 weeks: Dose impact on achieving desired serum 25(OH)D3 in a NICU population. van Wouwe JP, editor. PLoS One. 2017; 12:e0185950.
55. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011; 96:1911-30.
56. Brett NR, Gharibeh N, Weiler HA. Effect of Vitamin D Supplementation, Food Fortification, or Bolus Injection on Vitamin D Status in Children Aged 2-18 Years: A Meta-Analysis. Adv Nutr. 2018; 9:454-64.
57. Brett NR, Parks CA, Lavery P, Agellon S, Vanstone CA, Kaufmann M, et al. Vitamin D status and functional health outcomes in children aged 2–8 y: a 6-mo vitamin D randomized controlled trial. Am J Clin Nutr. 2018;107:355-64.
58. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. J Clin Endocrinol Metab. 2011;96:53-8.
59. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014;25:2359-81.
60. Grimnes G, Emaus N, Cashman KD, Jorde R. The effect of high-dose vitamin D supplementation on muscular function and quality of life in postmenopausal women-A randomized controlled trial. Clin Endocrinol (Oxf). 2017;87:20-8.
61. Mak JC, Mason RS, Klein L, Cameron ID. An initial loading-dose vitamin D versus placebo after hip fracture surgery: randomized trial. BMC Musculoskelet Disord. BMC Musculoskeletal Disorders; 2016;17:336.
62. Hin H, Tomson J, Newman C, Kurien R, Lay M, Cox J, et al. Optimum dose of vitamin D for disease prevention in older people: BEST-D trial of vitamin D in primary care. Osteoporos Int. 2017;28: 841-51.
63. Aoki K, Sakuma M, Endo N. The impact of exercise and vitamin D supplementation on physical function in community-dwelling elderly individuals: A randomized trial. J Orthop Sci. 2018;23: 682-7.
64. Imaoka M, Higuchi Y, Todo E, Kitagwa T, Ueda T. Low-frequency Exercise and Vitamin D Supplementation Reduce Falls Among Institutionalized Frail Elderly. Int J Gerontol. 2016;10:202-6.
65. Agencia Española de Seguridad Alimentaria y Nutrición, RedBEDCA. Base de Datos Española de Composición de Alimentos (BEDCA). 2019. [Internet] Available from: https://www.bedca.net/.
66. Valero Zanuy MÁ, Hawkins Carranza F. Metabolismo, fuentes endógenas y exógenas de vitamina D. Rev Osteoporos Metab Miner. 2007;16:63-70.
67. Miyauchi M, Hirai C, Nakajima H. The Solar Exposure Time Required for Vitamin D3 Synthesis in the Human Body Estimated by Numerical Simulation and Observation in Japan. J Nutr Sci Vitaminol (Tokyo). 2013;59:257-63.
68. Wacker M, Holick MF. Sunlight and Vitamin D. Dermatoendocrinol. 2013;5:51-108.
69. Jager N, Schöpe J, Wagenpfeil S, Bocionek P, Saternus R, Vogt T, et al. The Impact of UV-dose, Body Surface Area Exposed and Other Factors on Cutaneous Vitamin D Synthesis Measured as Serum 25(OH)D Concentration: Systematic Review and Meta-analysis. Anticancer Res. 2018;38:1165-71.
70. Nowson CA, McGrath JJ, Ebeling PR, Haikerwal A, Daly RM, Sanders KM, et al. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust. 2012;196:686-7.
71. American Academy of Dermatology. Position Statement on VITAMIN D. 2009. 2010. p. 4.[Internet] Available from: https://server.aad.org/Forms/Policies/Uploads/PS/PS-Vitamin% 20D.pdf?
72. Pierret L, Suppa M, Gandini S, del Marmol V, Gutermuth J. Overview on vitamin D and sunbed use. J Eur Acad Dermatology Venereol. 2019;33:28-33.
73. Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). Opinion on biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes. Luxembourg: European Commission; 2016 Nov 17 [Internet] Available from: http://ec.europa.eu/health/scientific_committees/scheer/docs/scheer_o_003.pdf.
74. Passeron T, Bouillon R, Callender V, Cestari T, Diepgen TL, Green AC, et al. Sunscreen photoprotection and vitamin D status. Br J Dermatol. 2019;181:916-31.
75. Antoniak AE, Greig CA. The effect of combined resistance exercise training and vitamin D 3 supplementation on musculoskeletal health and function in older adults: a systematic review and meta-analysis. BMJ Open. 2017;7: e014619.
76. Rosendahl-Riise H, Spielau U, Ranhoff AH, Gudbrandsen OA, Dierkes J. Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: a systematic review and meta-analysis. J Hum Nutr Diet. 2017;30:3-15.
