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Delphi Consensus on Therapeutic Strategies and Health Prevention of hypovitaminosis D

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Summary

Background: The high prevalence of hypovitaminosis D in Spain is considered a genuine epidemic with crucial health implications due to the multiple functions that vitamin D exerts both at the skeletal and extraskeletal levels. In order for people with insufficiency or deficiency in vitamin D to reach the most adequate serum levels, they must receive vitamin D supplements. This study was carried out to evaluate whether, in routine clinical practice, hypovitaminosis D management was done in accordance with international recommendations established by scientific societies.

Methods: Two rounds of a Delphi questionnaire were carried out among a panel formed by experts who regularly prescribe vitamin D.

Results: In general, the physicians on the panel recognized the high prevalence of hypovitaminosis D in Spain, the need for screening in the different risk groups and the benefits of supplementation in patients with insufficient or deficient vitamin D. However, no consensus was reached on some of the statements related to vitamin D quantification methods or recommendations for managing hypovitaminosis D.

Conclusions: The lack of agreement for some of the items revealed the need to carry out training actions aimed at providing adequate and updated knowledge about the scientific evidence and recommendations for the clinical practice of vitamin D supplementation.

Key words: Delphi consensus, vitamin D supplementation, vitamin D, hypovitaminosis D, skeletal and extraskeletal actions.

Introduction

Vitamin D is an essential hormone for skeletal metabolism, since it regulates the absorption of calcium and phosphorus at the intestinal level and bone remodeling[1,2]. In addition, some studies suggest that vitamin D performs other multiple functions at the extraskeletal level, acting as a protector against diseases such as cancer, inflammatory and autoimmune diseases, diabetes and cardiovascular diseases[1-4].

The main source of vitamin D is synthesis at the skin level by the action of ultraviolet B rays (UVB) on its precursor[2], giving rise to cholecalciferol or vitamin D3. Another less important source of cholecalciferol is found in food, mainly fish, eggs and dairy products. Regardless of its origin, cholecalciferol must be hydroxylated in the liver, becoming 25-hydroxyvitamin D3 [25(OH)D] or calcifediol and, subsequently in a highly regulated manner, in the kidney to give rise to the active metabolite, 1, 25-dihydroxyvitamin D3 [1,25(OH)2D] or calcitriol[1].

Serum levels of 25(OH)D offer the best biomarker to assess vitamin D levels, since its plasma concentration and half-life are higher than those of 1,25(OH)2D[2]. However, there is no clear consensus on the optimal levels of 25(OH)D in serum[3].

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Recent observational studies have revealed a high prevalence of hypovitaminosis D worldwide[5], associated with an increased risk of skeletal and extraskeletal diseases, due to the multiple functions of vitamin D.

In Spain, the prevalence of vitamin D deficiency is at least 80% among people over 65 years of age and up to 40% in the population under 65[6], despite the high degree of sunshine available, which should facilitate synthesis of vitamin D. Therefore, hypovitaminosis D has become a recognized epidemic with important health implications, so that a large portion of the population could benefit from vitamin D supplements.

In order to determine if hypovitaminosis D is diagnosed, treated and prevented in accordance with international recommendations and scientific evidence, current clinical practice of vitamin D supplementation has been analyzed based on the knowledge of those physicians who regularly prescribe supplementation.

Material and methods

The data presented in this study were obtained using the Delphi method[7]. To do so, our scientific committee prepared a questionnaire that was completed by a panel of experts made up of doctors from different specialties and geographical areas, those who regularly prescribe of calcifediol and/or cholecalciferol. After two rounds of circulation of the survey, the scientific committee met to collect, analyze and discuss the results.

Preparation of the questionnaire

Based on the current knowledge of hypovitaminosis D and its clinical consequences, as well as therapeutic and prevention strategies and diagnostic methods, the multidisciplinary scientific committee identified a total of 73 variables related to hypovitaminosis D and divided into 4 thematic blocks:

1. Vitamin D and general health (21 items)
2. Evaluation of vitamin D deficiency (26 items)
3. Treatment with vitamin D according to the patient's profile (19 items)
4. Differences between supplements (7 items)

Expert panel

The project was directed by a scientific committee of 10 vitamin D experts from different areas of specialization: endocrinology, rheumatology, nephrology, gynecology, internal medicine, primary care, dermatology, digestive and geriatrics.

In all, 180 specialists were invited to participate in the study, having fulfilled the following criteria: a minimum of 5 years of clinical experience, experience prescribing vitamin D on a regular basis, belonging to centers that serve heavily populated areas and, in the case of primary care, belonging to centers located in areas with high population density.

A first group of participants in the panel (40%) were chosen directly by the authors of the study taking into account the inclusion criteria. The remaining 60% was completed with the invitation to experts, through the delegates of the study sponsor, always respecting the established inclusion criteria.

