Sociedad Española de Investigación Ósea y del Metabolismo Mineral (SEIOMM) y Sociedades afines

Gómez de Tejada Romero MJ[1], Sosa Henríquez M[2], Del Pino Montes J[3], Jódar Gimeno E[4], Quesada Gómez JM[5], Cancelo Hidalgo MJ[6], Díaz Curiel M[7], Mesa Ramos M[8], Muñoz Torres M[9], Carpintero Benítez P[10], Navarro Ceballos C[11], Valdés y Llorca C[12], Giner Ruíz V[13], Blázquez Cabrera JA[14], García Vadillo JA[15], Martínez Rodríguez ME[16], Peña Arrebola A[16], Palacios Gil-Antuñano S[17]

1 Secretaria de la SEIOMM y coordinadora general del proyecto - 2 Presidente de la SEIOMM - 3 Vice-Presidente de la SEIOMM - 4 Tesorero de la SEIOMM - 5 Experto en vitamina D de la SEIOMM - 6 Por la Asociación Española para el Estudio de la Menopausia (AEEM) - 7 Por la Fundación Hispana de Osteoporosis y Enfermedades Metabólicas Óseas (FHOEMO) - 8 Por la Sociedad Española de Cirugía Ortopédica y Traumatología (SECOT-GEIOS) - 9 Por la Sociedad Española de Endocrinología y Nutrición (SEEN) - 10 Por la Sociedad Española de Fracturas Osteoporóticas (SEFRAOS) - 11 Por la Sociedad Española de Geriatría y Gerontología (SEGG) - 12 Por la Sociedad Española de Médicos de Atención Primaria (SEMERGEN) - 13 Por la Sociedad Española de Medicina Familiar y Comunitaria (SEMFyC) - 14 Por la Sociedad Española de Medicina Interna (SEMI) - 15 Por la Sociedad Española de Reumatología (SER) - 16 Por la Sociedad Española de Rehabilitación y Medicina Física (SERMEF) - 17 Por la Sociedad Iberoamericana de Osteoporosis y Metabolismo Mineral (SIBOMM)

Position document on the requirements and optimum levels of vitamin D

Introduction

In the last few years there has been a notable interest in vitamin D, not only due to its crucial importance in bone mineral metabolism, but also for its effects outside the bone, which, every day, are becoming better known.

Similarly, the existence of low blood levels of vitamin D, lower than what is desirable, has been found in different populations, both healthy and sick, and there is a discussion as to what would be the optimum levels of vitamin D in the blood.

For all these reasons, the Spanish Society of Bone and Mineral Metabolism Research (Sociedad Española de Investigación Ósea y Metabolismo Mineral – SEIOMM), jointly with all the scientific societies involved in the study of bone metabolism, have produced this position document on the requirements and optimum levels of vitamin D.

Material and method

The content of this document was developed in the following stages:

a) Meeting of a group of experts in osteoporosis to discuss and agree the relevant clinical questions related to vitamin D (Table1).

b) Creation of a systematic review team, formed by two experts in bone mineral metabolism who carried out the search, a standardised review, critical analysis and tabulation of the articles which had been published in Spanish and English between January 2000 and May 2010. The search was carried out using the MeSH (Medical Subject Headings) terms of the National Library of Medicine of the US National Institutes of Health, related to the topic. Using these terms, the following databases were consulted: PubMed, Medline Plus, Cochrane Library, Up to Date and OVID. Similarly, an ascending search was made of the previously published guides to clinical practice relevant to the topic, as well as articles suggested by the group of experts.

c) Those articles which provided the best level of evidence for each of the questions raised were included (Table 2).

d) Subsequently, following on from the results obtain in the search, a draft of the position document was put together by the group of clinical experts to respond to the questions previously formulated and to provide a consensus on recommendations, taking into account social, economic and health repercussions. In cases of disagreement, a majority opinion was formed, leaving the absence of unanimity on record.

PART 1. LITERATURE REVIEW

Introduction

1. Sources of vitamin D

More than 90% of the vitamin D in our bodies comes from the transformation of 7-dehydrocholesterol into previtamin D_3, and subsequently into vitamin D_3 by the action of ultraviolet B radiation from the sun on the skin. There is no danger of vitamin D intoxication due to an excess exposure to the sun, since any excess previtamins and vitamin D synthesised degrade in the skin itself into inactive metabolites.

The rest is obtained through intestinal absorption, either from the diet (although those foods which contain vitamin D do not provide sufficient quantities) or by taking supplements[1].

2. Physiology of vitamin D. Action inside and outside the bone

Vitamin D is actually formed from a family of chemical substances with similar action. But when we talk generically of vitamin D we are referring both to vitamin D_3 (coleclaciferol), and vitamin D_2 (ergocalciferol), the first being part of human physiology, and the second obtained by UV irradiation of ergosterol contained in yeasts. Dietary vitamin D absorbed by the fraction of the kilomicrons or synthesised in the skin, and later also its metabolites, circulate bonded to a transporter protein (DBP). In the liver it undergoes a hydroxylation by the action of 25-hydroxylase to form calcifediol or calcidiol (25 hydroxy-colecalciferol, 25 hydroxy-vitamin D, 25 (OH)D). The calcifediol has a high concentration and a long average life, of two or three weeks, which means that it is used to evaluate the status of vitamin D in the body (see later), and forms the ideal substrate for the formation of calcitriol or 1.25 dihydroxy-vitamin D ($1.25(OH)_2D$), the hormonally active metabolite in the endocrine system of vitamin D[1-3].

