Current perspectives on the role of vitamin D and calcium in the patient care for osteoporosis: an expert panel discussion

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Summary
Background: A better knowledge of the wide variety of actions of vitamin D is an essential step to improve the quality of osteoporosis care. This review of the current evidence of the binomium ‘vitamin D-osteoporosis’ is the result of a one-day expert panel meeting held in Madrid in 2008. The panel consisted of experts in osteoporosis and mineral bone metabolism pertaining to a range of clinical disciplines and drawn from throughout Spain.

Method: A literature search was performed on the MEDLINE database for clinical trials, randomized clinical trials, systematic reviews and meta-analyses for articles published between 2007 and 2008, using the terms osteoporosis, vitamin and calcium. The resulting articles were the material used for small-group discussions at the meeting.

Findings: Oral alendronate and risedronate are the aminobisphosphonates of choice because of their proven efficacy in vertebral, nonvertebral and hip fractures. The adequate dose of vitamin D could be defined as 800 IU/day for healthy adults and as 1000 IU/day for osteoporotic patients, and the adequate amount of calcium intake is 1000-1200 mg/day. The dose required for correct functioning of extraskeletal actions of vitamin D may be higher. Calcium supplementation could be secured through the diet but drug administration is required when vitamin D supplementation is given.

Conclusions: Optimization of the nutritional supply of vitamin D and calcium is the first step in the care of the patient with osteoporosis. Vitamin D supplementation does not exclude the intervention on other factors that may influence the risk of falls.

Key words: Vitamin D, Calcidiol, Calcitriol, Calcium, Osteoporosis, Vitamin D receptor, Risk of fracture, Aminobisphosphonates, Alendronate, Risedronate, Muscular weakness.
Introduction
It has been known for a long time that vitamin D intervenes in the regulation of blood calcium and phosphorus levels, and that a lack of vitamin D leads to rickets. However, recently it has become necessary to revise our knowledge of this vitamin, since the existing evidence indicates that vitamin D also exerts extraskeletal actions of great relevance, and which reflect its fundamental role in relation to musculoskeletal health. At present, however, we lack data of sufficient quality to firmly define the intervention of vitamin D in both the origin and treatment of osteoporosis. In view of this situation, and with the purpose of specifically addressing some points of controversy, the decision was taken to create a group of experts in osteoporosis and mineral metabolism pertaining to a range of disciplines (Internal Medicine, Endocrinology, Rheumatology, Traumatology and Orthopedic Surgery, Gynecology, Primary Care, Rehabilitation or Health Economics), in order to examine the role of vitamin D from the broad perspective of their different fields. In March 2008, Merck Sharp & Dohme Spain sponsored a one-day symposium in Madrid as a forum for discussion to allow a panel of experts to identify the current challenges of the binomium “vitamin D-osteoporosis”, supported by an analysis of the evidence-based literature, and with the aim of establishing a series of final conclusions based on consensus. The synthesis of this work is the subject of the present review.

Methods
In order to review the topics addressed in this meeting, a literature search was performed on the MEDLINE database. English-language and Spanish-language articles from January 2007 to February 2008 were included. Search terms used were ‘osteoporosis’, ‘vitamin D’ and ‘calcium’ (MeSH major topics). Other limits placed were ‘clinical trial’, ‘meta-analysis’, ‘randomized controlled trial’ and ‘review’ as type of article, and ‘all adult: 19+ years’ as ages.

Key experts from various areas belonging to different scientific societies, including the Spanish Society of Bone and Mineral Metabolism Research (SEIOMM), Spanish Society of Internal Medicine (SEMI), Spanish Society of Rheumatology (SER), Spanish Society of Endocrinology and Nutrition (SEEN), Spanish Society of Family and Community Medicine (SEMYFC), Spanish Society of Primary Care Physicians (SEMergen), Spanish Society of Traumatology and Orthopaedic Surgery (SECOT) and Spanish Association for the Study of Menopause (AEEM) were invited to attend one-day symposium to develop the current consensus document. Before the meeting, printed articles obtained from the literature search were distributed among the participants. At the time of the meeting, attendees were divided into small groups and discussed the topics of interest previously assigned to each group on the basis of the literature provided. Then, the leaders of the groups presented the conclusions reached in the different sub-meetings to the general audience and an open discussion was initiated. Final statements were accepted by consensus of all participants.

The literature search has been updated with any relevant publications that have been published from April 2008 to April 2009.

Discussion
Efficacy of aminobisphosphonates and vitamin D in reducing osteoporotic fractures
Osteoporosis is a very common condition in elderly people, and is associated with an increased risk of fracture. Osteoporotic fractures constitute an enormous public health problem, not only because of the healthcare costs involved, but also because of the increased morbidity and mortality, and decrease in the patient quality of life. Likewise, its increasing prevalence – due in part to the gradual aging of the population – has renewed interest in the efficacy and safety of the drugs available for treating the reduction in bone mineral density associated with osteoporosis.