Analysis of results

The participants prepared the questionnaire using an online platform. As in all Delphi questionnaires, the survey consisted of a series of statements. Respondents expressed their level of agreement with the each statement based on a numerical 1-to-9 scale (≤3, disagree; 4-6, doubtful; ≥7, agreement).

The median of the scores and the percentage of positioning were analyzed. Consensus was reached when less than a third of the respondents positioned themselves outside the region of three points that contained the median. Otherwise, when these respondents showed conflicting opinions (equivalent positioning in the extreme sectors of the scale) or when there was a greater dispersion of opinions (equivalent distribution of positioning in the three sectors of the scale), it was considered that there was no there was consensus due to polarization or indeterminacy, respectively. Items that did not reach consensus in the first round were kept in the second circulation round of the survey, the results of which were analyzed as described above.

To formalize the questionnaire, they were assigned a period of 26 days for the first round and 11 days for the second.

The data provided by the participants were subject to a confidentiality clause and were only used for statistical purposes with no dissemination by any channels.

Results

In our study, 146 experts participated out of the 180 invited (81%) in the first circulation round of the Delphi survey with the following distribution by specialties: nephrology 9, rheumatology 27, geriatrics 10, endocrinology 23, family and community medicine 39, gynecology and obstetrics 9, internal medicine 9, digestive system 9, pediatrics 1, dermatology 9 and urology 1. Of the initial 146 experts, 125 participated in the second round (85.6% participation compared to the first round). The 21 experts who withdrew in the second round did so due to lack of availability or compatibility with other professional activities. This panel of experts included representatives from different specialties and geographical areas as shown in the figure 1.

In the first round, 73 statements were analyzed, of which 47 (64.4%) reached consensus in agreement. The remaining 26 statements, 25 undetermined and one with polarized opinions, went on to the second round of circulation of the survey. In this phase, a new level of agreement was reached, reducing to 16 (21.9%) the non-consensual statements (figure 2), of which 14 remained indeterminate and 2 with polarized opinions. Therefore, after completing the second round, the level of consensus was obtained in agreement on 57 (78.1%) of the 73 statements in the survey (figure 2).

Block 1, *Vitamin D and health in general*, reached the greatest consensus. The respondents agreed with 19 (90.5%) of the 21 statements that made up this block (table 1), 16 in the first round and 3 in the second, while the remaining 2 (9.5%) were indeterminate. by dispersion or non-positioning of the experts.

In block 2, *Evaluation of hypovitaminosis D*, consensus was obtained on a total of 19 statements, 16 in the first round and 3 in the second, which corresponds to 73.1% of the 26 proposals (table 2). Of the 7 statements that did not reach consensus, 5 (19.2%) were indeterminate and 2 (7.7%) showed polarization in the position of the respondents at the end of the second round.

Block 3, *Treatment with vitamin D according to the patient's profile*, is the one that obtained a lower degree of consensus. The percentage of agreement was 68.4%,

Figure 1. Characteristics of the panel of physicians who participated in the study. (A) Distribution of doctors according to their specialty

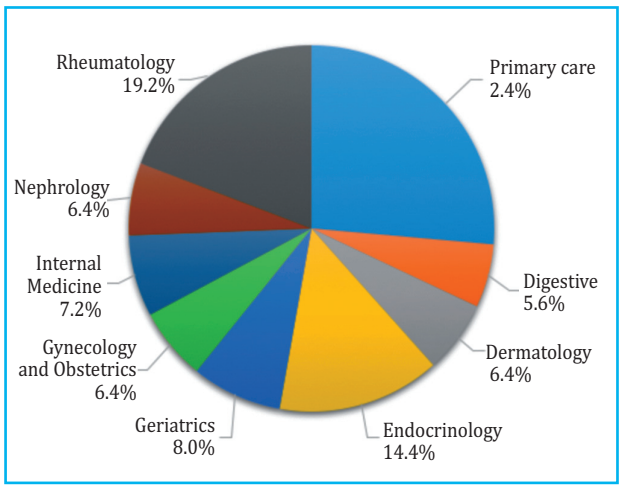


Figure 1. Characteristics of the panel of physicians who participated in the study. (B) Distribution of doctors according to the Autonomous Community in which they practice their profession

