VITAMIN D TESTING AND SUPPLEMENTATION IN ADULTS
SUN AND SHADOWS

Vitamin D testing and supplementation have increased dramatically in the recent years. However, there is uncertainty regarding the clinical benefits of vitamin D in settings other than osteomalacia and rickets. OBJECTIVE To assess the role of vitamin D testing and supplementation in different subpopulations. METHODS A literature search was performed of evidence published until March 2019 in MedLine and The Cochrane Library. This was extended to include clinical practice guidelines and health organizations´ position papers. RESULTS Controversy exists in reference vitamin D values and testing methods to assess vitamin D status. Vitamin D testing would be justified in institutionalized older adults, in subjects with parathyroid disease, phosphocalcium metabolism alterations and malabsorption syndromes. In general, vitamin D supplementation would be indicated in patients with chronic kidney disease with severe hyperparathyroidism, hypoparathyroidism, malabsorption, and in case of confirmed vitamin D deficiency in institutionalized older adults and in people with existing phosphocalcium metabolism alterations. It is recommended to avoid vitamin D supplementation in pregnant or lactating women, unless the benefits outweigh the harms. Exogenous vitamin D does not reduce mortality, cardiovascular events, metabolic diseases or cancer. CONCLUSIONS Vitamin D testing and supplementation is indicated in specific subpopulations. Evidence for beneficial effects of Vitamin D supplementation on clinically-relevant outcomes is limited.

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Introduction

The non-skeletal effects attributed to vitamin D, together with the development of calcifediol (25(OH)-D) assay methods, have resulted in a dramatic increase in vitamin D testing and supplementation in the recent years. Recent data report a 40% prevalence of vitamin D deficiency in the European population, defined as 25(OH)-D concentrations below 20 ng/ml.[1] Yet, 25(OH)-D levels below 20 ng/ml do not necessarily have clinical consequences. Most of the evidence on vitamin D has been provided in observational studies performed to assess the role of supplementation on intermediate variables such as serum calcifediol concentrations or bone mineral density. However, the most reliable and clinically-relevant variable for assessing bone status is the incidence of fracture.[2] Bone mineral density is a surrogate parameter with uncertain reliability in the prediction of individual fracture risk. Indeed, high bone density is not necessarily associated with a lower risk for fracture, since patients with a high bone density may be at a higher risk for fracture.[3]

The purpose of this study was to explore the benefits of vitamin D testing and supplementation on clinically-relevant outcomes such as bone fractures, cardiovascular events and mortality in at-risk population subgroups.

General aspects
Physiologic role of vitamin D

Vitamins are organic compounds categorized as micronutrients. Vitamin D is a fat-soluble compound with main precursor metabolites: ergocalciferol (vitamin D_2), present in plants and fungi; and colecalciferol (vitamin D_3) present in products of animal origin. These two compounds have no biologic activity and acquire their functional characteristics when synthetized into calcidiol or calcifediol (25(OH)-D) and subsequently into calcitrol (1,25(OH)-D).

About 80-90% of vitamin D is produced by skin exposure to ultraviolet radiation. Therefore, exposure to sunlight is the major determinant of circulating concentrations of 25(OH)-D. The synthesis of the active form of vitamin D involves the liver –where precursor 25(OH) D is formed; and the kidney –where this compound is transformed into 1,25(OH)-D –the active form of vitamin D. Only 10-20% of vitamin D comes from by dietary intake.[4]

Up to 80-90% of vitamin D is produced by skin exposure to ultraviolet radiation

Vitamin D is mainly involved in musculoskeletal function via interaction with calcium, phosphorus and parathyroid hormone (PTH) metabolism. Major consequences of severe vitamin D deficiency include rickets in children and osteomalacia in adults. However, vitamin D has been associated with effects at other levels.

Non-skeletal effects of vitamin D

A number of observational studies have suggested an association between low vitamin D levels and several non-skeletal pathologies including cardiovascular diseases, alterations in lipid and glucose metabolism, malignant neoplasms and others.[5-7] However, a cause and effect relation between these conditions and vitamin D deficiency has not been demonstrated to date. Indeed, it is suggested that vitamin D deficiency may be a result rather than a causative factor of these conditions.[8,9]

In the same line, several systematic reviews and meta-analyses of randomized controlled clinical trials have not found evidence that vitamin D supplementation provides any clinical benefit in the prevention or modification of the clinical course of these conditions.[6,9,10] The randomized clinical trials identified in the 2016 review of the Scientific Advisory Committee on Nutrition (SACN) of the UK revealed that vitamin D supplementation would not lead to a significant reduction of cancer risk of.[2] Similarly, this Committee considered the available evidence to be insufficient related to the effect of vitamin D on non-skeletal clinical events such as cardiovascular diseases, hypertension, all-cause mortality and others.[2]

In the same line, a randomized clinical trial was published in 2018 assessing the role of vitamin D supplementation in men of at least 50 years of age and women of at least 55 years of age in US. A total of 25,871 subjects were

included, with a median follow-up of 5.3 years. The study revealed that cholecalciferol supplementation at a dose of 2,000 IU/day plus omega-3 fatty acids as compared to placebo did not reduce the incidence of cancer, major cardiovascular events or mortality from cancer, cardiovascular events or any cause.[11]

In view of the aforementioned, vitamin D testing and supplementation to obtain non-skeletal benefits are not justified. This is consistent with the recommendations of the Spanish Society of Endocrinology and Nutrition,[12] the Endocrine Society[13] and the US Preventive Services Task Force.[14]

A systematic review assessing the effects of vitamin D supplementation on exacerbation of Chronic Obstructive Pulmonary Disease (COPD) was published recently.[15] The results showed that vitamin D supplementation does not significantly reduce the incidence of moderate or severe COPD exacerbation [3 trials, n=469, adjusted incidence rate ratio=0.94, 95% confidence interval (95%CI) (0.78 to 1.13)]; the proportion of participants with at least an episode of moderate/severe exacerbation, time to first moderate/severe exacerbation or mortality. Subgroup analysis revealed that vitamin D supplementation significantly reduced the rate of moderate or severe COPD exacerbation events only in subjects with baseline 25(OH)-D levels below 10 ng/mL [3 clinical trials, n=87, adjusted incidence rate ratio=0.55 95%CI (0.36 to0.84)]. However, in a general population without risk factors in our region, 25(OH)-D concentrations below 10 ng/mL are rare.[15]

Controversy about vitamin D "deficiency" and "inadequacy" criteria

Vitamin D status is generally determined by monitoring 25(OH)-D rather than the active metabolite 1,25(OH)-D. The reason is that 25(OH)-D is the main circulating form of vitamin D; therefore, it is the ideal marker of vitamin D status. Also, 25(OH)-D serum concentration is 1,000 fold higher and has a longer half-life (2-3 weeks vs 4 hours).[7,13]

The way in which vitamin D status was established has been the subject of intense controversy. Categories of vitamin D "deficiency", "inadequacy" and "sufficiency" were defined according to the theoretical effects of serum 25(OH)-D concentrations on bone function. However, bone functionality was determined indirectly using surrogate analytical parameters such as PTH and calcium intestinal absorption.[16] In the studies performed, PTH levels and calcium intestinal absorption were analyzed according to 25(OH)-D concentrations.[16] On this basis, cut-off points for vitamin D "sufficiency", "inadequacy" and "deficiency" were established using statistical criteria, under the assumption that vitamin D requirements have a normal distribution in the population.[16,17] More specifically, the 25(OH)-D level needed for optimal bone

Vitamin D supplementation does not prevent the development of cardiovascular and metabolic diseases or cancer, and does not reduce mortality

health was defined as that related to maximum calcium intestinal absorption and minimum PTH levels.[18] However, this association is subject to significant uncertainty, as PTH concentrations are influenced by additional factors such as age, ethnicity and renal function, among others.[16] In addition, PTH and calcium absorption are indirect markers of bone function, which in turn is dependent on other factors.