The complex formed by calcifediol and its transporter protein, [25(OH)D]-DBP, is bonded with megalin (a protein located in the plasmatic membrane of the renal tubular cells), which it introduces into the cells. Here, the 25(OH)D is released and directed to the mitochondria, where, by the action of 25-hydroxyvitamin D-1α-hydroxylase it is transformed into $1.25(OH)_2D$, which has as its principal endocrine function, the maintenance of calcium homeostasis. This balance, in turn, is fundamental to the various metabolic functions to be carried out normally, for adequate muscular transmission and for bone mineralisation to happen correctly. Its calciotropic function is carried out by acting on the intestinal, parathyroid, bone and renal cells, as we see below[1-3].

In the intestine, the action of vitamin D is fundamental for the absorption of calcium through the saturable transcellular pathway, especially when it derives from foods or compounds with low ionisability. When a deficiency in vitamin D occurs, the absorption of calcium reduces by 15% (and by up to 60% for phosphorus), thus reducing levels of ionized calcium in the blood. This decrease is detected by the calcium sensors in the parathyroid glands, which respond with an increase in the secretion of parathyroid hormone (PTH)[1,4], whose function is to maintain adequate levels of blood calcium, by acting on the kidneys, as we will see later, and in the bone, where it stimulates bone resorption. This final action it achieves by increasing in the osteoblasts the expression of RANKL, which bonds to the receptor, RANK, in the plasmatic membrane of the monocyte precursors of the osteoclasts, inducing their maturation. The mature osteoclasts then bond with the bone surface to initiate their resorptive action by releasing, above all, hydrochloric acid and collagenase. The calcium and phosphorus released in the process pass into the circulation, and thus increase their blood levels[1-3].

In the kidney, the PTH reabsorbs the filtered calcium (both in the distal and proximal tubules) and reduces the reabsorption of phosphorus, leading to phosphaturia and, therefore, hypophosphotemia. Both (PTH and hypophosphotemia) in turn powerfully stimulate the renal production of $1.25(OH)_2D$.

Calcium and phosphorus are essential for mineralisation to happen correctly; when the supply of calcium in the body is inadequate $1.25(OH)_2D$ helps to maintain calcium homeostasis, acting on the receptors for vitamin D (VDR) of the osteoblasts in which it induces in a similar way to PTH the formation of RANKL.

In addition to these endocrine actions, which we could call "traditional" or "classic", and which regulate calcium-phosphorus and bone homeostasis, the vitamin D endocrine system has other auto-paracrine functions in the organism as a whole[1,5]. The majority of tissues and cells, normal or neoplastic, such as muscle, heart, brain, blood vessels, breast, colon, prostate, pancreas, skin and immune system, among others, contain VDR and activator enzymes for 25(OH)D, such as 1-hydroxylase, in those locations not regulated by PTH, to synthesise $1.25(OH)_2D$, and, as happens in the kidneys, inactivator enzymes such as 24 hydroxylase, which catabolises both 25(OH)D and $1.25(OH)_2D$, and ends up forming calcitroic acid, which is soluble in water and biologically inactive.

The $1.25(OH)_2D$ bonds with its VDR with a strong affinity and regulates the transcription of approximately 3% of the human genome. It is involved in the regulation of cell growth and maturation, inhibits the production of rennin and increases the secretion of, and sensitivity to, insulin, modulating the function of activated B and T lymphocytes and the macrophages, among other actions, which means that it has important implications for health[5,6].

Questions raised by the Committee of Experts: search for evidence

1st. Optimum levels of vitamin D

Adequate levels of vitamin D are vital for the correct working of the endocrine system, not only

in the bone, but also in practically the whole organism. The principal indicator for the system is 25(OH)D, the metabolite with the longest average life and an essential substrate for the synthesis of $1.25(OH)_2D$, both in the kidneys as well as in other cells and tissues, which makes it commonly accepted as an indicator for the status of vitamin D[4,7].

A fundamental problem in the determination of 25(OH)D consists in the precision and reproducibility of the methods available for its measurement[6]. For a long time there was no consensus regarding what were the optimum levels of 25(OH)D in the population, although in recent years there has been a growing interest in establishing them. Some studies have shown that with levels of 25(OH)D above 30-40 ng/ml (75-100nmol/l), in adults the maximum intestinal absorption of calcium is achieved[8,9], and at the same time, lower levels of PTH, avoiding the appearance of secondary hyperparathyroidism[10]. It is assumed that children have the same requirements as adults, although no studies have been carried out which confirm this.

Table 1. Questions raised by the panel of experts

1. What are the optimum levels of vitamin D?
2. Are there adequate levels of vitamin D in the Spanish population? - Prevalence of hypovitaminosis D in Spain
3. What are the requirements for vitamin D? a- In the general population b- In specific situations: - In children and adolescents - In the postmenopause - In elderly people c- In pathological situations: - In patients with osteoporosis - In patients with fracture - In patients receiving corticoids
4. Vitamin D and falls, muscle strength and balance - Incapacitated patients
5. Treatment with vitamin D. Alone, or always with calcium? - In the prevention of osteoporosis - In the treatment of osteoporosis itself - Combined with other antiosteoporotic drugs

Generalising from these findings the view is that the optimum requirements of vitamin D are those which permit the maintenance of blood levels of 25(OD)D above 30 ng/ml (75 nmol/l)[11,12].