Regarding the efficacy of antiresorptive therapy, and in addition to the clinical practice guide to the treatment of postmenopausal osteoporosis developed by the study group of the Sociedad Española de Investigaciones Oseas y Metabolismo Mineral (SEIOMM), some systematic reviews and meta-analyses summarize the evidence derived from clinical trials and other type of studies.

In a now classical meta-analysis of randomized clinical trials and systematic reviews published by Cranney et al., the aminobisphosphonates alendronate and risedronate exhibited the greatest effect in terms of the reduction of vertebral fractures compared with vitamin D, calcitonin, raloxifene and etidronate. Likewise, a positive effect of hormone replacement therapy was demonstrated in terms of the incidence of vertebral fractures, though the existence of selection bias in the analyzed studies may have led to overestimation of the magnitude of the effect of treatment. Regarding nonvertebral fractures, convincing evidence was only recorded in favor of risedronate and alendronate. The magnitude of risk reduction was estimated to be 50% for alendronate in relation to both vertebral and nonvertebral fractures, versus a little over 33% for vertebral fractures and 25% for nonvertebral fractures in the case of risedronate. Another later meta-analysis has confirmed the efficacy of alendronate in reducing the risk of hip fractures (45-55%) in different populations of postmenopausal women. On the other hand, a review of randomized, placebo-controlled studies of the efficacy of different antiresorptive agents again found alendronate to offer great efficacy, with a reduction in the risk of hip and nonvertebral fractures of 45-55%. Efficacy was also demonstrated for hormone replacement therapy (25-30%) and risedronate (26-27%). Lastly, another recent systematic review also supports the efficacy of alendronate, risedronate and estrogens in preventing hip fractures among males and females with osteoporosis or diminished bone mineral density.
In relation to vitamin D, an extension of the findings of the meta-analysis conducted by Bischoff-Ferrari et al.,7 (in which a reduction in femoral fracture risk was recorded in individuals over 60 years of age administered a daily vitamin D dose of 700-800 IU), published by Boonen et al.,8 demonstrated that oral treatment with vitamin D only proved effective in reducing the risk of hip fracture (and of any nonvertebral fracture) when associated to a daily supplement of 1,000-1,200 mg of elemental calcium. To further increase uncertainty as to the effects of calcium, there also have been meta-analyses suggesting an increased risk of hip fracture when using calcium supplements, as well as an increased risk of cardiovascular events, or more recently, meta-analyses and controlled trials showing independent beneficial effects of vitamin D.

In summary, clinical trials published in the literature and their combined evaluations in the form of systematic reviews and meta-analyses offer conclusive results on the efficacy of the aminobisphosphonates alendronate and risedronate in reducing osteoporotic vertebral, nonvertebral, and hip fractures. Regarding the safety of long-term treatment, the best available data correspond to alendronate. The extension of the FIT (Fracture Intervention Trial) to 10 years (FIT Long-term Extension, FLEX)12 has demonstrated that the continuation of alendronate treatment in postmenopausal women (both 5 and 10 mg/day) during 10 years does not increase fracture risk, maintains bone mass, and reduces bone remodeling compared with discontinuation of treatment after 5 years. The data of the FLEX study have led to the recommendation to continue alendronate therapy for more than 5 years in women at high risk of suffering osteoporotic fractures.

There is consensus regarding the indication of aminobisphosphonates, including advanced age (over 65 years), in the presence of significant fracture risk. As regards calcium and vitamin D supplements, the existing evidence does not allow us to draw firm conclusions as to their effects in reducing the risk of osteoporotic fractures. On the other hand, since 2008, the Internet offers a new tool (the FRAX index) for evaluating the absolute osteoporotic fracture risk, developed by experts of the World Health Organization (WHO).11 The FRAX tool, which can be found at http://www.shef.ac.uk/FRAX/index_SP.htm, uses individual models that combine and integrate clinical risk factors with the bone mineral density of the femoral neck (if known), with evaluation of the following factors: age, sex, body mass index (BMI), previous fracture, hip fracture in the parents, active smoking, treatment with corticosteroids, rheumatoid arthritis, secondary osteoporosis, high daily consumption of alcohol, and bone mineral density of the femoral neck. The FRAX algorithms estimate the probability of hip fracture and of the most important osteoporotic fractures (clinical vertebral fracture, fracture of the proximal humerus, forearm and hip) after 10 years. This tool probably will have a significant impact on the evaluation of osteoporotic patients and on the indication and selection of treatments.

Regarding the influence of vitamin D deficiency as a risk factor for osteoporotic fractures, in a study of 2,546 postmenopausal women with osteoporosis that had been included in the placebo group of three prospective controlled studies of risedronate,14-16 six risk factors present at baseline showed a significant association with the risk of nonvertebral fracture in the logistic regression analysis, among which serum concentration of 25-hydroxy-vitamin D, which exhibited a strong impact similar to that of very advanced age (over 80 years). In the LASA (Longitudinal Aging Study Amsterdam)20, conducted in a representative cohort of 1,311 Dutch men and women in which vitamin D was measured and fractures were recorded during 6 years of follow-up, levels of ≤12 ng/mL were associated to increased fracture risk in the 65-75 years age group, but not in the 75-89 years age group. No statistically significant associations were recorded for other cutoff points (<10 ng/mL, 10-19.9 ng/mL, 20-29 ng/mL, ≥30 ng/mL) after adjusting for confounding variables.