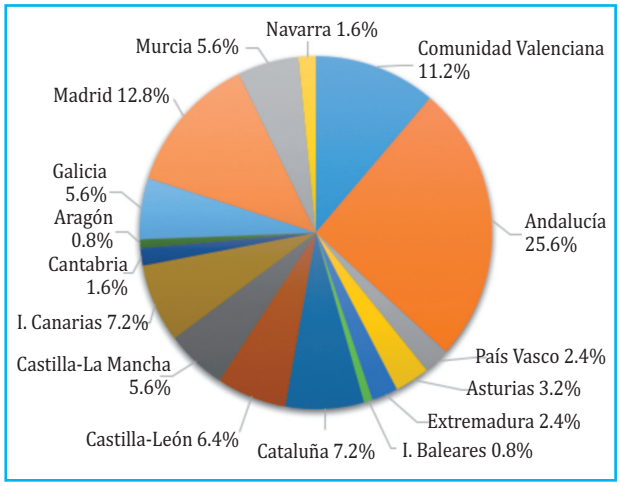
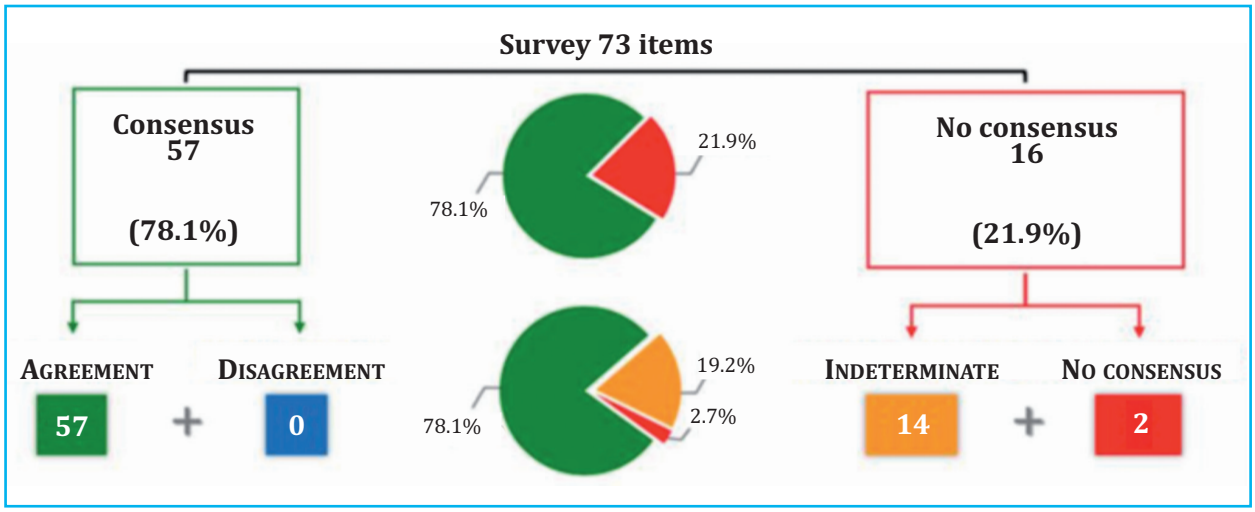


Figure 2. Delphi results



corresponding to 13 consensual statements, 10 in the first round and three in the second, of the 19 proposals (table 3). The remaining 6 statements remained indeterminate, giving rise to a 31.6% non-consensus due to dispersion of opinions. None of the non-consensual assertions of this block presented polarization in the results.

In block 4, *Differences between supplements*, consensus was obtained in 6 of the 7 proposed statements (table 4), all in the first round, which corresponds to a general percentage of consensus of 85.7%. The statement that did not obtain consensus was left as indeterminate.

Discussion

This Delphi survey reached consensus in 78.1% of the statements (figure 2) aimed at assessing knowledge about vitamin D and about the diagnosis, treatment and prevention of hypovitaminosis D.

In relation to vitamin D and health in general, there was agreement that hypovitaminosis D affects all population groups in Spain. The experts surveyed recognize its high prevalence in our country[6], and that its severity depends on environmental factors, such as time of day, season of the year[8] and geographical latitude, and of individual factors, such as skin pigmentation, diet, the use of sunscreens and clothing worn, since all of these factors condition cutaneous synthesis of vitamin D3. As the experts point out, diet is insufficient to satisfy the daily needs of vitamin D and this is due to the fact that there are few natural foods with a high content of this vitamin[2]. In addition, the reduction in sun exposure due to changes in lifestyle has been detrimental to the cutaneous synthesis of vitamin D. Given this situation, and as recognized by experts, an increase in the hours of effective sun exposure should be considered. and safe, taking into account the already known carcinogenic risks associated with it, so that a balance is achieved between sun exposure, diet and vitamin D supplementation, as measures for the prevention of hypovitaminosis D. According to the Spanish Research Society Bone and Mineral Metabolism (SEIOMM), 15 minutes of daily sun exposure on the arms and face are recommended, between the months of March and October, for the Caucasian population, with a protection factor between 15 and 30, bearing in mind radiation intensity and lati-

tude. In the elderly population and patients with osteoporosis, 30 minutes of daily sun exposure are recommended[9].

Due to individual variations in vitamin D supplementation, establishing the appropriate dosage for each patient is required. To this end, the experts agreed that, in addition to serum levels of 25(OH)D, the Body Mass Index (BMI) must be taken into account (considering the relationship between BMI and concentrations of 25(OH)D)[10], the degree of habitual sun exposure of the patient and the use of certain drugs that can alter the absorption and catabolism of vitamin D[11]. There was also agreement that supplementation can be established on a weekly, fortnightly or monthly basis without affecting its efficacy[12,13], and that it should be 800-1,000 IU/day in people over 65 years of age, to reach plasma concentrations enough of 25(OH)D[9].