Based on these studies, the term "deficiency" was defined as 25(OH)-D concentrations below which calcium absorption would be inadequate, thereby posing a risk for bone demineralization, which may ultimately cause rickets in children and osteomalacia in adults. The term "inadequacy", which is somewhat ambiguous, refers to 25(OH)-D concentrations that would meet the requirements of approximately half the population. The term "sufficiency" or adequate exposure was defined as 25(OH)-D concentration above which bone function would be adequate in virtually all the population. Concentrations above this cut-off point would not involve an additional benefit in terms of bone function.[16,17] Cut-off points of 25(OH)-D that define "deficiency", "inadequacy" and "sufficiency" vary according to the different scientific societies (table 1 and figure 1).[13,16,19,20]

The cut-off points of "deficiency" and "sufficiency" established by the Endocrine Society are higher than those defined by the IOM. This inconsistency is of great relevance to clinical practice. Thus, the use of higher cut-off points involves an increase in the prevalence of vitamin D "deficiency" and "inadequacy".[16]

A review conducted by the IOM professionals in collaboration with other scientists revealed that 25(OH)-D concentrations of 20 ng/mL would meet the needs of the majority of the population, and that higher levels would not provide an additional clinical benefit. This approach would challenge the more is better assumption. Additionally, they considered that the prevalence of vitamin D

"deficiency" and "inadequacy" has been overestimated in North America due to the use of inappropriate cut-off points for 25(OH)-D (30 ng/mL) largely exceeding vitamin D needs.[21]

As aforementioned, the studies on which 25(OH)-D cut-off points for vitamin D "deficiency", "inadequacy" and "sufficiency" were based did not assess their impact on relevant clinical parameters. Therefore, the validity of using 25(OH)-D levels as a marker of functionality or clinical status is questionable. In addition, there are doubts about the real clinical impact of vitamin D "deficiency" and "inadequacy".[16]

Calcidiol concentrations > 20 ng/mL do not require vitamin D supplementation.

Interests in relation to vitamin D testing and supplementation

Conflicts of interest about vitamin D are illustrated by the case of the American endocrinologist Michael F. Holick. Dr Holick is one of the most prolific authors on vitamin D and is the lead author of the 2011 Endocrine Society Practice Guideline for evaluation, treatment, and prevention of vitamin D deficiency.[13] According to a recent article published in The New York Times, this researcher used his prominent position in the medical community to promote practices, which would benefit corporations with economic interests in vitamin D.[22] More specifically he has worked as a consultant for Quest Diagnostics, a laboratory that provides vitamin D testing services. Moreover, he received 163,000 $ from pharmaceutical industry between 2013 and 2017, more specifically from Sanofi-Aventis, which markets vitamin

D supplements; from Shire and Amgen, which markets drugs for parathyroid alterations and osteoporosis; and from Roche Diagnostics and Quidel Corporation, which market vitamin D tests, among others. Dr. Holick also received funds from "UV Foundation", a foundation of UV cabin manufacturers and providers, for research purposes. However, although he declared that these facts did not influence him, he was found to have promoted the adoption by the Endocrine Society of a cut-off point for 25(OH)-D "deficiency" and "sufficiency" above the one established by the IOM. Dr Holick could also have influenced the dramatic increase in vitamin D tests and supplementation occurring in US in the last years. Thus, the use of vitamin D supplementation in US increased 9 fold in the past decade. Vitamin D tests increased by 547% (more than 10 million determinations of vitamin D in 2016 in Medicare patients), with an approximate cost of 365 million dollars.[22]

Table 1. Institute of Medicine (IOM) and Endocrine Society cut-off points of 25(OH)-D concentrations defining vitamin D "deficiency", "inadequacy" and "sufficiency".

	Institute of Medicine (IOM)	Endocrine Society
Risk for deficiency	<12 ng/mL	<20 ng/mL
Risk for inadequacy	12-19 ng/mL	21-29 ng/mL
Sufficiency	≥20 ng/mL	≥30 ng/mL

Conversion: 1 ng/mL 25(OH)-D equals 2.5 nmol/L 25(OH)-D
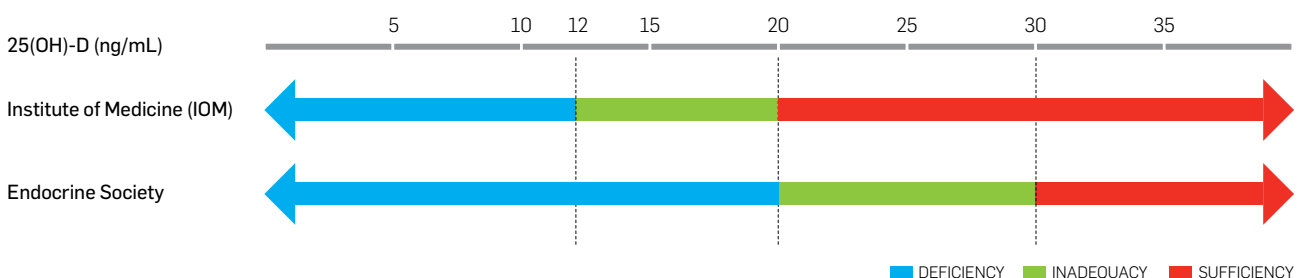
Figure 1. IOM and Endocrine Society definition of vitamin D "deficiency", "inadequacy" and "sufficiency".

Time course of vitamin D tests and supplementation in Navarra

Figure 2 displays the time course of the number of people covered by the Navarre Health Service (SNS-O) who were prescribed vitamin D supplements:

In the recent years the number of people who were prescribed vitamin D supplements has increased significantly in Navarre. Of the total people using vitamin D supplements in 2018, 84% were adults of at least 18 years of age.