In the group of 159,579 women between 50-79 years of age included in the Women’s Health Initiative (WHI), collected from an observational study and three clinical trials involving hormone therapy, diet modifications and treatment with calcium and vitamin D supplements, in which risk factors for fracture were examined, treatment with calcium/vitamin D failed to show a beneficial effect—probably because calcium intake was high and there were a very few women with calcium consumption of <400 mg. However, a meta-analysis of five clinical trials on femoral fractures (n = 9,294) and seven clinical trials on nonvertebral fractures (n = 9,820) concluded that oral supplementing with 700-800 IU/day of vitamin D reduced the risk of hip fracture by 26%, and the risk of any nonvertebral fracture by 23% versus calcium or placebo in institutionalized or outpatients elderly subjects. A 400 IU oral dose of vitamin D per day did not seem to suffice to prevent fractures. For this reason the authors recommended increasing the usual vitamin D dose of 400-500 IU/day to 700-800 IU/day.

The data of two meta-analyses confirm the efficacy of vitamin D supplements in preventing fractures only when combined with the administration of calcium. In the meta-analysis published by Boonen et al.,20 in which the cohorts of the RECORD study (Randomized Evaluation of Calcium OR vitamin D) and of the Women’s Health Initiative of calcium and vitamin D were analyzed, the combination of calcium and vitamin D resulted in a reduction of 18% in the risk of hip fracture compared with placebo or no treatment, and of 25% compared with the administration of vitamin D alone. In order to optimize the clinical efficacy of this treatment, the authors recommended a vitamin D dose of 700-800 IU/day and a total elemental calcium dose of 1000-1200...
mg/day. In the meta-analysis published by Tang et al., in which 29 randomized clinical trials were identified with a total of 63,897 subjects aged 50 years or older, treatment with calcium or with the combination of calcium and vitamin D led to a 12% reduction in the risk of all types of fractures, being significantly higher (24%) in those trials in which treatment compliance was high. The effect of treatment was better in case of daily doses of calcium of ≥ 1200 mg and daily doses of vitamin D ≥ 800 IU versus lower doses of both compounds. The authors concluded with the recommendation of a combined treatment of calcium (800 mg/day) and vitamin D (800 IU/day) for the prophylaxis of osteoporosis in people over 50 years of age. The convenience of combined treatment of calcium and vitamin D is also supported by the results of the meta-analysis of Bischoff-Ferrari et al.

In a recent meta-analysis on the efficacy of oral supplemental vitamin D in preventing nonvertebral and hip fractures in subjects ≥ 65 years of age, 12 double-blind randomized controlled trials for non-vertebral fractures (n = 42,279) and 8 for hip fractures (n = 40,886) comparing oral vitamin D, with or without calcium, with calcium or placebo were assessed. To incorporate adherence to treatment, the dose was multiplied by the percentage of adherence to estimate the mean received dose for each trial. The pooled relative risk (RR) was 0.86 (95% confidence interval [CI], 0.77-0.96) for prevention of non-vertebral fractures and 0.91 (95% CI, 0.78-1.05) for the prevention of hip fractures, but with significant heterogeneity for both endpoints was observed. Including all trials, anti-fracture efficacy increased significantly with a higher dose and higher achieved blood 25-hydroxy-vitamin D levels for both end points. For the higher dose (> 400 IU/day), the pooled RR was 0.80 (95% CI, 0.72-0.89) for non-vertebral fractures and 0.82 (95% CI, 0.69-0.97) for hip fractures. The higher dose reduced non-vertebral fractures in community-dwelling individuals and institutionalized older individuals and its effect was independent of additional calcium supplementation. The authors conclude that non-vertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older.

In a population of community-dwelling women and men (older than 20 years of age) U.S. NHANES III population-based survey, vitamin D status seems to be the dominant predictor of body mass density relative to calcium intake. Only women with vitamin D concentrations < 50 nM (19.4 ng/mL) seem to benefit from a higher calcium intake. In another study, treatment with anti-resorptive agents over 13 months was associated with for three to fivefold lower bone mineral density changes and 1.5-fold increased risk of incidence fracture in vitamin D insufficient as compared to vitamin D repleted postmenopausal osteoporotic women. Finally, in a prospective cohort of 175 previously bisphosphonate-responsive patients, 39 had a significant decrease of bone mineral density at follow-up. Twenty (51%) of these patients had vitamin D insufficiency. Correction of vitamin D insufficiency (100,000 IU/week for 5 weeks) was associated with significant increases in bone mineral density at the lumbar spine and the femoral neck.