Regarding the clinical consequences of hypovitaminosis D, the experts surveyed recognized that the risk of osteoporosis[1] and fractures[14] increases in the skeletal tissue, in addition to being associated with rickets[2] and osteomalacia[2], while the risk of cardiovascular diseases increases in the extraskeletal system[2,15] and the appearance of some types of cancer, especially breast, prostate and colorectal[3,16]. Despite an observed tendency towards agreement, however, there was no consensus that hypovitaminosis D is associated with an increased risk of type 2 diabetes (DM2) and autoimmune diseases. Most of the experts who disagreed acknowledged that certain studies had shown an association between hypovitaminosis D and DM2[17] or autoimmune diseases[18], but not a direct causal relationship. This suggests that the participants interpreted the statements as intending to establish a relationship of cause-effect between hypovitaminosis D and DM2 or autoimmune diseases, which could explain the lack of consensus. In fact, the real contribution of low levels of vitamin D as a cause of DM2 or autoimmune diseases is controversial, especially considering the discrepancies between observations and clinical trials of intervention. These discrepancies also exist in studies of the benefits of vitamin D at the extraskeletal level in general. This is because, in many of these intervention studies, the participants had normal serum 25(OH)D levels at baseline, so it would be difficult to observe vitamin D supplementation benefit. This is the case from the study by Pittas et al.[19] on the benefits of vitamin D in the prevention of DM2, and from the VITAL[20] study on the effects of vitamin D supplementation in the prevention of cancer and cardiovascular diseases, both with negative results. From a pathophysiological point of view, vitamin D supplementation may not provide any protection if there is no evidence of hypovitaminosis D[21,22], so intervention studies should be performed in patients with vitamin D deficiency as recommended by different authors[21,22].

As for assessing hypovitaminosis D, the experts recognized that the levels of 25(OH)D are the best biomarker of vitamin D status[1,2,11], since they reflect both the dietary contribution and that of sun exposure and the supplementation. There was also agreement that serum concentrations of 25(OH)D below 30 ng/mL indicate vitamin D insufficiency, while values below 10 ng/mL indicate severe deficiency[13].

However, the lack of consensus in the disagreement in considering insufficiency when 25(OH)D concentrations are less than 20 ng/mL shows that the definitions of insufficiency (<30 ng/mL) and deficiency (<20 ng/mL /mL) of vitamin D are not so clear[3]. There was also variability of opinion regarding safe concentrations of 25(OH)D. Although until recently it was considered that concentrations of 25(OH)D less than 150 ng/mL did not present any risk of toxicity[11,13], currently it is recommended to maintain serum levels between 30-50 ng/mL[6]. This is due to the observations that serum 25(OH)D values greater than 50 ng/mL are associated with an increased risk of cardiovascular mortality[23], although two studies were published in 2017 that cast doubt on these results[24,25]. In the first of them, upon standardizing serum 25(OH)D values from a previous study, no higher mortality was found[24], and in the second, which was the first and only meta-analysis that has used standardized values of 25(OH)D and individual data, no higher mortality was observed with serum values above 50 ng/mL[25].

On the other hand, once the recommended levels of 25(OH)D have been reached, patients must continue with a maintenance dose so that hypovitaminosis D does not reappear, since the causes of the insufficiency remain.

Regarding the screening of vitamin D deficiency, scientific societies such as the National Institute for Health and Care Excellence (NICE), the United States Preventive Services Task Force (USPSTF), the Endocrine Society and the Spanish Society of Endocrinology, have positioned themselves against universal screening[6,11,26,27], probably because there is no evidence that it is cost-effective. In this sense, many experts recognized that screening should only be carried out in patients with pathologies associated with hypovitaminosis D and in risk groups such as institutionalized elderly, as established by the recommendations. However, some of those surveyed believed that screening should be universal from the age of 18, a position that is possibly due to the high prevalence of hypovitaminosis D. Despite these discrepancies, there was agreement that measuring 25(OH)D levels was required in older people at risk of falls, in patients with osteoporosis with or without osteoporotic fracture, fragility fractures, chronic kidney disease, liver disorders or intestinal disease and in patients treated with drugs that can interact with vitamin D[6,12]. The experts also recognized that parathyroid hormone is a valid marker of vitamin D deficiency since there is an association between vitamin D deficiency and secondary hyperparathyroidism[2,3].