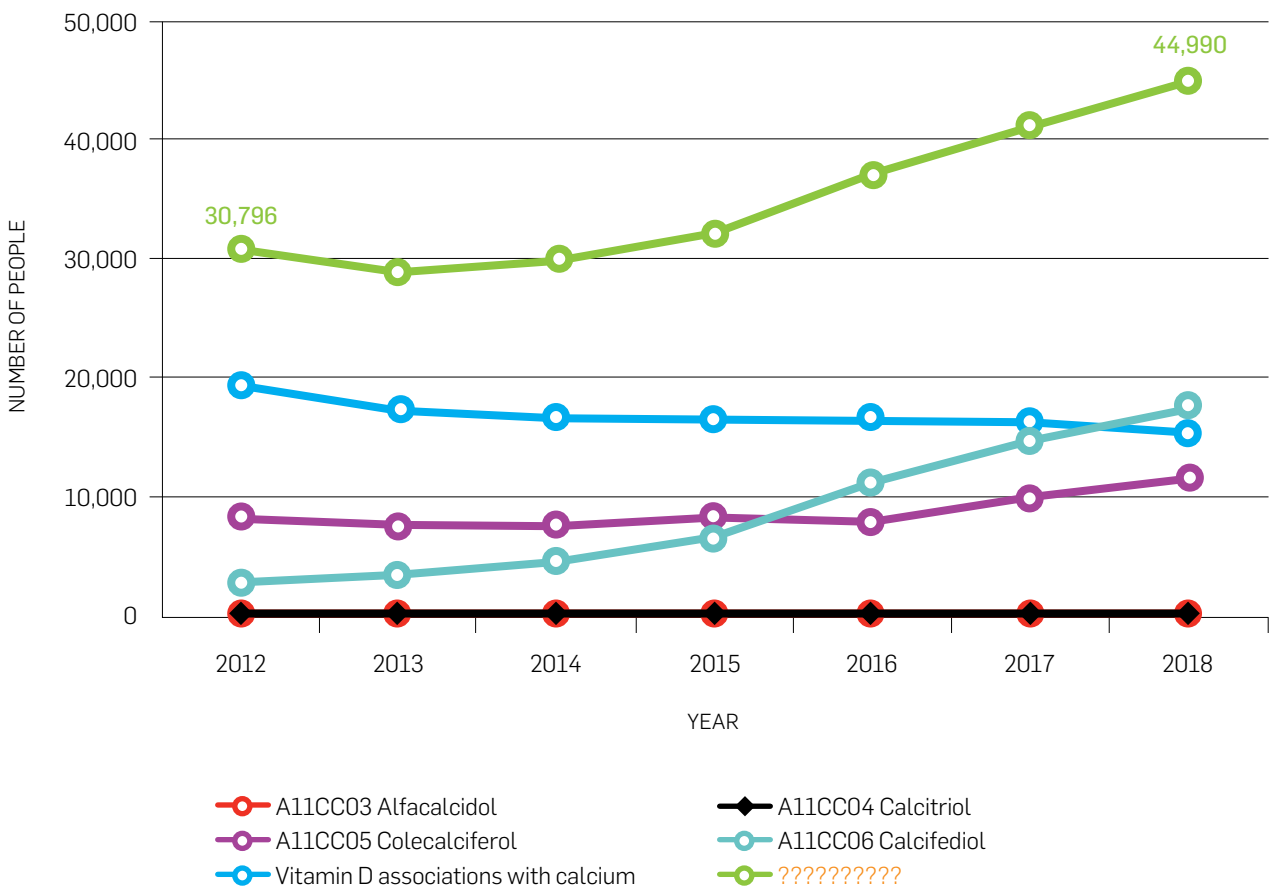The time course of the number of 25(OH)-D tests performed in SNS-O is shown in figure 3.

Limitations to determinations of serum 25(OH)-D concentration

Determination of 25(OH)-D levels can be performed using different analytical assays including automated immunoassays, high-resolution liquid chromatography or liquid chromatography tandem mass spectrometry. Although the last technique is the gold standard for 25(OH)-D measurement, the most frequently used method for its high efficiency is immunoassay.[2,23] Nevertheless, there is variability in the sensitivity and specificity of immunoassays developed by different manufacturers.[23] In addition, the different techniques and laboratories are subject to variability in the accuracy, which may lead to differences in the concentrations obtained based on the technique used.[2,23] The Vitamin D External Quality Assurance Scheme, which audits vitamin D test quality for a total of 700 laboratories worldwide, has reported a 15-20% variability in 25(OH)-D concentrations depending on the method of measurement employed. This may result in many patients being erroneously classified in terms of vitamin D deficiency.[2,24] This fact may hinder comparability of studies and the correct interpretation of results from studies assessing the correlation between vitamin D concentrations and clinical effects. It also has relevant clinical implications, as 25(OH)-D levels are used as a reference when it comes to prescribe or not vitamin D supplementation.[2,5]

Correlation between dietary vitamin D intake and 25(OH)-D concentrations

Serum 25(OH)-D levels are not linearly related to the dose of vitamin D supplemented due to the complex pharmacokinetics of vitamin D and other environmental variables that may interfere with the levels obtained.[25]

Figure 2. Displays the time course of the number of people covered by the Navarre Health Service (SNS-O) who were prescribed vitamin D supplements.
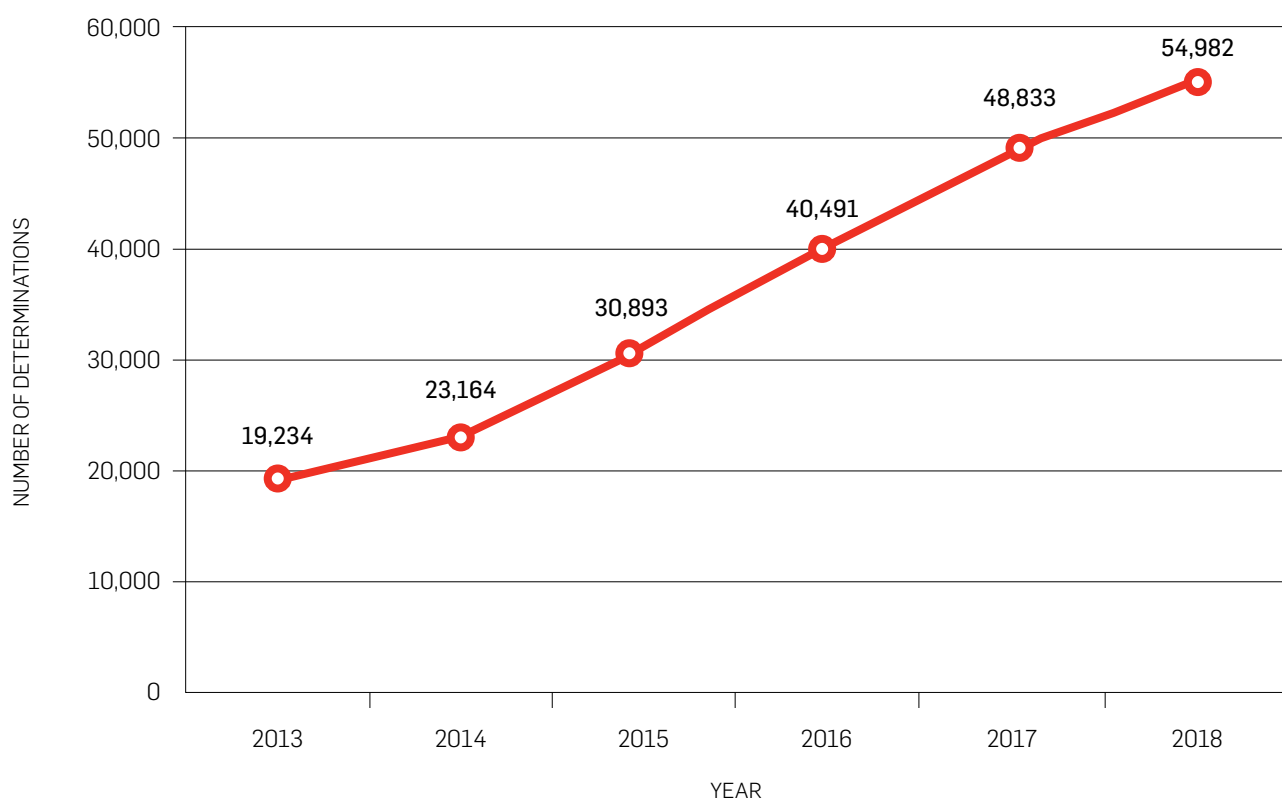
Figure 3. Time course of the number of 25(OH)-D tests performed in SNS-O (Data provided by the SNS-O Service of Clinical Tests).