**Influence of dietary calcium in the treatment of osteoporosis**

The relationship between calcium and osteoporosis can be systematized by five points: Is the administration of calcium necessary for the treatment of osteoporosis? And if so, how much should be administered? What amount of calcium do Spaniards consume? Should calcium be administered as a drug supplement or as food? And finally, can a guiding regimen be suggested?

Regarding the need to administer calcium for the treatment of osteoporosis, the results of many studies can be used as arguments both in favor and against such administration. In a study of 1,471 postmenopausal women treated with 1 g of calcium citrate a day for 5 years, no reduction in fracture risk was noted, though the bone mineral density increased. In a series of 208 postmenopausal Afro-American women, the administration of 1,200 mg of calcium a day, with or without 800 IU of vitamin D, did not modify bone mineral density. In a double-blind, placebo-controlled trial with a duration of 5 years, in which 1,460 women over 70 years of age were randomized to 1,200 mg/day of calcium carbonate or placebo, the treatment proved ineffective in preventing clinical fractures, though the authors attributed this result to poor compliance. A double-blind, randomized controlled trial for a 2-year period carried out in 323 healthy men, the administration of 1,200 mg/day of calcium had beneficial effect on bone mineral density comparable with those found in postmenopausal women but a dosage of 600 mg/day was ineffective.

The analysis of prospective cohort studies included in a meta-analysis showed that the administration of calcium was not associated with the risk of fracture in males or females, while the analysis of controlled clinical trials showed that the use of calcium supplements did not reduce the risk of hip fracture but rather increased such risk. In the case of nonvertebral fractures, the effect observed in the clinical trials proved neutral. In fact, these and also some other studies show that calcium increases bone mineral density in postmenopausal women, but that calcium alone does not reduce the risk of fracture although its combination with vitamin D may be useful. However, although the clinical evidence suggests that calcium supplements do not reduce osteoporotic fracture risk, the data from the meta-analysis of Tang et al. indicate that the administration of calcium supplements alone or in combination with vitamin D is effective in the prevention of osteoporotic fractures (relative risk 0.90, 95% CI 0.80-0.100). The inconsistencies between the studies in favor and against cal-
Dairy food and calcium intakes have been hypothesized to play roles in cancer. Recently, dairy food and calcium intakes in relation to total cancer as well as cancer at individual sites were identified. In both men and women, dairy food and calcium intakes up to 1,300 mg/day were associated with a decreased risk of cancers of the digestive system, particularly with colorectal cancer. However, there are important variations, so that each patient requires an individualized evaluation.

As regards the question as to whether calcium administration should be in the form of drug supplements or from food sources, calcium contained in food offers the following advantages: the gastric pH does not interfere with absorption as in the case of the drug supplement; the patient does not have the impression of being medicated, which means a benefit on quality of life; adherence to therapy is probably favored; some nutrients favor its absorption (carbohydrates); and some studies indicate that calcium contained in food exerts a greater effect upon bone mineral density than calcium supplied as drug supplements. In turn, the administration of calcium as drug supplements has other advantages: it is easier to know the precise amount ingested; dose distribution over the course of the day is easier; reaching the required daily amount is also easier; and a lesser ingestion of proteins (milk proteins) is involved. This latter point is important, since excessive proteins increase calcium losses in urine. In this respect, the results of different studies appear to exclude the possibility that milk proteins may be deleterious for bone metabolism.

With a view to affording a guiding regimen, the usual intake of a given patient is easy to calculate, and thus it is not difficult to know the calcium increments needed to secure an adequate provision of the element – taking into account that the “basal” diet (without any dairy product consumption) affords an amount of calcium that varies according to the amount of food ingested (in sum, the caloric content), which in turn is very often dependent upon the age and physical activity of the patient. In principle, a daily amount of 300 mg can be estimated for elderly individuals, versus 400 mg for younger people. On the other hand, it can be calculated that a glass of milk without calcium enrichment (skimmed or otherwise) contains about 250 mg of calcium. In comparison, a glass of calcium-enriched milk may contain about 350 mg, versus 125-150 mg in the case of yogurt. Once the amount of calcium ingested by a given patient has been estimated from the corresponding dietary history, the amount to be added as either milk or as a drug supplement can be determined.

A number of practical aspects should be taken into account: a) Since the intestine reduces the percentage of calcium absorbed as the total ingested amount of the element increases, the body is better able to assimilate small calcium doses distributed over the course of the day (e.g., 500 mg every 12 hours) than high doses in the form of a single dose (e.g., 1,000 mg once a day); b) If the patient prefers calcium supplements instead of milk, they should be taken with meals (dinner, or lunch and dinner), unless the diet is rich in phytic acid; c) It has been considered (but not demonstrated) that in order to avoid the nocturnal PTH peak, one of the calcium doses should be administered with dinner; and d) If the patient is being treated with proton pump inhibitors and for some reason takes calcium on an empty stomach, the dose preferably should consist of calcium citrate, which requires no acid pH for absorption.
Vitamin D, muscle function and reduction of the risk of falls