Faced with these results, there is ever increasing agreement in accepting these levels as those most beneficial to ensure healthy bone[8,13]. Minimum desirable blood concentrations of 25(OH)D for anyone ought to be higher than 20 ng/ml, which would imply an average of around 30 ng/ml in the whole population[14]. Bischoff-Ferrari et al. even suggest that, to ensure other non bone-related health objectives, the optimum levels of 25(OH)D should be higher, between 36 and 40 ng/ml[12]. These data are corroborated by a study carried out in populations highly exposed to the sun, in which it is very difficult to surpass blood concentrations of 25(OH)D of 65-70 ng/ml[15].

The IOF, in its recent recommendations on vitamin D in elderly people[16], advises that these levels be reached, and the NOF recommends that the general public should maintain levels of 25(OH)D above these values (www.nof.org). Below these optimum levels, it is generally considered that there is a deficiency when the levels are between 20 and 30 ng/ml (50 and 75 nmol/l); vitamin D deficiency, observed in individuals with osteomalacia or rickets, appears at values lower than 20 ng/ml (50 nmol/l)[4,8,10,13] (Table 3).

Thus, blood levels of 25(OH)D of between 30 and 75 ng/ml would seem to be the most physiologically appropriate, and as such, the most recommendable. With respect to higher values, in a review of thirty works there was no evidence of toxicity in patients with levels of 25(OH)D below 100 ng/ml. It has been proposed that the minimum threshold for toxicity is above 150 ng/ml (375 nmol/l)[4,9].

2nd Levels of vitamin D in the Spanish population

At present, insufficiency, and frankly, deficiency in 25(OH)D constitutes a pandemic which affects more than half the general population[8,17], and both children and adolescents[18-21], as well as adults[22], postmenopausal women[23] and elderly people[24-26]; in this last group, if they have osteoporotic fractures, the prevalence of hypovitaminosis D reaches 100%[4]. Holick and Chen, in 2008, described vitamin D deficiency as a global health problem with diverse pathological consequences[8], and a recent review carried out by Mithal et al. of studies on hypovitaminosis D across the world concluded that this deficit was emerging globally as a major health problem[27].

This situation is occurring also in Spain, as can be observed from the various studies carried out in this country[28-35]. Despite having a propitious climate which could result in an adequate synthesis of vitamin D by solar exposure, the general levels are similar or even lower than those described in central Europe or Scandinavia in earlier studies[36,37], although the variation in methodologies between laboratories makes a rigorous comparison difficult.

There has been an attempt to explain the paradoxical state of hypovitaminosis D which is obser-

ved in our country, and which is also seen in other Mediterranean countries, by the scarce supply of dietary vitamin D which cannot be compensated for by cutaneous synthesis[38]. On the other hand, it is important to understand that the greater part of the Iberian peninsula is above the latitude of 35° N, which means that the inclination of the sun's rays reduces the possibility of synthesising vitamin D during the months of winter and spring[36].

However, vitamin D deficiency in Spain ought not to be explained solely by geographic factors; some studies have observed low levels of vitamin D in populations with an adequate, or even, abundant, exposure to sun, such as that carried out in habitual surfers in Hawaii, by Binkley et al.[39]. In our country, where there is a significant seasonal variation in levels of vitamin D between the months of greater sunshine (summer-autumn) and those with lower (winter-spring), it has been observed, however, that they scarcely normalise after the first months[28]. This insufficiency is observed in children and young people[29,30], persists in adults[31], in healthy postmenopausal women[32,33] and women with osteoporosis[36], and, logically, is patent in elderly people, both those living in their own homes as well as, even more so, in those living in residential homes[28,34,35].

3rd Vitamin D requirements

It is logical to think that the requirements for vitamin D should be those which maintain the optimum levels of 25(OH)D. However, the quantities of vitamin D which have come to be recommended until recently for the healthy population (200 UI/day from birth until 50 years of age, 400 UI for adults up to 70 years of age and 600 UI daily for those over 71 years of age) seem insufficient for purpose, as various authors have indicated[4,8,40,41]. Coming to the same conclusion are Ginde et al., who carried out a demographic study to look at the trend of vitamin D insufficiency in the population of the US[42] comparing the levels in the population studies in NHANES during the years 1988 to 1994 (18,883 people), with those recorded in people studied during the years 2001 to 2004 (13,369 people), and observing a marked decrease in levels of 25(OH)D over time.

If we take into account the different population groups, various authors already consider it necessary that children and adolescents should acquire 400 UI daily of vitamin D to reach optimum blood levels of 25(OH)D[43]. In 2008, the American Academy of Pediatrics increased the recommended daily dose of vitamin D for children and adolescents to 400 UI, and when this is not achieved through diet and exposure to sun, it should be acquired through supplements[44].