In relation to the methods for determining 25(OH)D and despite the differences observed between them[1,11], there was no consensus in disagreement that all the methods were similar or that most of them overestimated the levels of 25(OH)D. (OH)D, which suggests that many of the respondents had not considered or were unaware of the importance of the method for determining 25(OH) vitamin D. However, they did recognize the importance of using the same method in all measurements of follow-up of vitamin D supplementation, which should be carried out in the days prior to the next dose, every 3-4 months from the start of treatment until reaching adequate levels of 25(OH)D[6], and then at intervals every 6 -12 months. There was also agreement that these techniques need to be standardized. This can be done by implementing the reference materials for the National Institute of Standards and

Table 1. Level of agreement reached in block 1: Vitamin D and health in general

Variable	Round	Mean	Median	Range	% outside median	Result
1. Hypovitaminosis D in Spain affects all population groups	1	7.29	8	2	18.49	Agreement
2. The time of day conditions the cutaneous synthesis of vitamin D due to the greater or lesser inclination of the solar radiation	1	7.42	8	2	17.81	Agreement
3. The season of the year determines the cutaneous synthesis of vitamin D due to the greater or lesser inclination of solar radiation	1	7.92	8	1	8.9	Agreement
4. Geographical latitude conditions the cutaneous synthesis of vitamin D due to the greater or lesser inclination of solar radiation	1	7.82	8	2	12.33	Agreement
5. Skin pigmentation conditions skin synthesis of vitamin D due to melanin content	1	7.52	8	2	21.23	Agreement
6. The use of sunscreens with a high protection factor conditions the cutaneous synthesis of vitamin D due to the blocking of UVB rays on the skin	1	7.68	8	2	18.49	Agreement
7. The way of dressing conditions the cutaneous synthesis of vitamin D because it can reduce skin exposure to the sun	1	7.77	8	1	13.01	Agreement
8. The diet followed by most people is insufficient to meet daily vitamin D needs	1	7.28	8	2	23.97	Agreement
9. Increasing the hours of effective sun exposure has been shown to be useful in preventing vitamin D deficiency	2	6.64	7	2	29.6	Agreement
10. Vitamin D supplementation has been shown to be useful in the prevention of hypovitaminosis D	1	8.32	9	1	4.11	Agreement
11. For the maintenance of bone health in people over 65 years of age doses between 800-1,000 IU/day of vitamin D are necessary	1	8.02	8	1	8.9	Agreement
12. In addition to serum levels of vitamin D, when calculating the dose of vitamin D to administer, we must take into account both BMI and sun exposure	1	6.99	7	3	29.45	Agreement
13. As vitamin D is fat-soluble, we can administer it in weekly, fortnightly or monthly doses	1	8.21	9	1	8.9	Agreement
14. Certain drugs interact with vitamin D reducing its absorption	1	7.68	8	2	19.86	Agreement
15. Insufficient vitamin D is associated with an increased risk of osteoporosis because it is essential for proper bone metabolism	1	8.35	9	1	5.48	Agreement
16. Insufficient vitamin D is associated with an increased risk of failure in the treatment of osteoporosis, since it determines a greater probability of fractures and less bone mass gain even when receiving effective anti-catabolic/anti-resorptive treatment	1	8.14	8	1	6.85	Agreement
17. Deficiency rickets and osteomalacia are associated with a severe vitamin D deficit	1	8.44	9	1	4.11	Agreement
18. Hypovitaminosis D is associated with an increased risk of type 2 diabetes	2	6.44	7	2	36	Indeterminate
19. Hypovitaminosis D is associated with an increased risk of cardiovascular diseases	2	6.75	7	2	31.2	Agreement
20. Hypovitaminosis D is associated with an increased risk of autoimmune diseases	2	6.71	7	2	34.4	Indeterminate
21. Hypovitaminosis D has been associated with the appearance of some types of cancer, especially breast, prostate and colorectal cancer	2	6.63	7	2	31.2	Agreement

Technology measurement of 25(OH)D[11]. In general, most hospitals use immunoassays to measure serum concentrations of 25(OH)D, although these methods are not standardized and overestimate these concentrations[28] due to cross-reactivity with other inactive metabolites of vitamin D, such as 24-25 (OH)D and the epimer C3. In contrast, liquid chromatography with tandem mass spectrometry (LS-MS/MS), which is the reference method, does not present the problem of overestimation of 25(OH)D, since it allows independent analysis of each one of the metabolites of vitamin D[28], which translates into an increase in the percentage of hypovitaminosis D[29]. However, this method is not applicable to clinical routine because it is more complex, time-consuming and expensive than immunoassays. In addition, the values that define vitamin D insufficiency and deficiency are based on the results of immunoassays, therefore, despite the fact that there was no agreement among the experts, these methods are acceptable to determine the concentration of 25(OH)D in clinical practice. There was also no agreement on establishing that 25(OH)D monitoring should be done in winter or early spring, when vitamin D synthesis is more deficient. In general, monitoring should be performed in all patients at risk of hypovitaminosis D, regardless of the time of year. However, primary care centers with limited access to 25(OH)D measurement and who cannot request it without justification, could choose to measure 25(OH)D concentrations in winter or early spring, which is the time when the patient is most likely to have hypovitaminosis D.