Hypovitaminosis D is very common in the general population, particularly among elderly people and subjects with osteoporosis. The postulated underlying causes include a low dietary vitamin D intake, limited exposure to sunlight, reduced cutaneous efficacy in the production of vitamin D, a reduction in kidney active metabolite 1,25(OH)₂D₃ or calcitriol) conversion capacity, and a certain resistance among elderly osteoporotic individuals to the effects of active vitamin D⁴⁵. The prevalence of low vitamin D levels increases with age, particularly in elderly people confined to their homes or living in nursing homes. This reduction in turn is associated to muscular weakness, loss of bone mass due to secondary hyperparathyroidism, and an increased risk of falls and hip fractures, which are responsible for an elevated morbidity and mortality⁵⁶. Many studies have demonstrated an increase in the prevalence of fractures with age, and this tendency can be expected to increase with the gradual aging of the population in the industrialized world⁵⁷. As an example, among the women with the least functional deficit in the Women's Health and Ageing Study, severe hypovitaminosis D increased significantly from 8.3% in the 65-74 years age range to 14% in the 75-84 years interval, and 17.4% for those women aged 85 years or older⁵⁸. The existing scientific evidence supports the importance of correcting vitamin D deficiency by means of a supplement (800 IU/day as a minimum dose) as a strategy to reduce the risk of falls⁵⁹.

Numerous studies in recent years support the hypothesis that vitamin D deficiency alters muscular function and, therefore, increases the risk of falls, which is particularly relevant in the elderly population. Muscular weakness is a prominent sign of hypovitaminosis D and an important muscular compromise may be present before the appearance of biochemical evidence of bone alterations⁴⁹. Clinically, muscular weakness associated to hypovitaminosis D is predominantly proximal with loss of muscular mass, hypotonia and pain in response to movements. Histologically, type II muscular fiber atrophy is observed. Such fibers are needed for intense, rapid and short-lasting motor activities, i.e., their correct function is essential for sudden muscle effort such as that in preventing falls. A lack of vitamin D is associated to muscular weakness in a way similar to the situation seen in patients with osteomalacia.

The effects of vitamin D upon skeletal muscle appear to be more related to 1,25(OH)₂D₃ than to calcitriol or 1,25(OH)₂D₃. Vitamin D exerts direct action upon skeletal muscle through three different mechanisms: classical genomic action resulting from the binding of 1,25(OH)₂D₃ to its nuclear receptor, and actions that are non-genomic (rapid) and mediated by a vitamin D receptor at muscle cell membrane level and by allelic variants of the vitamin D receptor (VDR)⁶⁰,⁶¹. In this context, vitamin D polymorphisms can affect muscular function, with a difference of 23% in quadriceps strength between VDR genotypes bb and BB in non-obese women over 70 years of age⁶².

In a study of the risk factors related to bone health and falls, all patients of both sex and aged over 50 years with clinical fracture seen in the Emergency Service or admitted to Maastricht University Hospital due to clinical fracture in the course of a year were contacted to participate in a systematic risk factors screening program⁶³. Bone densitometry was performed in all patients. The study population consisted of 354 females and 101 males (median age of 67 years). The women were compared with a control group of postmenopausal women without fractures. Bone-related risk factors included the following: a history of fracture after 50 years of age, maternal history of fracture, body weight under < 60 kg, severe immobility, corticosteroid treatment, vertebral fracture and more than one bone factor. Regarding the risk of falls, the study considered more than one fall in the last year, the use of psychoactive drugs, low daily life activity levels before the fracture, joint symptoms, vision disorders, urinary incontinence, Parkinson’s disease, and more than one fall risk factor. The prevalence of osteoporosis was defined by a T-score ≤ -2.5 in the lumbar spine and/or femoral neck. The prevalence of fall risk factors was found to be 75%, with a prevalence of bone risk factors of 53%, and a prevalence of osteoporosis at the time of fracture of 35%. In 50% of the patients the bone and fall risk factors were found to overlap. After adjusting for age, body weight and height, women with fractures were seen to have been diagnosed with osteoporosis more often than the controls (odds ratio 2.9; 95% CI 2.0-4.1), and had a comparatively more extensive history of falls (odds ratio 4.0; 95% CI 2.7-5.9). This study led to the conclusion that the risk factors related to falls in patients over 55 years of age and with recent fractures are greater than the risk as predicted on the basis of their osteoporosis. On the other hand, the risk factors were seen to overlap, were heterogeneous, and were present in multiple combinations. However, findings of this study should be interpreted taking into account the limited number of patients, the lack of laboratory testing, the lack of inclusion of certain bone risk factors, the facts that risk factors were documented during the period of fracture treatment, and that the control group was exclusively formed by women.