For adults, although the daily acquisition of 400 UI of vitamin D[13] has for a long time been recommended in order to reach optimum blood levels of 20-30 ng/ml (50-75 nmol/l) much higher amounts are needed , approximately 1,700 UI/day[45]. When a daily dose of 1,000 UI is given over 3 or 4 months, blood levels of 25(OH) increase 10 ng/ml, so that a subject with levels of 10 ng/ml would need 2,000 UI/daily to reach the 30 ng/ml considered to be optimum[46]. The fear of toxicity has limited the recommendations of authors, since, as we mentioned in the earlier section, the upper safety limit in order to avoid the risk of producing hypercalcemia is 150 ng/ml (375 nmol/l) of blood 25(OH)D. For some years some authors have already been recommending higher quantities, both in women and men, of between 700 to 1,000 UI[11,13,47,48,49], and others indicate that even higher daily doses, of 1,000 - 2,000 UI[50], and up to 2,600 UI, can be much more effective to achieve more adequate levels of 25(OH)D with no risk of toxicity[11]. In 2007, a panel of experts produced a consensus document for nutritional guides for vitamin D[51], and in it they stated that the maximum safe intake of vitamin D, established at 2,000 UI daily, should be re-evaluated and raised to allow the carrying out of studies which evaluate the effects of high daily doses of vitamin D in the maintenance of better general health. In the same year, Hathcock et al.[52] in a review on the safety of vitamin D based on the risk of hypercalcemia, concluded that the upper limit for the ingestion of vitamin D in adults should be 10,000 UI daily. This indicates that the safety limit is much higher than any of the recommended quantities. Very recently, the IOF in its position document recommends doses of 800-1,000 UI/day, although with subjects at risk of low blood levels of 25(OH)D (obesity, osteoporosis, malabsorption, low exposure to sunlight, etc.) these daily doses should rise to 2,000 UI[16].

In postmenopausal women, the same as with elderly people, both populations with a high risk of bone loss, the quantities which the experts recommend become higher, between 2,000 and 3,000 UI/day[26,53,54]. Bacon et al. evaluated the safety and effectiveness of high doses, such as 500,000 in a single dose, an initial dose of 500,000 UI and 50,000 UI monthly for maintenance, or 50,000 UI monthly, showing that they were both safe and effective[57].

Up until now, we have talked of the desirable requirements for healthy subjects; evidently, patients with osteoporosis should be considered in a special way, since in these patients vitamin D plays an important role in the etiopathogeny of the disease. Even though it is not clear whether vitamin D supplements alone, are sufficient to treat osteoporosis, it is recognised worldwide these patients should be supplied with sufficient quantities of vitamin D, which in the majority of cases they do not acquire through diet and exposure to sun. Later we dedicate a specific section to treatment of osteoporosis with vitamin D and its complication, fractures. Related to both osteoporosis and vitamin D, we should not forget that those patients receiving corticoid therapy. In these patients, the action of the drug results in a lower intestinal absorption of calcium, along with a higher rate of urinary elimination, which produces secondary hyperparathyroidism Although the studies carried out with regard to its effectiveness in preventing bone loss or fractures are highly heterogeneous and involve low

numbers of patients (and are therefore not generally conclusive), it is generally recognised that vitamin D (combined with calcium) should be prescribed in all those patients in long term treatment with corticoids at high doses, with the aim of maintaining bone metabolism; although it is also generally considered that they should not be prescribed alone, but with an antiosteoporotic drug (biphosphonates, teriparatide), especially when dealing with patients with high risk of fracture[56-63].

There is neither agreement nor unanimity regarding the dose of vitamin D which patients in treatment with glucocorticoids ought to receive. In the Guide on Corticoid Osteoporosis, published by the Spanish Society of Internal Medicine in 2007 it is recommended that vitamin D be administered at a dose of 800-1,000 UI/day, combined with 500-1,000 mg/day of calcium[63].

4th. Vitamin D and falls, muscle strength and balance

Apart from the well known effects of vitamin D on bone metabolism, hypovitaminosis D is also associated with muscular weakness, predominantly in the proximal musculature. It has been demonstrated in experimental studies that the metabolites of vitamin D have an influence on the maturation and function of muscle through the receptors for these metabolites which the muscle cells possess[64]. In a sample of 976 people older than 65 years of age it has been confirmed that their levels of vitamin D were inversely correlated with being in poor physical shape. Given the high prevalence of vitamin D deficiency in the older population, studies aimed at clarifying this correlation appear justified, especially since there is an ever-increasing number of elderly people in whom there will be have to be identified potentially modifiable risk factors for disability[65].

Stewart et al. recently carried out a study in 242 healthy postmenopausal women (aged between 48.8 and 60 years) with the aim of understanding the relationship between levels of 25(OH)D to obesity, risk of falls

Table 2. Levels of evidence. CEBM Oxford

Level of evidence	Type of study
1a	Systematic review of randomised clinical trials, with homogeneity
1b	Randomised clinical trials with narrow confidence interval
1c	Clinical practice ("all or nothing") (*)
2a	Systematic review of cohort studies, with homogeneity
2b	Cohort study or randomised clinical trial of low quality(**)
2c	"Outcomes research" (†), ecological studies
3a	Systematic review of case-control studies, with homogeneity
3b	Case-control study
4	Case series or cohort and case-control studies of low quality (‡)
5	Opinion of experts without explicit critical validation, or based on physiology, "bench research" or " first principles" (§)

A minus sign (-) should be added to indicate that the level of evidence is not conclusive if:
-Randomised clinical trial with wide confidence interval and not statistically significant.
-Systematic review with heterogeneity statistically significant.
(*) When all the patients die before a specific treatment becomes available, with which some patients survive, or when some patients used to die before its availability, and with it, none die.
(**) For example, with follow up low than 80%
(†) The term "outcomes research" makes reference to cohort studies of patients with the same diagnosis in whom the events which occur are related to the therapeutic measures which they receive.
(‡) Cohort study: without clear definition of the groups compared and/or without objective measurement of exposures and events (preferably blind) and/or without identifying or adequately controlling known confusion variables and/or without complete or sufficiently prolonged follow up. Case-control study: without clear definition of the groups compared and/or without objective measurement of exposures and events (preferably blind) and/or without identifying or adequately controlling known confusion
(§) The term "first principles" makes reference to the adoption of a specific clinical practice based on physiopathological principles.