Regarding treatment with vitamin D, although some experts contemplated its interruption in summer if it was accompanied by a diet rich in vitamin D and provided that hypovitaminosis D was not serious and there were no diseases that perpetuated it, withdrawal of supplementation is not recommended in summer. In this sense, as with the monitoring of 25(OH)D, it must be taken into account that the difference between the concentrations of 25(OH)D in summer and winter is small and that there are many factors that, together with variations in sun exposure, they can intervene in hypovitaminosis D.

Although the experts recognized that supplementation should be performed only after confirming hypovitaminosis D, even in patients over 65 years of age, there was a dispersion of opinions on the fact of prescribing vitamin D supplements to the institutionalized elderly without determining serum levels of 25(OH)D. In this sense, the ideal is to know the serum levels of 25(OH)D to adjust the dose. However, the prevalence of hypovitaminosis D in this population group is 87%[30] so, if there is no access to the determination of 25(OH)D levels, supplementation with safe doses, such as those doses between 1,000 and 2,000 IU daily of vitamin D, which are recommended by the International Osteoporosis Foundation (IOF) for this population[13], is probably the situation with the most effective cost-benefit, especially at the level of prevention of fractures and loss of muscle strength.

On the other hand, there was no agreement that vitamin D supplementation in all people over 65 years of age is cost-effective. Some experts commented in this regard that in order to know this data, cost-effectiveness studies similar to those carried out by the NICE guidelines in the United Kingdom should be carried out in Spain, in which vitamin D supplementation is directly recommended in people over 65 years of age, pregnant women and infants and children under 4 years of age[27].

According to experts, vitamin D supplementation is necessary in all patients with vitamin D insufficiency or deficiency. In this sense, there was agreement that knowing the sun exposure habits of patients would be useful to identify those at risk of hypovitaminosis D. There was also agreement that patients receiving treatment with corticosteroids or drugs that increase the catabolism of vitamin D require supplementation, which implies that they recognized that these patients are at risk of hypovitaminosis D[6,13]. In addition, it must be taken into account that certain diseases interfere with the synthesis and bioavailability of vitamin D, so there was agreement that patients with intestinal malabsorption, chronic kidney disease, liver disease or obesity required doses of vitamin supplementation highest D[13]. This need was not agreed upon for patients with photosensitivity, in which case the most advisable thing would be to establish the dose of vitamin D based on the serum levels of 25(OH)D and not prescribe higher doses, as some experts contemplate, because the sun exposure of these patients is less or less effective due to the use of sun protection creams.

In addition, the experts recognized the importance of maintaining adequate levels of 25(OH)D in patients with osteoporosis, since it can reduce the risk of both hip and non-vertebral fractures[13]. However, there was no agreement that fracture reduction by vitamin D supplementation was dose dependent. This result is not surprising considering the discrepancies between different studies. Thus, while the meta-analysis by Bischoff-Ferrari et al shows that daily doses of 800 IU or higher are more beneficial for reducing fractures in patients over 65 years of age[31], the study by Bolland et al finds no evidence that supplements of vitamin D reduce fractures[32], although it should be noted that the latter has many limitations[22].

There was also no consensus, despite the orientation towards agreement, in considering that, in patients with DM2, vitamin D supplements contribute to better glycemic control. Although most of the experts who disagreed thought that there were no conclusive studies in this regard, it should be noted that it has been shown that vitamin D supplements contribute to better glycemic control[33], inducing a significant improvement when 25(OH)D levels are less than 20 ng/mL, although this does not occur when they are above 20 ng/mL.

Regarding the differences between supplements, the experts recognized that calcifediol is more potent than cholecalciferol, therefore lower doses are required, it increases 25(OH)D concentrations more quickly and is more effective in maintaining them above 30 ng/mL6,[34]. There was also agreement that calcifediol is the drug of choice in patients with deficient hepatic hydroxylation due to liver disease or advanced age (>70 years) as it does not require hepatic hydroxylation[34,35], and in patients with intestinal disease because it is better absorbed than the other metabolites[34].

Recently, the Spanish Medicines Agency has published an informative note on the appearance of hypercalcaemia due to cholecalciferol overdose in children and calcifediol in adults[36], although the most recent studies on the use of calcifediol have not described any toxicity associated with this drug[12,37].