In a cross-sectional study conducted in Valladolid (Spain) of elderly individuals living at home, in a nursing home, or admitted to hospital, 454 subjects were evaluated with the purpose of establishing the prevalence of vitamin D deficiency and insufficiency in these three groups⁶⁴. Vitamin D deficiency was defined by 25-hydroxycholecalciferol levels below 10 ng/mL, while insufficiency was defined by levels of less than 20 ng/mL. Serum 25 hydroxycholecalciferol concentration is the best indicator of vitamin D status, since it has a half-life longer than three weeks, and is not subjected to enzyme regulation. The
Individuals living at home showed a 79% and 31% prevalence of vitamin D insufficiency and deficiency, respectively. In the case of the patients living in nursing homes and admitted to hospital, these figures were 91% and 32%, and 92% and 52%, respectively. Likewise, the mean serum concentrations of 25(OH)D₃ were 14.8 ± 8 ng/mL, 13.2 ± 6.8 ng/mL, and 10.8 ± 5.6 ng/mL in each of these respective groups — these values being far below the threshold of 30 ng/mL recommended for adequate bone health and the reduction of fracture risk. Given the high prevalence of vitamin D deficiency, patients over 65 years of age constituted a fall and fracture risk group due to the muscular weakness associated with hypovitaminosis D. Dietary recommendations are therefore needed to increase ingestion and the use of vitamin D supplements, with a view to correcting this deficit.

The effect of vitamin D upon falls has been examined in a meta-analysis analyzing only randomized, double-blind and controlled trials with an explicit definition of falls, in individuals over 60 years of age. Based on the data from 5 trials with 1,237 participants (81% women, with a mean age of 70 years), the administration of vitamin D reduced the risk of falls by 22% compared with calcium supplementing only or placebo — the number needed to treat (NNT) to avoid a single fall being 15 patients. The inclusion of 5 additional studies with 10,001 patients suggests that the size of the effect is independent of calcium supplementing, the type of vitamin D, patient sex, and the duration of treatment. This meta-analysis allowed the conclusion that vitamin D supplementation reduces the risk of falls by more than 20% in both ambulatory and institutionalized patients.

In a secondary analysis of a randomized, double-blind and controlled trial including 64 institutionalized women aged 65-97 years, an evaluation was made to determine whether vitamin D and calcium supplementation avoided the risk of falls through postural or dynamic balance. Both types of balance were shown to be predictors of the risk of falls, and vitamin D and calcium supplementation was seen to reduce the frequency of falls by 60%, with a 22% involvement of the postural balance and 14% of the dynamic balance. In 242 community-dwelling seniors, supplementation 1000 mg of calcium plus vitamin D reduced the risk of falls by 27% at month 12 and 39% at month 20 as compared with supplementation with calcium only. Combined calcium and vitamin D supplementation proved superior to calcium alone in reducing the number of falls and improving muscle function in community-dwelling older individuals.

Likewise, an analysis has been made of the differences in cost-effectiveness of combined treatment with alendronate 70 mg and vitamin D₃ 5,600 IU/week versus no treatment and risedronate 35 mg/week, in the prevention of fractures among postmenopausal women over age 60 years, with a history of vertebral fractures. For this study recently conducted in the Netherlands, data were used from a previous meta-analysis of randomized trials that included vitamin D₃ 800 IU/day, alendronate and risedronate, incorporated to a Markov model to evaluate cost-effectiveness in terms of cost per QALY (quality-adjusted life years) gained as a result of the different options. For a 10-year horizon, in comparison with no treatment, combined alendronate and vitamin D treatment avoided between 13.2 fractures per 100 treated women for the 60 years age segment, and 22.5 fractures for the 80 years age segment. On the other hand, combined treatment with alendronate and vitamin D avoided between 0.6 and 2.6 additional fractures compared with risedronate. It was thus concluded that treatment with alendronate and vitamin D is the economically dominant treatment option versus risedronate in postmenopausal women over 60 years of age with a history of vertebral fracture.

**Additional benefits of vitamin D in other disorders**

Vitamin D is implicated in a broad range of endocrine and metabolic processes; of these, the maintenance of calcium homeostasis is one of the most important. The vitamin has a dual origin: exogenous when consumed with the diet, and exogenous when ultraviolet radiation in sunlight converts 7-dehydrocholesterol present in the skin to vitamin D₃. The latter in turn undergoes thermal isomerization and transforms into biologically inert vitamin D₃ that must undergo two hydroxylation reactions in the liver to produce 25-OH-D₃ or calcidiol (the serum concentration of which defines the body vitamin D reservoir), and another in the kidney mediated by the enzyme activity of 1-alpha-hydroxylase (CYP27B1) in order to yield the biologically active hormone, 1,25(OH)₂D₃ or calcitriol.

The biological actions of calcitriol take place through the nuclear receptor for vitamin D (VDR), which is ubiquitously expressed in a great variety of tissues and cells. Calcitriol, transported by the vitamin D binding protein (DBP) and probably introduced within the cells by endocytosis, binds to the nuclear VDR and heterodimerizes with other hormone receptors — particularly with the family of retinoid X receptors. This complex binds to DNA sequences known as vitamin D response elements (VDREs) in the promoter regions of the regulated genes. The activated VDR/RXR heterodimers form complexes with an additional series of proteins known as coactivators, to form a bridge in the VDR/RXR complex that joins the VDREs to the proteins responsible for transcription — causing the cellular machinery to start transcription of the respective RNA, and culminating in translation of the protein specifically coded for by it. Thus, VDR acts as a transcription factor which when activated by its ligand (calcitriol) induces a protein synthesis response on the part of genes that are regulated by vitamin D.