Table 3. Valuation the levels of 25 (OH) D serum

	ng/ml	nmol/l
Adequate vitamin D levels	> 30 ng/ml	> 75 nmol/l
Vitamin D insufficiency	20 - 30 ng/ml	50 - 75 nmol/l
Vitamin D deficiency	< 20 ng/ml	< 50 nmol/l

1 ng/ml equivalent to 2.5 nmol/l

and muscular weakness. 19.4% had values of 25(OH)D < 50 nmol/l (20 ng/ml). For these subjects, a correlation was sought with some indicators for good physical health, such as the android fat mass, lean body mass, balance and the hand grasp strength, the strength of the torso and of the lower limbs. They found that the levels of vitamin D were correlated with all the indicators, except with the strength of the torso and lower limbs, concluding that the blood levels of 25(OH)D can be a contributor to the indices of physical health in healthy postmenopausal women[66].

The aforementioned muscular weakness associated with hypovitaminosis D, if it surpasses a certain limit, can affect functional capacity and mobility, which puts , especially elderly people, at greater risk of falls, and therefore, of fractures. The provision of vitamin D supplements to elderly people in situations of deficiency can improve muscle strength and functional capacity, which results in a reduction in falls and therefore, of non-vertebral fractures[67]. Bunout et al. evaluated the effects of resistance training and the provision of vitamin D supplements on the physical condition of 96 healthy elderly people with low levels of vitamin D, concluding that the addition of this treatment improved their walking speed and stability, while the training improved muscle strength[68].

Some authors have found that in healthy elderly people vitamin D supplements did not prevent a decrease in muscle strength due to age-related involution[64,69]. In a review carried out by Annweiler et al. the results around the association of vitamin D with physical function were contradictory[70]. Dhesi et al. carried out a study in 139 mobile subjects older than 65 years of age with a history of falls and hypovitaminosis (levels of 25(OH)D ≤ 12 µg/l), and to whom were randomly allocated either a single dose of 600,000 UI of intramuscular ergocalciferol, or a placebo. The results showed that at 6 months, the subjects who had received the vitamin D supplement had significant benefits in terms of their physical function, reaction times and balance, although not muscle strength[71]. A more recent study continued the controversy: More-Pfrimer at al. studied muscle strength in 46 institutionalised subjects ≥ 65 years of age, to whom they administered over 6 months either daily calcium plus a placebo, or daily calcium plus oral colecalciferol (initial dose of 150,000 UI monthly for two months followed by 90,000 UI monthly for 4 months), randomly allocated. At 6 months, and without having taken physical exercise, the strength of the hip flexors increased in the group which received vitamin D by 16.4% (p= 0.0001), and the strength of the extensors of the knee by 24.6% (p = 0.0007)[72]. Lips et al. carried out a study in which were assigned randomly a dose of 8,400 UI weekly of colecacliferol, or a placebo, to 226 subjects ≥ 70 years of age whose concentrations of 25(OH)D were between 6 and 20 ng/ml. To evaluate muscle function and balance their mediolateral body sway with eyes open was measured at 8 and 16 weeks with an AccuSway^{PLUS} platform and a battery of short physical exercises (SPPB, Short Physical Performance Battery) carried out. In the results obtained vitamin D did not reduce the mediolateral body sway or improve the SPPB, although by grouping the subjects according to their baseline mediolateral sway, those who had the greatest instability (≥ 0.46 cm) improved significantly when they had been treated with vitamin D for 16 weeks (p= 0.047). It is important to indicate that even though the levels of 25(OH)D increased in patients treated at 8 weeks, they did not reach adequate levels (30 ng/ml) during the whole period of the study (16 weeks)[73].

In terms of its effect on the reduction in falls, the same studies which showed that the vitamin D supplements favoured muscular function and balance, suggest that there should also be a reduction in falls, and therefore, in fractures[71]. Various meta-analyses published in recent years indicate that vitamin D supplements reduce the risk of falls in the elderly[74], although some specify that the dose should be 700-1,000 UI daily, since at lower doses (or blood concentrations < 60 nmol/l) this reductor effect is not produced, which could be as much as 22% (adjusted OR: 0.78; 95% CI: 0.64-0.92) compared with those patients who had received calcium alone or a placebo[75]. This is corroborated in a review of Cochrane carried out by Gillespie et al. who observed that vitamin D supplements do not reduce the risk of falls (RR 0.96; 95% CI: 0.92-1.01), but indicate that they may do so in those with low blood levels of vitamin D[76]. Another review carried out more recently, found that these supplements reduce the rate of falls (rate *ratio*, RaR 0.72: 95% CI: 0.55-0.95), but not the risk of falls (risk *ratio*, RR 0.98; 95% CI: 0.89-1.09) 77. To add more controversy, in a recently published study, carried out in 2,252 women of ≥ 70 years of age who were not institutionalised, to see the effect of a single high dose of 500,000 UI of colecacliferol, it was observed that the group which took the high dose of vitamin D showed an increase in the number of falls and fractures as opposed to the group which had taken the placebo[78].