77. Englund DA, Kirn DR, Koochek A, Zhu H, Travison TG, Reid KF, et al. Nutritional Supplementation With Physical Activity Improves Muscle Composition in Mobility-Limited Older Adults, The VIVE2 Study: A Randomized, Double-Blind, Placebo-Controlled Trial. Journals Gerontol Ser A. 2018;73:95-101.
78. Stemmle J, Marzel A, Chocano-Bedoya PO, Orav EJ, Dawson-Hughes B, Freystaetter G, et al. Effect of 800 IU Versus 2000 IU Vitamin D3 With or Without a Simple Home Exercise Program on Functional Recovery After Hip Fracture: A Randomized Controlled Trial. J Am Med Dir Assoc. 2019;20: 530-536.e1.
79. Cangussu LM, Nahas-Neto J, Orsatti CL, Poloni PF, Schmitt EB, Almeida-Filho B, et al. Effect of isolated vitamin D supplementation on the rate of falls and postural balance in postmenopausal women fallers. Menopause. 2016;23:267-74.
80. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol. 2018;6:847-58.
81. Khaw K-T, Stewart AW, Waayer D, Lawes CMM, Toop L, Camargo CA, et al. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol. 2017;5:438-47.
82. Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int. 2016;27:367-76.
83. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007;370:657-66.

84. Zhao J-G, Zeng X-T, Wang J, Liu L. Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults. JAMA. 2017;318:2466.
85. Brenner H, Jansen L, Saum K-U, Holleczek B, Schöttker B. Vitamin D Supplementation Trials Aimed at Reducing Mortality Have Much Higher Power When Focusing on People with Low Serum 25-Hydroxyvitamin D Concentrations. J Nutr. 2017;147:1325-33.
86. Vitamin D Supplementation and Prevention of Type 2 Diabetes. N Engl J Med. 2019;381:1784-6.
87. Bolland MJ, Avenell A, Grey A. Assessment of research waste part 1: an exemplar from examining study design, surrogate and clinical endpoints in studies of calcium intake and vitamin D supplementation. BMC Med Res Methodol. 2018;18:103.
88. Bolland MJ, Grey A, Avenell A. Assessment of research waste part 2: wrong study populations- an exemplar of baseline vitamin D status of participants in trials of vitamin D supplementation. BMC Med Res Methodol. 2018;18:101.
89. Navarro-Valverde C, Sosa-Henríquez M, Alhambra-Expósito MR, Quesada-Gómez JM. Vitamin D3and calcidiol are not equipotent. J. Steroid Biochem. Mol. Biol. 2016; 164:205-208.
90. Vélayoudom-Céphise FL, Wémeau JL. Primary hyperparathyroidism and vitamin D deficiency. Ann Endocrinol (Paris). 2015;76:153-62.
91. Chao Y-S, Brunel L, Faris P, Veugelers P. The Importance of Dose, Frequency and Duration of Vitamin D Supplementation for Plasma 25-Hydroxyvitamin D. Nutrients. 2013;5:4067-78.
92. Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL, Vieth R. Comparison of Daily, Weekly, and Monthly Vitamin D3 in Ethanol Dosing Protocols for Two Months in Elderly Hip Fracture Patients. J Clin Endocrinol Metab. 2008;93:3430-5.
93. Gallo S, Hazell T, Vanstone CA, Agellon S, Jones G, L'Abbé M, et al. Vitamin D supplementation in breastfed infants from Montréal, Canada: 25-hydroxyvitamin D and bone health effects from a follow-up study at 3 years of age. Osteoporos Int. 2016;27:2459-66.
94. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology. 2007;46:1852-7.
95. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women. JAMA. 2010;303:1815.
96. Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength. JAMA. 2019;322:736.
97. Pop LC, Sukumar D, Schneider SH, Schlussel Y, Stahl T, Gordon C, et al. Three doses of vitamin D, bone mineral density, and geometry in older women during modest weight control in a 1-year randomized controlled trial. Osteoporos Int. 2017;28:377-88.
98. Jetter A, Egli A, Dawson-Hughes B, Staehelin HB, Stoecklin E, Goessl R, et al. Pharmacokinetics of oral vitamin D3 and calcifediol. Bone. 2014;59:14-9.
99. Grossman DC, Curry SJ, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults. JAMA. 2018;319:1592.
100. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30:33-44.
101. Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Rheumatol. 2017;69:1521-37.
102. Sociedad Española de Reumatología. Recomendaciones SER sobre Osteoporosis. 2019. [Internet] Available from: https://www.ser.es/wp-content/uploads/2018/03/Recomendaciones_OP_DEF.pdf.