VDREs are not restricted to the classical target tissues of vitamin D, such as the intestine, bone, kidneys and parathyroid glands related to calcium.
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and phosphorus homeostasis, but are found in almost all cells of normal and neoplastic tissues, which explains the great variety of endocrine, paracrine, and autocrine functions of calcitriol within the body. The broad distribution of VDR and of 1-alpha-hydroxylase (CYP27B1), the enzyme required to convert circulating calcidiol into calcitriol, allows many cell types to form their own calcitriol, provided that an adequate supply of circulating serum calcidiol is available.

The effects of calcitriol upon the tissues that contain VDR are pleiotropic and focus much of the current expectations regarding the use of vitamin D and its analogs. Improved knowledge of the different mechanisms of action of vitamin D and the underlying molecular bases in relation to autocrine/paracrine activities, the capacity to control genes associated to innate or acquired immune response, cell growth proliferation and differentiation, the inhibition of angiogenesis and the regulation of apoptosis, as well as the secretion of different hormones, has been crucial for estimating the importance of procuring and maintaining adequate levels of 25(OH)2D3 for the optimal function of many biological processes.

Approximately 75% of the world population presents low vitamin D levels. This is alarming, particularly when considering the many functions and physiological properties of vitamin D, beyond the acknowledged benefits in relation to bone and mineral metabolism. In Spain there is a high prevalence of vitamin D insufficiency in both males and females, regardless of the season of year or the geographical setting – reaching up to 50% for the serum concentration threshold of < 20 ng/mL, and up to 70% for the threshold < 30 ng/mL. Although vitamin D deficiency is important in all stages of life, this high prevalence is particularly relevant in patients with osteoporosis, postmenopausal women, and elderly people. This situation requires the urgent adoption of measures to increase the intake and to correct vitamin D deficiency. The importance of securing a vitamin D supplement is reflected by the results of a meta-analysis of 18 controlled clinical trials involving a total of 57,311 subjects. In these studies, the daily vitamin D dose ranged from 300-2000 IU/day (mean 528 IU/day) and the mean duration of follow-up was 5.7 years. Compared with the control group, the interventional group showed a relative risk of death due to any cause of 0.93 (95% CI 0.87-0.99), although this decrease in risk did not vary according to the concomitant administration of calcium supplements in the interventional group. These results suggest that the ingestion of vitamin D supplements seems to be associated with a reduction in the overall mortality rates.

The implications of the non-classical actions of vitamin D associated to the presence of VDR throughout the body, and to the expression of 1-alpha-hydroxylase in immune cells such as dendritic cells, macrophages, B cells, certain T cell subpopulations and other cell types, particularly through interaction with TLRs (toll-like receptors), have broad clinical repercussions regarding the participation of vitamin D in aspects such as innate immunity against infection (e.g., Mycobacterium tuberculosis), immune modulation, reduction in the risk of autoimmune diseases, certain cancers and cardiovascular risk, as well as increased sensitivity and secretion of insulin.

In reference to the therapeutic considerations of vitamin D in autoimmune diseases, studies in different animal models have demonstrated the beneficial effects of vitamin D supplementation in relation to disorders including autoimmune encephalomyelitis, collagen-induced arthritis, type 1 diabetes mellitus, inflammatory bowel disease, and systemic lupus erythematosus. The prevalence of these latter two pathologies is moreover related to solar exposure, and thus to low serum concentrations of vitamin D.

In a prospective, nested case-control study of 257 patients with multiple sclerosis matched for age, sex, race and dates of blood sampling for the determination of vitamin D concentrations with two controls, the risk of multiple sclerosis was seen to decrease significantly with increasing vitamin D levels, suggesting that high serum vitamin D levels could be associated to a lesser risk of multiple sclerosis. Recently, a systematic review and meta-analysis of observational studies and case-control studies evaluating the effect of vitamin D supplementation on the risk of developing type 1 diabetes mellitus has shown a risk reduction (odds ratio 0.71, 95% CI 0.60-0.84) in the vitamin D-supplemented group versus the group not administered the vitamin. Likewise, a dose-dependent effect was recorded, with greater risk reduction in association with higher vitamin D doses. As regards to type 2 diabetes, hypovitaminosis D is associated with insulin resistance and alpha cell dysfunction.