Therefore, vitamin D management and supplementation should not only be based on serum 25(OH)-D concentration, as it is a surrogate marker subject to wide variability and uncertainty.

Prevalence of vitamin D deficiency and population subgroups at risk

Endogenous vitamin D synthesis by exposure to sunlight depends on multiple factors such as seasonality, latitude, and skin pigmentation, to name a few.[16] Based on the 12 ng/mL threshold established by the IOM, the mean 25(OH)-D concentrations throughout the year would correspond to "deficiency" in about 13% of European youngsters and adults, with a higher prevalence in the October-March period (17.7%) and lower in the April-November period (8.3%). Conversely, based on the 20 ng/mL cut-off point established by the Endocrine Society, the prevalence of vitamin D deficiency in Europe would increase to 40.4%, being this figure higher in northern Europe as compared to central Europe (92% vs 57-64%).[1,5]

Furthermore, the proportion of subjects with low 25(OH)-D concentrations is higher among older adults. A study conducted in Spain involving 239 community-dwelling subjects older than 64 years revealed that 25(OH)-D levels ranged 11 to 25 ng/mL in 70% of subjects, and 17% had levels below 10 ng/mL.[26] As to older institutionalized adults, a Spanish study in 100 subjects with

Available calcidiol assays can yield markedly differing results

ages ranging from 61 to 96 years showed that 87% had 25(OH)-D levels lower than 25 ng/mL.[27] Although this result may cause alarm, only 19 of the 87 subjects (21.8%) with 25(OH)-D levels below 25 ng/mL had secondary hyperparathyroidism.[27] In addition, only the relationship between 25(OH)-D concentrations and PTH levels was assessed in these studies. Yet, the impact of low 25(OH)-D levels on bone function as assessed based on clinical parameters such as the incidence of fractures was not explored.[26,27] In this sense, as mentioned before, the risk of developing bone mineralization disorders would be generally associated with 25(OH)-D levels lower than 12 ng/mL, according to the IOM.[16]

Apart from older adults, a number of institutions and scientific societies have identified specific subgroups for which vitamin D testing and/or supplementation

would be indicated due to an increased risk of vitamin D deficiency. That is the case of people with rickets, chronic kidney disease, liver failure, malabsorption syndromes, hyperparathyroidism, obesity, pregnant women and patients under treatment with antiepileptics and glucocorticoids, to name a few.[12,13] However, in most cases, robust evidence supporting vitamin D testing and supplementation in each of these settings has not been provided. Therefore, except for cases where the need for vitamin D supplementation is sufficiently established, as in people with rickets or osteomalacia, the role of vitamin D must be carefully examined.

Evidence based on patient's profile

Our purpose is to determine the benefits of vitamin D testing and supplementation on clinically-relevant outcomes including fractures, cardiovascular events and mortality.

Adult asymptomatic population without vitamin D deficiency risk factors

Almost the totality of vitamin D is produced physiologically through skin exposure to ultraviolet radiation. Skin exposure to ultraviolet radiation is estimated by the Minimum Erythematous Dose (MED), which is the amount of ultraviolet radiation that causes a minimal erythema in the skin (slightly rosy tone). In general terms, sun exposure of a healthy young or mean-age adult to 1 MED would cause 25(OH)-D levels comparable to those obtained with the intake of 10,000-25,000 IU of vitamin D3. Hence, exposure of the face, arms and hands to 1/6-1/3 MED would be enough to produce the amount of vitamin D required. Sun exposure needed to reach this target varies according to external factors such as latitude, season of the year, time of the day, ozone concentrations, and cloudiness, among other factors; and to individual factors such as skin pigmentation and age.[16] In this sense, face, arms and hands exposure to sunlight for 10-15 minutes 2-3 times per week between 10 a.m. and 3 p.m. in summer, spring and fall at 40º latitude –which corresponds to central Spain– would be enough to meet vitamin D needs.[28,29]

The evidence published so far has not demonstrated that vitamin D testing confers any clinical benefit to the general asymptomatic population without risk factors for vitamin D deficiency. Risk factors include limited sun exposure, advanced age, malabsorption syndromes, hyperparathyroidism and others. The US Preventive Services Task Force concluded that there is insufficient evidence to support assessing the risk-benefit balance of vitamin D testing in asymptomatic adults.[14,24] Other health institutions and scientific societies including Choosing Wisely, the UK National Osteoporosis Society, the Endocrine Society, and Spanish Society of Endocrinology and Nutrition have gone further and do not recommend vitamin D

Vitamin D testing in asymptomatic adult population is not justified

testing in the general population.[12,13,30,31] This means that, to this date, vitamin D testing and supplementation in the general population without risk factors is not justified.

Community-dwelling older adults

Six relevant reviews were identified exploring the effects of vitamin D supplementation in community-dwelling older adults. Data are shown in Table 2.[32-37]

Added to these studies, a review on medical overuse performed in 2018 revealed that vitamin D and calcium supplementation does not provide any clinical benefit in terms of bone fractures in community-dwelling older adults; therefore, vitamin D supplementation is not recommended for this population.[38]

Notably, the systematic review conducted by Zhao et al. demonstrated that annual high-dose vitamin D was associated with an increased risk for hip fracture of 41% [3 clinical trials, relative risk (RR)=1.41 95%CI (1.02 to 1.96)] vs placebo or no treatment.[34] In the same line, in a review carried out by Guirguis-Blake et al., the only clinical trial where the effects of annual high-dose cholecalciferol supplementation (500,000 IU) was assessed vs placebo revealed a significant increase in falls [incidence rate ratio=1.16 95%CI (1.03 to 1.31)], injurious falls [incidence rate ratio=1.15 95%CI (1.02 to 1.29)] and fallers [RR=1.08 95%CI (1.03 to 1.14)] with cholecalciferol.[36] No differences were reported in the review by Bolland et al. in the incidence of hip fractures, total fractures and falls, when high-dose vitamin D supplementation was compared to low-dose vitamin D supplementation.[37]

As to safety reports, Kahwati et al. reported an increase in the incidence of kidney stones with vitamin D and calcium supplementation [3 clinical trials, n=39,213, pooled absolute risk difference (ARD)= 0.33% 95%CI (0.06% to 0.60%)].[35]

The available evidence does not demonstrate that vitamin D supplementation alone or in combination with calcium reduces the risk for falls, factures, mortality or cardiovascular events. In addition, supplementation of intermittent high-dose vitamin D did not yield clinical benefit.