On the other hand, it has been suggested that there could be an inverse relationship between levels of vitamin D and intensity of muscular-skeletal pain, which means that optimum levels of vitamin D could be useful in patients with secondary pain due to osteoporotic complications[79,80].

In this section we should make special mention of the effect vitamin D supplements can have in patients affected by multiple sclerosis (MS). Originally, the hypothesis that a sufficient supply could prevent the disease was established to explain its geographic distribution; and since then, hypovitaminosis D has been considered one of the environmental risk factors for MS[81-83]. However, recently, studies have been carried out which have shown an association of low blood levels of 25(OH)D with the prevalence of MS, the risk of suffering MS, its incapacity and the frequency between two breaks[84,85].

Table 4. Reference studies with drugs used in the treatment of osteoporosis in postmenopausal women. Principal objective: incidence of fractures

Drug	Study name	Year	First author (ref.)	Group treated	Calcium and vitamin D	Monitoring
Etidronate	---	1990	Storm (101)	Women with OP postmenopausal	Calcium and vitamin D (quantities ND)	3 years
Alendronate	FIT	1996	Black (102)	Postmenopausal women with BMD with FxV/without FxV	Calcium carbonate (500 mg/day of calcium element) and vitamin D (250 UI/day) if diet low in calcium (< 1,000 mg/day)	3 years
Risedronate	VERT	1999/2000	Harris / Reginster (103/104)	Postmenopausal women < 85 years with at least 2 FxV or one FxV and low BMD (T-score < -2)	Calcium carbonate (1,000 mg/day) and vitamin D (500 UI/day) if 25(OH) vit D < than 16 ng/ml or 40 nmol/l	3 years
	HIP	2001	McClung (105)	Women of 70-79 years of age and osteoporosis; or aged ≥ 80 years with at least one clinical risk factor for hip Fx		3 years
Ibandronato	BONE	2004	Chesnut (106)	Postmenopausal women with T-score ≤ -2 in at least one lumbar vertebra and between 1 and 4 FxV	Calcium (500 mg/day) and vitamin D (400 UI/day)	3 years
Zoledronate	HORIZON	2007	Black (107)	Women with densitometric OP with T-score < -2.5 without fractures; or T-score < -2.5 and ≥ 1 FxV	Calcium (100-1.500 mg/day) and vitamin D (400-1.200 UI/day)	3 years
Raloxifene	MORE	1999	Ettinger (108)	Women with ≥ 2 years of menopause with densitometric OP	Calcium (500 mg/day) y cholecalciferol (400-600 UI/day)	3 years
Teriparatide	---	2001	Neer (109)	Postmenopausal women with at least one FxV	Calcium (1.000 mg/day) and vitamin D (400-1.200 UI/day)	3 initial years (19 months)
PTH 1-84	TOP	2007	Greenspan (110)	Postmenopausal women of between 45 and 54 years with T-score < -3; or T-score < - 2.5 plus 1-4 FxV	Calcium citrate (700 mg/day) y vitamin D (400 UI/day)	18 months
Strontium ranelate	TROPOS	2005	Reginsterb (111)	Postmenopausal women with T-score < -2.5; or if > 70 years, also with 1 risk factor for Fx	Calcium (>1.000 mg/day) and vitamin D (400-800 UI/day)	5 years (preliminary 3 years)
	SOTI	2004	Meunier (112)	Postmenopausal women (>5 years), aged > 50, with at least 1 FxV and BMD ≤ 0.840 g/cm^2	Calcium (>1.000 mg/day) and vitamin D (400-800 UI/day)	3 years
Calcitonin	PROOF	2000	Chesnut (113)	Postmenopausal women with established OP	Calcium (1.000 mg/day) and vitamin D (400 UI/day)	5 years

OP: osteoporosis; BMD: bone mineral density; Fx: fracture; FxV: vertebral fracture; ND: unavailable

However, its therapeutic potential in established MS has not yet been sufficiently studied. A recently published work by Burton et al. was carried out in 49 patients with MS of average age of 40.5 years and average blood levels of 25(OH)D of 78 nmol/l, with an average EDSS (Expanded Disability Status Scale) of 1.34. They were randomly assigned to a placebo group (n= 24), or to treatment with a dose which was increased step by step until it reached 40,000 UI/day at 28 weeks, thus rapidly raising their blood levels of 25(OH)D and thereby evaluating its tolerability. The dose was then maintained at 10,000 UI daily over 12 weeks, subsequently being reduced to 0 UI/day (n= 25). During the whole study 1,200 mg/day of calcium was given. In spite of blood levels of 25(OH)D reaching a peak of 413 nmol/l, there were no significant adverse effects. The group treated with vitamin D appeared to have fewer breaks and a persistent reduction in the proliferation of T lymphocytes, compared with the control group. Despite recognising that there were confusion variables in the clinical results, the authors concluded that high doses of vitamin D supplements had an evident immunomodulator effect on the MS, in addition to being safe[86]. All the researchers considered it necessary that more studies be carried out in this area.