103. Nakamura Y, Suzuki T, Kamimura M, Murakami K, Ikegami S, Uchiyama S, et al. Vitamin D and calcium are required at the time of denosumab administration during osteoporosis treatment. Bone Res. 2017;5.
104. Peris P, Martínez-Ferrer A, Monegal A, Martínez de Osaba MJ, Muxi A, Guañabens N. 25 hydroxyvitamin D serum levels influence adequate response to bisphosphonate treatment in postmenopausal osteoporosis. Bone. 2012;51:54-8.
105. Vanlint S. Vitamin D and Obesity. Nutrients. 2013;5:949-56.
106. Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal Relationship between Obesity and Vitamin D Status: Bi-Directional Mendelian Randomization Analysis of Multiple Cohorts. PLoS Med. 2013;10.
107. Migliaccio S, Greco, Fornari, Donini, Lenzi. Is obesity in women protective against osteoporosis? Diabetes, Metab Syndr Obes Targets Ther. 2011;273.
108. Zhao L-J, Liu Y-J, Liu P-Y, Hamilton J, Recker RR, Deng H-W. Relationship of Obesity with Osteoporosis. J Clin Endocrinol Metab. 2007;92:1640-6.
109. Palermo A, Tuccinardi D, Defeudis G, Watanabe M, D'Onofrio L, Lauria Pantano A, et al. BMI and BMD: The Potential Interplay between Obesity and Bone Fragility. Int J Environ Res Public Health. 2016;13:544.
110. Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. PLoS One. 2014;5;9 (11):e111265.9.
111. Hultin H, Stevens K, Sundbom M. Cholecalciferol Injections Are Effective in Hypovitaminosis D After Duodenal Switch: a Randomized Controlled Study. Obes Surg. Obesity Surgery; 2018;28: 3007-11.
112. Gröber U, Holick MF, Kisters K. Vitamin D and drugs. Med Monatsschr Pharm. 2011;34:377-87.
113. Davidson ZE, Walker KZ, Truby H. Do Glucocorticosteroids Alter Vitamin D Status? A Systematic Review with Meta-Analyses of Observational Studies. J Clin Endocrinol Metab. 2012;97:738-44.
114. Walker Harris V, Brown TT. Bone Loss in the HIV-Infected Patient: Evidence, Clinical Implications, and Treatment Strategies. J Infect Dis. 2012;205:S391-8.
115. Behrens G, Pozniak A, Puoti M, Miro JM. EACS Guidelines v.9.1. Eur AIDS Clin Soc. 2018;104. [Internet] Available from: https://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf.
116. Yildiz EP, Poyrazoglu Ş, Bektas G, Kardelen AD, Aydinli N. Potential risk factors for vitamin D levels in medium- and long-term use of antiepileptic drugs in childhood. Acta Neurol Belg. 2017;117(2):447-453.
117. Viraraghavan VR, Seth A, Aneja S, Singh R, Dhanwal D. Effect of high dose vitamin D supplementation on vitamin d nutrition status of pre-pubertal children on anti-epileptic drugs – A randomized controlled trial. Clin Nutr ESPEN. 2019; 29:36-40.
118. Fashandi AZ, Mehaffey JH, Hawkins RB, Schirmer B, Hallowell PT. Bariatric surgery increases risk of bone fracture. Surg Endosc. 2018;32:2650-5.
119. Khalid SI, Omotosho PA, Spagnoli A, Torquati A. Association of Bariatric Surgery With Risk of Fracture in Patients With Severe Obesity. JAMA Netw open. 2020;3:e207419.
120. Zhang Q, Dong J, Zhou D, Liu F. Comparative risk of fracture for bariatric procedures in patients with obesity: A systematic review and Bayesian network meta-analysis: Bariatric procedures and fracture risk. Int J Surg. 2020; 75:13-23.
121. Muschitz C, Kocijan R, Haschka J, Zendeli A, Pirker T, Geiger C, et al. The Impact of Vitamin D, Calcium, Protein Supplementation, and Physical Exercise on Bone Metabolism after Bariatric Surgery: The BABS Study. J Bone Miner Res. 2016;31:672-82.
122. Chakhtoura MT, Nakhoul N, Akl EA, Mantzoros CS, El Hajj Fuleihan GA. Guidelines on vitamin D replacement in bariatric surgery: Identification and systematic appraisal. Metabolism. 2016;65:586-97.
123. Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L. American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. Surg Obes Relat Dis. 2017;13:727-41.
124. Cianferotti L, Cricelli C, Kanis JA, Nuti R, Reginster JY, Ringe JD, et al. The clinical use of vitamin D metabolites and their potential developments: a position statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF). Endocrine. 2015;50(1):12-26.