Table 2. Level of agreement reached in block 2: Assessment of hypovitaminosis D

Variable	Round	Mean	Median	Range	% outside median	Result
22. Screening for hypovitaminosis D should be applied to the entire population over 18 years	2	3.78	3	3	44	Indeterminate
23. The measurement of 25(OH)D is the best indicator to know the status of vitamin D	1	7.93	8	2	10.27	Agreement
24. The determination of 25(OH)D reflects the total vitamin D obtained both from intake and from sun exposure and pharmacological treatments	1	7.3	8	3	25.34	Agreement
25. Vitamin D insufficiency is understood as a level of 25(OH)D less than 30 ng/mL	1	6.99	8	3	26.03	Agreement
26. Vitamin D insufficiency is understood as a level of 25(OH)D less than 20 ng/mL	2	5.6	7	7	44.8	No consensus
27. Severe vitamin D deficiency is understood as a level of 25(OH)D less than 10 ng/mL	1	8.05	9	1	8.22	Agreement
28. Serum levels of 25(OH)D must be maintained below 50 ng/mL due to possible increased risk of total mortality and cardiovascular and other side effects	2	5.03	5	4	75.2	No consensus
29. It is essential to carry out periodic controls of serum levels due to individual variability in vitamin D supplements	2	6.74	7	1	24	Agreement
30. All vitamin D quantification methods are similar	2	4.03	4	2	48.8	Indeterminate
31. Immunoassay methods, despite the lack of standardization and interference with other metabolites, are clinically acceptable to assess the concentration of calcidiol	2	6.1	6	2	40.8	Indeterminate
32. As the half-life of calcidiol is 18-21 days, it is important that the blood draw for monitoring of 25(OH)D be performed in the days prior to the next intake	2	7.13	7	2	30.4	Agreement
33. For the monitoring of 25(OH)D, it is important that the determination is made in winter or early spring, which are the seasons in which the synthesis of vitamin D is most deficient	2	6.22	7	2	40.8	Indeterminate
34. Most of the laboratory techniques used overestimate the levels of 25(OH)D by also quantifying inactive metabolites	2	5.22	5	0	24.8	Indeterminate
35. It is important to monitor vitamin D always using the same determination method	1	7.9	8	2	7.53	Agreement
36. Clinical laboratories should be integrated into programs of standardized vitamin D measurement	1	8.08	8	1	6.16	Agreement
37. The results of studies that do not have standardized measurements of 25(OH)D	1	7.86	8	2	10.96	Agreement
38. Vitamin D levels should be determined (calcidiol) in cases of chronic kidney, liver and intestinal disease	1	8.34	9	1	2.74	Agreement
39. Vitamin D levels should be determined in cases of osteoporosis without osteoporotic fracture	1	8.35	9	1	3.42	Agreement
40. Vitamin D levels should be determined in all patients with fragility fractures	1	8.5	9	1	2.05	Agreement
41. Vitamin D levels should be determined in all elderly patients at risk of falls	1	8.07	8	1	8.9	Agreement
42. Vitamin D levels should be determined in all patients treated with drugs that can interact with vitamin D: anticonvulsants, glucocorticoids, antiretrovirals, antifungals and absorption modifiers of lipids (cholestyramine, orlistatin, etc.)	1	8.27	9	1	5.48	Agreement
43. In patients with vitamin D deficiency who start supplementation, serum concentrations of 25(OH)D should be determined every 3-4 months until adequate levels are reached	1	7.36	8	2	22.6	Agreement
44. After reaching adequate levels of vitamin D after supplementation, annual analysis is recommended	1	7.52	8	2	17.81	Agreement
45. Parathyroid hormone can be considered a marker of vitamin D insufficiency due to increased levels from 25(OH)D levels below 31 ng/mL	1	6.83	7	2	32.19	Agreement
46. Patients with vitamin D insufficiency have secondary hyperparathyroidism	2	7.12	7	2	25.6	Agreement
47. In the case of secondary hyperparathyroidism, the levels of parathyroid hormone decrease after correction of vitamin D insufficiency	1	7.68	8	2	16.44	Agreement

Table 3. Level of agreement reached in block 3: Treatment with vitamin D according to the patient's profile