Therefore, to this date vitamin D testing and routine supplementation in community-dwelling older adults would not be justified. This is consistent with the recommendation of the US Preventive Services Task Force.[39] In agreement with these recommendations, the UK National Osteoporosis Society does not support routine 25(OH)-D testing in the elderly.[31]

Institutionalized older adults

Studies included in this section refer to people of an advanced age who reside in institutions (nursing homes or residential care homes) and long-term care. The available evidence in this respect is summarized in Table 3.[33,40]

Cameron et al. reviewed safety data, although evidence provided in the studies included was very limited and of very low quality. No severe adverse events associated with vitamin D supplementation were reported in any of the studies. Safety data related to vitamin D with calcium supplementation were only provided in a study (vitamin D 3,800 IU + calcium carbonate 1,200 mg daily), where three cases of hypercalcemia were reported in the intervention arm.[40]

Vitamin D testing would be justified for institutionalized elderly as a preliminary step prior to considering supplementation. In this sense, only 25(OH)-D concentrations below deficiency threshold (12 ng/mL) would affect bone mineralization. Where appropriate, the administration of vitamin D in association with calcium should be considered.

Parathyroid or kidney disease, and phoshocalcium metabolism alterations

Vitamin D concentrations are closely related to levels of calcium, phosphorus and PTH. Therefore, it may be of interest to assess the effects of vitamin D supplementation on relevant variables in patients with parathyroid, renal or phosphocalcium metabolism alterations.

Parathyroid disease

Serum vitamin D concentrations are inversely associated with PTH levels. Thus, it has been suggested that vitamin D supplementation may help reduce PTH levels in patients with hyperparathyroidism. However, this relationship is in turn influenced by other factors such as age, dietary calcium intake, renal function, ethnicity, and magnesium and vitamin D binding protein status.[31]

The limited data available is provided in a review of nine observational studies involving a total of 547 subjects. This review assesses the effect of vitamin D supplementation in subjects with mild primary hyperparathyroidism and concomitant vitamin D deficiency. Vitamin D supple-

Vitamin D supplementation in community-dwelling older adults does not provide any clinical benefit

mentation was associated with a significant increase in 25(OH)-D concentrations, but did not yield significant changes in PTH.[41] On the other hand, evidence on the impact of vitamin D supplementation on clinical variables of interest in patients with hyperparathyroidism is very limited. However, Kidney Disease: Improving Global Outcomes (KDIGO) guidelines indicate that vitamin D supplementation would be justified in patients with chronic kidney disease with secondary severe or progressive hyperparathyroidism.[42]

In patients with hyperparathyroidism, vitamin D testing would be justified for diagnostic purposes to determine if hyperparathyroidism is primary or secondary. Routine vitamin D supplementation in these patients would not be justified, as there is no evidence on its effects on clinical variables, although it may be indicated for patients with chronic kidney disease with severe or progressive hyperparathyroidism.

Hypoparathyroidism is associated with hypocalcemia. Therefore, the conventional approach to hypoparathyroidism is based on vitamin D and calcium supplementation. PTH drives vitamin D conversion into its active form, which stimulates intestinal calcium absorption. Thus, in the presence of hypoparathyroidism, it is necessary to administer vitamin D in its active form (calcitriol).[43] In general in patients with hypoparathyroidism, vitamin D testing would be justified to rule out the presence of inadequate vitamin D levels.

Kidney disease

A review published in 2013 assessed the effects of vitamin D in patients with chronic kidney disease not requiring dialysis. A total of 18 trials were identified, most of moderate quality. The review revealed that vitamin D supplementation was associated with a reduction in the risk for proteinuria [n=685, RR 2.00 95%CI (1.42 to 2.81), I2=39.9%] as compared to placebo or no treatment. However, no significant differences were observed in glomerular filtration rate, progression to dialysis or mortality. Vitamin D supplementation increased the

Table 2. Evidence of vitamin D supplementation in community-dwelling older adults.

Author, year	Population or population subgroups of interest	Baseline 25(OH)-D levels	Intervention and comparator	Variable	Results		Interpretation
Gillespie et al. 2012[32]	Community-dwelling, ≥60 years	Mean ranging from 10 and 72.6 ng/mL	Vitamin D±calcium vs. control/placebo	Rate of falls*	Rate ratio=1.00 95%CI (0.90 to 1.11), I²=69% (7 clinical trials, n=9,324)		
				Risk of falling**	RR=0.96 95%CI (0.89 to 1.03), I²=58% (13 clinical trials, n=26,747)		No benefit
				Fracture	RR=0.94 95%CI (0.82 to 1.09), I²=49% (10 clinical trials, n=27,070)		
Avenell et al. 2014[33]	Community-dwelling, mean/median age >65 years	Mean ranging from 11 and 34 ng/mL	Vitamin D + calcium vs. Control/placebo	Hip fracture	RR=0.91 95%CI (0.77 to 1.09), I²=0% (7 clinical trials, n=46,000)		No benefit
Zhao et al. 2017[34]	Community-dwelling, >50-year	Mean ranging from 11 and 30.8 ng/mL	Vitamin D vs. Placebo/no treatment		**Vitamin D alone**	**Vitamin D + calcium**	
				Hip fracture	RR=1.21 95% CI (0.99 to 1.47), I²=0% (9 clinical trials, n=20,672) ARD=0.00 95%CI (-0.00 to 0.01)	RR=1.09 95%CI (0.85 to 1.39), I²=0% (7 clinical trials, n=17,927) ARD=0.00 95%CI (-0.00 to 0.00)	
				Vertebral fracture	RR=0.97 95%CI (0.54 to 1.77), I²=39% (4 clinical trials, n=7,689)	RR=0.63 95%CI (0.29 to 1.40), I²=0% (3 clinical trials, n=6,140)	No benefit
				Nonvertebral fracture	RR=1.10 95%CI (1.00 to 1.21), I²=0% (8 clinical trials, n=20,443)	RR=0.88 95%CI (0.75 to 1.03), I²=0% (6 clinical trials, n=6,764)	
				Total fractures	RR=1.01 95%CI (0.87 to 1.17), I²=20% (14 clinical trials, n=13,106)	RR=0.90 95%CI (0.78 to 1.04), I²=0% (8 clinical trials, n=10,064)	
Kahwati et al. 2018[35]	≥50 years community-dwelling, without previous history (or at least, unknown) of vitamin D deficiency, osteoporosis or prior fracture		Vitamin D±calcium vs. placebo	Hip fracture	ARD=-0.01% 95%CI (-0.80% to 0.78%), I²=0% (3 clinical trials, n=5,496) RR=1.08 95%CI (0.79-1.48), I²=0%	ARD=0.14% 95%CI (-0.34% to 0.07%) (2 clinical trials, n=36,727)	No benefit
				Total fractures	Non-adjusted ARD=-2.26% 95%CI (-4.53% to 0.00%) (1 clinical trial, n=2,686) Non-adjusted RR= 0.80 95%CI (0.63 to 1.00)	ARD= -0.35% 95%CI (-1.02% to 0.31%) (1 clinical trial, n=36,282)	Vit D: very limited clinical benefit, within statistical significance limit. Vit D+calcium: no benefit
				All-cause mortality	ARD=-0.74% 95%CI (-1.80% to 0.32%), I²=19.6% (4 clinical trials, n=10,599) RR=0.91 95%CI (0.82 to 1.01), I²=0.0%	1 clinical trial (n=2,303): ARD=-0.19% 95%CI (-0.90% to 0.52%) RR=0.77 95%CI (0.29 to 2.07) 1 clinical trial (n=36,282): ARD=-0.36% 95%CI (-0.78% to 0.05%) Hazard ratio=0.91 95%CI (0.83 to 1.01)	No benefit
				Cardiovascular disease	No statistically significant differences (3 clinical trials, n=8,021)	No statistically significant differences (1 clinical trial, n=36,282)	
Guirguis-Blake et al. 2018[36]	Community-dwelling, ≥65 years	Mean ranging from 18 and 32 ng/mL	Vitamin D vs. placebo	Rate of falls*	Incidence rate ratio=0.97 95%CI (0.79 to 1.20), I²=75.8% (5 clinical trials, n=3,529)		
				Risk for falling**	RR=0.97 95%CI (0.88 to 1.08), I²=60.3% (6 clinical trials, n=6,519)		No benefit
				Mortality	RR=1.08 95%CI (0.83 to 1.40), I²=0% (6 clinical trials, n=7,084)		
Bolland et al. 2018[37]	Mostly ≥65 years community-dwelling	6% <10 ng/mL; 57% <20 ng/mL; 99% <30 ng/mL	Vitamin D vs. placebo/no treatment	Hip fractures	RR=1.11 95%CI (0.97 to 1.26), I²=0% (20 clinical trials, n=36,655)		
				Total fractures	RR=1.00 95%CI (0.93 to 1.07), I²=5% (36 clinical trials, n=44,790)		No benefit
				Fall	RR=0.97 95%CI (0.93 to 1.02), I²=41% (37 clinical trials, n=34,144)		