5th. Calcium and vitamin D supplements in the prevention and treatment of osteoporosis

There is near unanimity among researchers in concluding that vitamin D on its own is insufficient for the prevention of osteoporotic fractures[87-91], and those who find a positive impact on the risk of fracture indicate that this improves with the addition of calcium, with a reduction of 30% in this risk[92]. The same occurs with calcium supplements, which are considered insufficient in themselves in reducing the risk of hip fracture[93-94], although some have obtained results which indicate that calcium supplements alone are sufficient to reduce the risk of fractures in general[95], and even vertebral fractures[96].

But the majority of studies and researchers concede that supplements of calcium plus vitamin D have a positive effect in the reduction of risk of fractures in the region of 20%[89-91,97]. And this is demonstrated in various meta-analyses on this subject. Thus, Bischoff-Ferrari et al. published a meta-analysis in 2005 in which they analysed the effect of calcium and vitamin D on the prevention of hip and non-vertebral fractures. The authors observed that at a dose of 700-800 UI/day of vitamin D, the reduction in the risk of hip fracture was 26% (relative risk, RR: 0.74; 95% CI: 0.61-0.88) and for non-vertebral fractures, 23% (RR: 0.77; 95% CI: 0.68-0.87), while for lower doses of vitamin D, below 400 UI/day, no protection against fractures was observed[98].

Subsequently, Boonen et al. delved deeper into the earlier meta-analysis of Bischoff-Ferrari and found that in 4 randomised clinical studies, which included 9,083 patients, the relative risk for hip fracture was not statistically significant (RR: 1.10 95% CI: 0.89-1.36). Instead, in the 6 randomised studies in which calcium and vitamin D were administered, which included a total of 45,509 patients, the risk of hip fracture was reduced by 18% (RR: 0.82; 95% CI: 0.71-0.94). No heterogeneity was observed between the studies, and an adjusted indirect comparison of the combined relative risks of both meta analyses found a reduction in risk of fracture of 25% in those patients who had received calcium and vitamin D as against those who had only taken vitamin D (RR: 0.75; 95% CI: 0.58-0.96)[91].

More recently, Tang et al. carried out another meta-analysis using 29 randomised studies which included a total of 63,897 patients, analysing both the reduction in the relative risk of all fractures and the increase in bone mineral density. Studying those publications in which the principal objective was the reduction in risk of fracture, 17 studies were included with a total of 52,625 patients. In these patients a reduction of 12% in the risk of suffering new fragility fractures (RR: 0.88; 95% CI: 0.83-0.95; p= 0.0004) was found, and they concluded that the evidence supported the use of calcium, or calcium combined with a vitamin D supplement in the treatment of osteoporosis in people of 50 years of age or over, and that for a maximum therapeutic effect a dose of 1,200 mg/day of calcium and 800 UI/day of vitamin D was necessary[48].

According to the last clinical practice guides, for it to be able to be effective in the prevention of risk of fracture, the minimum daily dose of supplements recommended are 1,000-1,200 mg of calcium element, plus 800 UI (or 20 µg) of vitamin D_3[99,100]. To guarantee the necessary intake of calcium, should it be needed, it recommended that this be through food, whenever possible.

Administration of calcium and vitamin D jointly with other antiosteoporotic drugs

An adequate provision of calcium and vitamin D is essential when a treatment with any antiosteoporotic drug is prescribed, be it antiresorptive, anabolic or of mixed action. Given the difficulty in achieving this through diet and exposure to the sun alone, it is necessary to administer jointly supplements of calcium and vitamin D. In all the clinical trials which have been carried out with the different antiresorptive drugs to demonstrate their antifractural efficacy, supplements of calcium and vitamin D were administered to all participants, which indicates that this efficacy has not been demonstrated in the absence of correct levels of calcium and vitamin D. In Table 4 we show these trials and the quantities of calcium and vitamin D which were administered[101-113].

2nd PART. RESPONSES TO THE QUESTIONS RAISED. RECOMMENDATIONS

1.- What are the optimum levels of vitamin D?

- We consider that the optimum levels of vitamin D should be between 30 and 75 ng/ml, and that levels below 20 ng/ml are clearly pathological.

2.- Are levels of vitamin D in the Spanish population adequate?

- No. The majority of the Spanish population does not achieve optimum levels of vitamin D. Depending on the type of population studied and the cut off point, the prevalence of vitamin D deficiency (< 20 ng/ml) varies between 30% in young people and 87% in institutionalised elderly people, with the ages in between and the non-institutionalised elderly at between 50% and 70%.

3.- What are the requirements for vitamin D?

- In general, they are those which ensure optimum levels of vitamin D in the blood. The means of acquiring these optimum levels may be through adequate exposure to sun, foods and vitamin D supplements.

- In specific situations, the panel makes the following recommendations, although they take the view that when there is vitamin D deficiency, higher doses are necessary to achieve optimum levels:

- Children, adolescents: 400-600 UI/day.
- Postmenopause: 600-800 UI/day.
- Elderly people: 800-1,000 UI/day.
- Patients with osteoporosis: 800-1,000 UI/day.
- Patients with fracture: 800-1,000 UI/day. On the basis of a high prevalence of serious vitamin D deficiency in patients with osteoporotic fractures of the hip, the panel considers it advisable to perform an assessment of levels of vitamin D, and when this not possible it recommends the use of a higher dose.
- Patients receiving corticoids: 800-1,000 UI/day.

4.- Vitamin D and falls, muscle strength and balance

- The panel estimates that in the special case of institutionalised elderly people, due to the great difficulty in their achieving necessary levels of vitamin D through hygiene-dietetic measures, the requirements should be met through vitamin D supplements.