Variable	Round	Mean	Median	Range	% outside median	Result
48. Vitamin D levels should always be determined before administer supplements	1	7.01	8	3	30.14	Agreement
49. Sun exposure habits should be determined in the clinical history to identify patients at risk of vitamin D deficiency	1	7.26	8	2	24.66	Agreement
50. Treatment with vitamin D supplements should be interrupted in summer if the patient increases their sun exposure	2	4.9	5	4	67.2	Indeterminate
51. Vitamin D supplementation is necessary in all patients with hypovitaminosis D because diet and sun exposure do not cover daily needs	1	7.26	8	2	21.23	Agreement
52. In patients receiving treatment for osteoporosis, adequate levels of vitamin D must be guaranteed	1	8.49	9	1	3.42	Agreement
53. Treatment of vitamin D insufficiency can decrease the risk of hip fractures	1	7.84	8	2	11.64	Agreement
54. Treatment of vitamin D insufficiency can decrease the risk of non-vertebral fractures	1	7.65	8	2	15.07	Agreement
55. When there is evidence of hypovitaminosis D, vitamin D supplements offer dose-dependent protection against fractures	2	6.81	7	2	33.6	Indeterminate
56. In patients with type 2 diabetes, vitamin D supplements contribute to better glycemic control	2	6.46	7	2	38.4	Indeterminate
57. Vitamin D supplementation in all people over 65 years of age is cost-effective	2	6.84	7	3	33.6	Indeterminate
58. People over the age of 65 should take vitamin D supplements only in case of hypovitaminosis D	2	7.33	8	1	18.4	Agreement
59. In the institutionalized elderly, vitamin D supplements should be prescribed without the need for prior determination of its levels	2	5.62	7	4	49.6	Indeterminate
60. Patients who present photosensitivity require higher doses of vitamin D than usual	2	6.28	7	3	46.4	Indeterminate
61. Patients with intestinal malabsorption require doses of vitamin D higher than usual	1	7.33	8	2	20.55	Agreement
62. Obese patients need higher doses of vitamin D than usual due to its lower bio-availability	2	7.7	8	2	17.6	Agreement
63. Patients with chronic kidney disease (CKD) require higher doses of vitamin D than usual	2	7.1	8	1	24	Agreement
64. Patients with liver disease require higher doses of vitamin D than usual	2	6.66	7	2	32.8	Agreement
65. Patients under treatment with drugs that increase the catabolism of vitamin D should receive supplementation	1	7.19	8	3	26.71	Agreement
66. Patients receiving corticosteroid treatment should receive vitamin D supplements because corticosteroids can cause resistance to this vitamin	1	7.14	8	3	30.14	Agreement

Table 4. Level of agreement reached in block 4: Differences between supplements

Variable	Round	Mean	Median	Range	% outside median	Result
67. Calcifediol has been shown to be more effective than cholecalciferol in maintaining serum levels of 25(OH)D >30 ng/mL	1	7.32	8	3	25.34	Agreement
68. Calcifediol has been shown to be more potent than cholecalciferol by thus, fewer doses are needed to maintain serum 25(OH)D levels >30 ng/mL	1	7.57	8	2	17.12	Agreement
69. Because calcifediol is more powerful than cholecalciferol, it has a higher risk of hypercalcaemia	2	4.73	5	2	42.4	Indeterminate
70. Calcifediol increases 25(OH)D concentrations more rapidly than vitamin D3	1	7.47	8	2	21.23	Agreement
71. Calcifediol is recommended instead of cholecalciferol in patients with liver disease as they do not need hepatic hydroxylation	1	7.63	8	2	19.86	Agreement
72. Calcifediol is recommended instead of cholecalciferol in patients older than 70 years due to deficient hepatic hydroxylation	1	7.05	7	2	29.45	Agreement
73. Calcifediol is chosen in cases of intestinal disease because its absorption is better than that of other metabolites	1	7.14	7	2	26.03	Agreement

To sum up, the data from this study show that there is a consensus on the high hypovitaminosis D prevalence in Spain and the need to prescribe vitamin D supplements in patients with insufficiency and deficiency of this vitamin. However, the lack of consensus for some items reveals inadequate knowledge about vitamin D among the experts surveyed, especially regarding the recommendations for evaluating and treating this vitamin deficiency. Therefore, training sessions are required to provide adequate current knowledge to those who regularly prescribe vitamin D.

Conflict of interests: Dr. Javier Aguilar del Rey has received fees as a consultant, speaker, editor and grants for attending conferences from Amgen, FAES Pharma, Gebro, Italdrug, LACER and Lilly.
Dr. Esteban Jódar works as a consultant for Amgen, AstraZeneca, FAES Pharma, GSK, Helios-Fresenius, Italdrug, Lilly, MSD, Mundipharma, Novo Nordisk, Shire, UCB. He is a clinical investigator for Amgen, Boehringer, AstraZeneca, Faes, GSK, Janssen, Lilly, MSD, Novo Nordisk, Pfizer, Sanofi, Shire, UCB and speaker for Amgen, Asofarma, Astellas, AstraZeneca, Bayer, Boehringer, BMS, FAES Pharma, Lilly, MSD, Mundipharma, Novartis, Novo Nordisk, UCB and Theramax.
Dr. Fátima Brañas has received fees from MSD MISP funds; she has acted as a speaker at symposiums organized on behalf of MSD, ViiV Healthcare, Amgen, Fresenius and Janssen. She has developed various materials for MSD and is a member of the scientific committee of ViiV Healthcare and FAES Pharma.
Dr. Carlos Gómez has received grants and personal fees as a consultant and training courses from Amgen, Kiowa-Kirin, Italfarmaco, FAES, UCB and Gebro.
Dr. Jorge Malouf-Sierra is a speaker for Angelini, FAES, Gebro and Italdrug.
Dr. Rafael Sánchez has received research funds from Astellas and personal fees from Seid and LACER Laboratories.

FAES PHARMA laboratories and the technical secretary of Luzán collaborated in this study. It complies with all the precepts of the Declaration of Helsinki on clinical studies. FAES PHARMA has not intervened in the choice of questions, in the results analysis or in the writing of the article, which have been the sole responsibility of the listed authors.

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