95%CI: 95% confidence interval; ARD: absolute risk difference; RR: relative risk.
(*) Number of falls per person-time.
(**) Number of subjects who had at least 1 fall.

Table 3. Evidence of vitamin D supplementation in institutionalized older adults.

Author, year	Population or population subgroups of interest	Baseline 25(OH)-D levels	Intervention and comparator	Variable	Results		Interpretation
Avenell et al. 2014[33]	Institutionalized older adults (Chapuy 1992: ≥69 years, Chapuy 2002: mean age: 85 years)	Mean ranging from 10 and 72.6 ng/mL	Vitamin D+calcium vs. placebo	Hip fracture	RR=0.75 95%CI (0.62 to 0.92) ARR=0.03 95%CI (0.01 to 0.05) (2 clinical trials. n=3,853)		Statistically significant differences, but with limited benefit in absolute terms
Cameron et al. 2018[40]	≥65 years institutionalized or hospitalized	About 90% <24 ng/mL. Mean about 19-20 ng/mL.	Vitamin D±calcium vs. placebo±calcium, calcium alone or no treatment		**Vitamin D alone**	**Vitamin D + calcium**	
				Rate of falls*	Razón de tasas=0,72 IC95% (0,55 a 0,95), I²=62% (4 ensayos clínicos, n=4.512)		Benefit
				Risk for falling**	RR=0.92 95%CI (0.76 to 1.12), I²=42% (4 clinical trials, n=4,512)	RR=1.03 95%CI (0.90 to 1.18), I²=non-applicable (1 clinical trial, n=583)	No benefit
				Risk for fall-related fractures	RR=1,09 IC95% (0,58 a 2,03), I²=63% (3 ensayos clínicos, n=4.464)	RR=0,62 IC95% (0,36 a 1,07), I²= no aplica (1 ensayo clínico, n=583)	

95%CI: 95% confidence interval; ARR: absolute risk reduction; RR: relative risk.
(*) Number of falls per person-time.
(**) Number of subjects who had at least 1 fall.

risk for hypercalcemia [n=1,378, RR 4.78 95%CI (2.20 to 10.37), I2=0%].[44]

Another review carried out in 2015 involving patients with chronic kidney disease in predialysis revealed that active vitamin D analogues (calcitrol and paricalcitol) were linked to a reduction in cardiovascular events as compared to a control group [n=715, RR 0.27 95%CI (0.13 to 0.59), I2=0%]. However, in agreement with the previous case, the risk for hypercalcemia increased with paricalcitol [n=718, RR 7.85 95%CI (2.92 to 21.10), I2=0%].[45]

A more recent review included 17 clinical trials with a total of 1,819 patients with chronic kidney disease. This review showed that vitamin D supplementation did not significantly reduce all-cause or cardiovascular mortality vs no supplementation.[46] Added to this review there is a randomized, open-label clinical trial involving 976 patients on hemodialysis without secondary hyperparathyroidism published in 2018. In this study, no significant differences were reported in terms of cardiovascular events or all-cause mortality in subjects treated with alfacalcidol vs no alfacalcidol.[47]

The 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder Guideline does not recommend routine supplementation of calcitriol and vitamin D analogs in patients with G3a-G5 chronic kidney disease (glomerular filtration rate $\leq$ 59 ml/min/1.73 m^2) not on dialysis. According to these guidelines, the administration of calcitriol and vitamin D analogs should be reserved to patients with chronic kidney disease not receiving dialysis with secondary severe and progressive hyperparathyroidism. The reason is that vitamin D supplementation in patients with moderately elevated PTH levels does not provide any clinical benefit. In patients with G5D chronic kidney disease (glomerular filtration rate < 15 ml/min/1.73 m2) on dialysis who require PTH-lowering therapy, it is recommended to administer calcimimetics, calcitriol, vitamin D analogues or their combinations.[42,48]

In general, in patients with impaired kidney function, vitamin D supplementation does not yield any benefit in terms of total or cardiovascular mortality and seems to increase the risk for hypercalcemia. With regard to cardiovascular events, inconsistent results have been obtained. Therefore, vitamin D testing and supplementation in all patients with chronic kidney disease would not be justified. In any case, vitamin D testing and supplementation would be justified in patients with chronic kidney disease that present with severe or progressive hyperparathyroidism.

Phosphocalcium metabolism alterations

Vitamin D deficiency is usually accompanied by normal blood levels for calcium and phosphorus.[49] This explains that vitamin D supplementation is associated with a

higher risk for hyperphosphatemia and hypercalcemia, mostly in patients with kidney disease who do not receive dialysis and following the administration of high doses of vitamin D (>50,000 IU/day of cholecalciferol).[50,51] Therefore, vitamin D testing in patients receiving vitamin D supplementation with elevated phosphorus and calcium levels, especially in a setting of kidney failure, would be justified to rule out the existence of elevated vitamin D levels. Should it be the case, supplementation should be discontinued.