There is also evidence that inadequate vitamin D photosynthesis or an insufficient dietary intake of the vitamin is related to an increased incidence of colon, breast and prostate cancer. The analysis of the different dose-response gradients derived from a number of observational studies indicates that a vitamin D dose of 1,000 IU/day is associated with a 50% reduction in colorectal cancer compared with a reference dose of 100 IU/day. In the case of breast cancer, it has been reported that a daily intake of 4,000 IU of vitamin D may increase the serum concentrations to 52 ng/mL – this being the threshold associated to a 50% reduction in the incidence of breast cancer (a daily dose of 2,000 IU in turn eliciting a 30% reduction in breast cancer incidence). Moreover, different studies have reported an increase in cardiovascular risk in situations of moderate or severe hypovitaminosis D. This could have important public health implications, given the high prevalence of hypovitaminosis D in industrialized countries, the contribution of life style and geographical setting to vitamin D status, and the safety, simplicity and low cost of treating vitamin D deficiency.

Finally, the association of low 25-hydroxy vitamin D levels with all-cause, cancer, and cardiovascular...
cicular disease mortality in 13,331 nationally representative adults 20 years or older from the Third National Health and Nutrition Examination Survey (NHANES III) linked mortality files has been recently examined⁹⁰. Participant vitamin D levels were collected from 1988 through 1994, and individuals were passively followed for mortality through 2000. Compared with the highest quartile, being in the lowest quartile (vitamin D levels < 17.8 ng/mL) was associated with a 26% increased rate of all-cause mortality (mortality rate ratio, 1.26; 95% CI, 1.08-1.46). In a prospective cohort study of 3258 consecutive male and female patients⁹⁰, quartiles according to 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were performed. Multivariate-adjusted hazard ratios (HRs) for patients in the lower two 25-hydroxyvitamin D quartiles (median, 7.6 and 13.3 ng/mL) were higher for all-cause mortality (HR = 2.08, 95% CI 1.60-2.70 and HR = 1.53, 95% CI 1.17-2.01, respectively) and for cardiovascular mortality (HR = 2.22, 95% CI 1.57-3.13 and HR = 1.82, 95% CI 1.29-2.58, respectively) compared with patients in the highest 25-hydroxyvitamin D quartile (median 28.4 ng/mL). It is concluded that low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels are independently associated with all-cause and cardiovascular mortality.

Conclusions
Optimization of the nutritional supply of vitamin D and calcium is the first step in the care of the patient with osteoporosis. Although guidelines for the prevention and treatment of osteoporosis include recommendations regarding calcium and vitamin D intake, the use of an adequate supplementation is frequently deficient in daily practice. In this respect, it is essential to increase awareness among physicians and educational measures for patients regarding the important role of vitamin D and calcium in terms of bone health⁹¹,⁹². Based on a review of the current evidence-based literature, the experts participating in the round table discussions in Madrid reached consensus on the following points:

- Oral aminobisphosphonates, alendronate and risedronate, are the treatment of choice for osteoporosis according to the proven efficacy of these agents in vertebral, nonvertebral, and hip fractures.
- The scientific evidence regarding the impact of vitamin D deficiency upon vertebral and nonvertebral fracture risk is of lesser quality and less conclusive than the evidence related to treatment with alendronate. The adequate vitamin D dose could be defined as 800 IU/day for healthy adults and as 1000 IU/day for osteoporotic patients, in order to secure the optimum cut-off serum concentration of 20–30 ng/mL.
- Despite uncertainty regarding the efficacy of calcium per se for the reduction of the risk of fracture, specific treatment of osteoporosis should be accompanied by the administration of calcium and vitamin D.
- The mean calcium ingestion in Spain is about 900 mg/day, of which two-thirds correspond to dairy products and the rest to non-dairy products. Since there are important differences, each patient must be analyzed individually.
- In principle, it appears preferable to ingest the calcium in the form of food (mainly milk). However, in the event of difficulty in securing the required intake, drug supplementation should be used.
- The amount of calcium intake is 1,000-1,200 mg/day. This means two glasses of milk a day and some yogurt, although if only part of this amount of dairy products is ingested, a calcium tablet should be taken. If the patient does not consume milk, two calcium tablets should be administered (one dose being required at bedtime). The calcium should be taken with food, except when the latter is rich in oxalate or phytic acid, in which case it is advisable for calcium administration to be independent of food.
- The etiology of osteoporotic fractures is multifactorial, and risk factors for bone fragility and falls are equally relevant as causative factors as the reduction in bone mineral density. People over 65 years of age show a high prevalence of vitamin D deficiency. Hypovitaminosis D is associated with muscular weakness, and correction of the deficiency state improves muscular muscle strength. The correction of vitamin D deficiency reduces the risk of falls (minimum dose 800 IU/day). Although calcium supplementation could be secured through the diet, drug administration is required in the case of vitamin D supplementation. Vitamin D supplementation does not exclude the intervention on other factors that may influence the risk of falls.
- In reference to good bone health, the required daily dose of vitamin D is at least 800-1,200 IU in order to ensure adequate 25(OH)D₃ levels. However, the dose required to maintain an optimum 25(OH)D₃ concentration to allow the correct function of the remaining extraskeletal actions of the vitamin is unknown, but the current evidence suggests that the doses required may be higher. Multidiscipline efforts are needed to define the doses and levels of vitamin D necessary to reduce the risk of diseases linked to the noncalcemic actions of the vitamin.

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