In relation to the prevention of hypocalcemia following a thyroidectomy, a review published in 2013 revealed that vitamin D and calcium supplementation prevents symptomatic hypocalcemia, in comparison with no supplementation [5 clinical trials, n=1,084, OR=0.37 95%CI (0.26 to 0.52), I2=56.4%]. Yet, heterogeneity in the results obtained renders this conclusion questionable. Additionally, the effects of vitamin D supplementation alone (calcitriol) vs no supplementation were only assessed in a study. However, the small sample size of the study (less than 50 participants) hinders drawing firm conclusions.[52] In a subsequent review,[53] another clinical trial that assessed the role of vitamin D (alfacalcidol) in the prevention of hypocalcemia following thyroidectomy was identified.[54] This study, which was based on a sample of 219 subjects, revealed that vitamin D supplementation was associated with a lower incidence of symptomatic hypocalcemia as compared to no supplementation (11% vs. 22%, p=0.02), although no differences were observed in the number of patients with postoperative hypocalcemia. Similarly, calcium and vitamin D levels were reported to be similar in the two groups at five weeks after surgery.[54]

In general terms, vitamin D testing would be justified in patients with hypophosphatemia and hypocalcemia to exclude vitamin D deficiency. Should it be the case, supplementation would be required. Nevertheless, the effects of vitamin D supplementation on clinically important outcomes are unknown.

Malabsorption syndromes

The term "malabsorption syndrome" encompasses conditions such as celiac disease, inflammatory bowel disease, Crohn's disease, cystic fibrosis and gastric or small bowel surgery.[25,55] According to a meta-analysis of observational studies, serum vitamin D levels would be lower in patients with Crohn's disease as compared to patients without the disease, with an inverse relationship between circulating 25(OH)-D concentrations and Crohn's disease severity.[56]

Only small studies of limited quality have been published on the effects of vitamin D supplementation in celiac patients, patients undergoing bariatric surgery and patients with cystic fibrosis. These studies focus on the effects of supplementation on bone mineral density, but

not on other clinically-relevant variables.[57-59] A Cochrane systematic review identified six randomized and quasi-randomized clinical trials (n=239) comparing the effect of vitamin D supplementation vs placebo in patients with cystic fibrosis. The sample size was limited and supplementation was not found to yield any clinical benefit. The effect of vitamin D supplementation on the incidence of bone fractures was not assessed in any of the included studies. No adverse events were reported in any of the studies either.[60]

The Endocrine Society recommends increasing dietary vitamin D intake in patients with malabsorption syndromes.[13] Based on the physical inability of these patients to absorb vitamin D, vitamin D testing and supplementation may be recommended. However, no conclusive evidence has been published to date demonstrating that supplementation would provide significant clinical benefits.

Pregnancy and breastfeeding

Vitamin D levels in the fetus and neonate depend on maternal vitamin D status. The National Institute for Health and Care Excellence (NICE) recommends supplementing vitamin D in all women during pregnancy.[61] Notwithstanding the above, NICE noted that supplementation is better grounded for pregnant women at risk for vitamin D deficiency and remarks that evidence on the benefits of supplementation in low-risk pregnant women is limited.[61] This recommendation contradicts that of institutions such as IOM, the Endocrine Society, SACN, and the European Food and Safety Authority (EFSA), which recommend the same dietary vitamin D intake for pregnant and breastfeeding women as to the rest of women.[2,13,16,62]

A Cochrane review published in 2016 analyzed the effect of vitamin D supplementation vs placebo or no supplementation in pregnant women, excluding those with pre-existing conditions such as gestational diabetes. No statistically significant differences were observed in the risk for preeclampsia [2 clinical trials, 219 women, RR=0.52 95%CI (0.25 to 1.05), I2=0%, low quality] or the risk for gestational diabetes [2 clinical trials, 219 women, RR=0.43 95%CI (0.05 to 3.45), I2=0%, very low quality]. As to its effects on neonates, vitamin D supplementation during gestation was associated with a lower risk for preterm labour [3 clinical trials, 477 women, R= 0.36 95%CI (0.14 to 0.93), I2=10%, moderate quality] and having a baby with a birth weight below 2,500 g [3 clinical trials, 493 women, RR=0.40 95%CI (0.24 to 0.67), I2=4%, moderate quality] vs no intervention/placebo. No statistically significant differences were observed in the incidence of caesarean sections or the risk for neonatal death.[63]

Another review published in 2018 revealed that vitamin D supplementation in pregnant women was associated with a lower risk of birth weight below the 10th percentile for the corresponding gestational age [6 clinical trials, n=898, RR=0.72 95%CI (0.52 to 0.99), risk difference=-5.60% 95%CI (-0.86% to -10.34%)]. However, differences were not statistically significant in terms of fetal or neonatal mortality, congenital abnormality, gestational age, low birth weight or preterm birth. Paradoxically, whereas vitamin D supplementation at a dose of 2,000 IU/day or less was associated with a statistically significant reduction in fetal or neonatal mortality [RR=0.35 95% CI (0.15 to 0.80)], no significant differences were obtained with doses higher than 2,000 IU/day [RR=0.95 95%CI (0.59 to 1.54)].[64]

In general, vitamin D supplementation during gestation has not proven to yield any benefit in terms of maternal outcomes. As to neonates, the results reported for preterm birth and birth weight are inconsistent. No significant differences were found in fetal or neonatal mortality or gestational age.

Safety of vitamin D supplementation

As endogenous synthesis of vitamin D is regulated physiologically, long exposure to sunlight does not result in excessive vitamin D production.[31] Exogenous vitamin D supplementation is not associated with safety problems if used in accordance with the posology established for each pharmaceutical form. However, high-dose vitamin D supplementation or in combination with calcium could increase the risk for adverse events.[31] In addition, some patients could have a higher risk for adverse events, as it is the case of subjects with kidney impairment, normocalcemic hyperparathyroidism, or granulomatous diseases such as sarcoidosis and tuberculosis or genetic pre-disposition such as childhood idiopathic hypercalcemia.[2]

The most frequent adverse event associated with vitamin D supplementation is hypercalcemia. Elevated plasma calcium levels could potentially cause soft tissue calcification, thereby affecting cardiovascular and kidney function. It could also lead to hypercalciuria, which is a risk factor for kidney stones in the long term.[2,31]

A systematic review was conducted to analyze the evidence published until 2015 on the risk for hypercalcemia, hypercalciuria and kidney stones following vitamin D supplementation for at least 24 weeks. Forty-eight clinical trials were identified involving a total of 19,833 adults (including hospitalized, ambulatory, institutionalized, non-institutionalized and healthy adults). The risk for hypercalcemia [37 clinical trials, RR=1.54 95%CI (1.09 to 2.18)] and hypercalciuria [14 clinical trials, RR=1.64 95%CI (1.06 to 2.53)] was reported to increase with vitamin D supplementation vs placebo. However, supplementation was not associated with a significant increase in the risk for kidney stones [9 clinical trials, RR=0.66 95%CI (0.41 to 1.09)]. No differences were observed in these variables based on baseline 25(OH)-D

levels, vitamin D dose, duration of supplementation or according to the combination with calcium.[65]

A larger review was performed later by the same authors to assess the risk for noncalcemic adverse events and of withdrawals after vitamin D supplementation for at least 24 weeks in adults. A total of 128 clinical trials were identified involving a total of 52,297 subjects. No statistically significant differences were observed in the incidence of adverse events as compared to placebo or control group. Vitamin D supplementation was not associated with a higher number of withdrawals.[66]

The same authors collected data published until 2018 on the risk for adverse events of any type potentially associated with the administration of vitamin D2 or D3 at doses of at least 2,800 IU/day for one year or longer. Vitamin D supplementation as compared to placebo was not found to significantly increase the risk for total adverse events (10 clinical trials, n=1,731), kidney stones (5 clinical trials, n=1,336), hypercalcemia (10 clinical trials, n=2,598) or hypercalciuria (3 clinical trials, n=276).[67]

Regarding the safety of vitamin D supplementation during pregnancy and breastfeeding, recommendations included in product labels are summarized in Table 4.[68]

Table 4. Recommendations for the administration of vitamin D during pregnancy and breastfeeding period.

Active substance	Pharmaceutical form	Pregnancy	Lactance
Alfacalcidol	Alfacalcidol 0.25 and 0.5 mg capsules Alfacalcidol 2 mcg/mL oral drops Alfacalcidol 1 mcg and 2 mcg injectable solution	Do not use unless clearly required.	Consider whether to interrupt breastfeeding or interrupt/not initiate alfacalcidol therapy after balancing the benefit of lactance for the infant against and the benefit of the treatment for the mother. Breastfeed infants to mothers using alfacaldidol should be tested for hypercalcemia.
Calcifediol	Calcifediol 0.266 mg capsules, 0,266 mg oral solution, 0.1 mg/mL oral drops	As a safety measure, avoid using calcifediol during pregnancy, unless its potential benefit outbalances the potential risks for the fetus.	Avoid use.
	Calcifediol 3 mg ampoule for oral solution	Contraindicated	
Calcitriol	Calcitriol 1 mcg/mL injectable solution	Calcitriol 1 mcg/mL should only be administered if its potential benefit outbalances the potential risks for the fetus or neonate.	
	Calcitriol 0.25 mcg and 0.5 mcg capsules	This form should only be administered if its expected benefits outbalance its potential risks for the fetus.	In case calcitriol is used by breastfeeding mothers, serum calcium concentrations should be tested in both, the mother and infant.
Colecalciferol	Cholecalciferol 25,000, 50,000 and 100,000 ampule for oral solution.	It is not recommended during pregnancy. During pregnancy, the daily dose of vitamin D should not exceed 600 IU.	Cholecalciferol can be prescribed, if necessary.
	Cholecalciferol 10,000 and 25,000 IU/mL oral drops	The recommended daily intake of this form in pregnant women is 400 IU. However, in women with vitamin D deficiency, it can be administered at a higher dose (up to 2,000 IU/day). Pregnant women should follow their physician's instructions, as vitamin D needs may vary with the severity of their disease and depend on patient's response to therapy.	
	Cholecalciferol 800 IU tablets	Cholecalciferol can be used during pregnancy only in case of vitamin D deficiency. The daily intake should not exceed 600 IU of vitamin D.	Cholecalciferol can be used by breastfeeding women.

IU: International Units.

In general, the administration of alfacalcidol, calcifediol, calcitriol and cholecalciferol are not recommended during pregnancy and breastfeeding. In any case, they should only be administered if the potential benefit for the mother outbalances the potential risk for the fetus or neonate. In all cases, calcifediol 3 mg ampoules for oral solution are contraindicated during pregnancy and breastfeeding. The administration of these compounds at high doses during pregnancy can cause hypercalcemia in the mother, which could in turn lead to supravalvular aortic stenosis, retinopathy and physical and mental retardation in the fetus and neonate. In addition, these compounds are excreted in breast milk, so maternal exposure to high doses of vitamin D can result in high concentrations in breast milk, thereby causing hypercalcemia in the breastfeed infant.[68]

The Spanish Medicines and Health Devices Agency recently published an informative note motivated by reports of severe cases of hypercalcemia due to vitamin D overdosing in adults and children. The note highlights the importance of selecting the adequate pharmaceutical form for each setting and ensuring that the patient understands and follows the posology prescribed to avoid medication errors.[69]

Recommendations for vitamin D testing and supplementation for different population subgroups according to the revised evidence are summarized in table 5.

Pregnant or lactating women have the same vitamin D requirements than women not in those situations

Patients with kidney failure or hyperparathyroidism with normal calcium levels, among other, are at a higher risk for experiencing AEs associated with vitamin D supplementation

Table 5. Recommendations for vitamin D testing and supplementation in different population subgroups:

Population subgroup	Justification for 25(OH)-D testing	Justification for vitamin D supplementation
Asymptomatic general population without risk factors	NO	NO
Community-dwelling older adults	NO	NO
Institutionalized older adults	YES (as an intervention prior to considering supplementation)	Only if deficiency is confirmed. Preferably in combination with calcium.
Parathyroid disease	YES	In patients with chronic kidney disease with severe or progressive hyperparathyroidism. In hypoparathyroidism (administer calcitriol)
Kidney disease	Only in patients with chronic kidney disease with severe or progressive hyperparathyroidism	Only in patients with chronic kidney disease with severe or progressive hyperparathyroidism
Phosphocalcium metabolism alterations	YES	Only if vitamin D deficiency is confirmed.
Malabsorption syndromes	YES	YES
Pregnancy and breastfeeding	Only in the presence of additional vitamin D deficiency risk factors.	Avoid unless potential benefit outbalances the potential risk

Conclusions

Vitamin D should not be tested in the general population. Vitamin D testing would be justified in institutionalized older adults, in subjects with parathyroid diseases, alterations in phosphocalcium metabolism alterations and malabsorption syndromes. In the case of patients with kidney disease, vitamin D testing should only be performed in patients with concomitant severe or progressive hyperparathyroidism. Vitamin D testing should not be performed in community-dwelling older adults.

Vitamin D supplementation does not prevent the development of adverse cardiovascular events, metabolic diseases or cancer, and does not reduce mortality. Vitamin D supplementation in asymptomatic populations without risk factors for deficiency is not justified. Vitamin D supplementation in community-dwelling older adults does not provide any clinical benefit. In institutionalized older adults, vitamin D supplementation would only be justified in subjects with confirmed vitamin D deficiency, in which case it should be administered in combination with calcium. Supplementation may be indicated in patients with chronic kidney disease with severe or progressive hyperparathyroidism and in those patients with hypoparathyroidism. In patients with

hypocalcemia and hypophosphatemia, vitamin D should only be administered in case deficiency is confirmed. Vitamin D supplementation is also justified in patients with malabsorption syndromes, although there is no evidence demonstrating that supplementation provides benefit on important clinical outcomes.

Pregnant women without additional risk factors have the same vitamin D needs as non-pregnant women. There is uncertainty about the clinical benefits and safety of vitamin D supplementation during pregnancy. In general terms, administration of vitamin D supplements should be avoided during pregnancy unless the potential benefits outweigh the potential harms.

Vitamin D supplementation at the doses established in the product label is not generally associated with safety problems. However, certain situations may predispose to an increased risk for adverse events, as in the case of patients with renal impairment or normocalcemic hyperparathyroidism, among others. The most common adverse event is hypercalcemia, which may contribute to renal and cardiovascular impairment.

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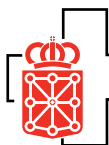
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