On the other hand, we cannot conclude that the provision of vitamin D improves muscle strength.

5.- Treatment with vitamin D. Alone, or always with calcium?

a. – In the prevention of osteoporosis:

- The panel considers that the prevention of osteoporosis should be carried out through good hygiene-dietetic habits (adequate exposure to sun, consuming foods rich in calcium). The use of calcium and vitamin D drugs are not indicated for this task, save in those cases where there is a difficulty in obtaining optimum levels of these substances, when they should be supplemented pharmacologically.

b. – In the treatment of osteoporosis in itself.

- The panel considers that there is no evidence that exclusive treatment with calcium and vitamin D has antifractural efficacy, except in specific populations, such as institutionalised elderly people.

c. – Jointly with other antiosteoporotic drugs.

- When using an antiosteoporotic drug supplements of calcium and vitamin D should always be added. However, the panel considers that in those patients in whom there is a guarantee of an adequate provision of calcium in the diet, the use of a calcium supplement is not necessary.

Bibliography

1. Holick MF. Vitamin D. Photobiology, metabolism, mechanism of action, and clinical applications. En: Primer on the metabolic bone disease and disorders of mineral metabolism, 6ª edición. Washington DC. Ed. American Society for Bone and Mineral Research 2006;129-37.
2. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004;80(Suppl.6):1689-96.
3. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol 2005;289:8-28.
4. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
5. Quesada JM, Sosa M. Nutrición y Osteoporosis. Calcio y vitamina D. Rev Osteoporos Metab Miner 2010;2. [Epub ahead of print].
6. Binkley N, Krueger D, Gemar D, Drezner MK. Correlation among 25-hydroxy-vitamin D assays. J Clin Endocrinol Metab 2008;93:1804-8.
7. Quesada Gómez J. Insuficiencia de calcifediol (25(OH)D). Implicaciones para la salud. Drugs Today 2009;45(Suppl.A):1-31.
8. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008;87:1080-6.
9. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr 2003;22:142-6.
10. Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 2005;90:3215-24.
11. Binkley N, Krueger D. Evaluation and correction of low vitamin D status. Curr Osteoporos Rep 2008;6:95-9.
12. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18-28.
13. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713-6.
14. Roux C, Bischoff-Ferrari HA, Papapoulos SE, de Papp AE, West JA, Bouillon R. New insights into the role of vitamin D and calcium in osteoporosis management: an expert roundtable discussion. Curr Med Res Opin 2008;24:1363-70.
15. Barger-Lux MJ, Heaney RP. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab 2002;87:4952-6.
16. Dawson–Hugues B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GEH, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 2010;27. [Epub ahead of print].
17. Stechschulte SA, Kirsner RS, Federman DG. Vitamin D: bone and beyond, rationale and reccomendations for supplementation. Am J Med 2009;122;793-802.
18. Greer FR. Defining vitamin D deficiency in children: beyond 25-OH vitamin D serum concentrations. Pediatrics 2009;124:1471-3.
19. Mansbach JM, Ginde AA, Camargo CA. Serum 25-hydroxyvitamin D lebels among US children aged 1 to 11 years: do children nedd more vitamin D? Pediatrics 2009;124:1404-10.

20. Stoffman N, Gordon CM. Vitamin D and adolescents: what do we know? Curr Opin Pediatr 2009;21:465-71.
21. Saintonge S, Bang H, Gerber LM. Implications of a new definition of vitamin D deficiency in a multiracial US adolescent population: The National Health and Nutrition Examination Survey III. Pediatrics 2009;123:797-803.
22. Yerley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr 2008;88:558-64.
23. Gaugris S, Heaney RP, Boonen S, Kurth H, Bentkover JD, Sen SS. Vitamin D inadequacy among postmenopausal women: a systematic review. Q J Med 2005;98:667-76.
24. Baraké R, Weiler H, Payette H, Gray-Donald K. Vitamin D supplement consumtion is required to achieve a minimal target 25-hydroxyvitamin D concentration of ≥ 75 nmol/L in older people. J Nutr 2010;140:551-6.
25. Pekkarinen T, Turpeinen U, Hämäläinen E, Löyttyniemi E, Alfthan H, Välimäki MJ. Serum 25 $(OH)D_3$ vitamin status of elderly Finnish women is suboptimal even after summer sunshine but is not associated with bone density or turnover. Eur J Endocrinol 2010;162:183-9.
26. Leidig-Bruckner G, Roth HJ, Bruckner T, Lorenz A, Raue F, Frank-Raue K. Are commonly recommended dosages for vitamin D supplementation too low? Vitamin status and effects of supplementation on serum 25-hydroxyvitamin D levels – an observational study during clinical practice conditions. Osteoporos Int 2010;17. [Epub ahead of print].
27. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson –Hugues B, Eisman JA, et al. Global vitamin D status and determinants of hipovitaminosis D. Osteoporos Int 2009;20:1807-20.
28. Gomez-Alonso C, Naves-Diaz ML, Fernandez-Martin JL, Diaz-Lopez JB, Fernandez-Coto MT, Cannata-Andia JB. Vitamin D status and secondary hyperparathyroidism: the importance of 25-hydroxyvitamin D cut-off levels. Kidney Int 2003;63(Suppl.85):44-8.
29. Calatayud M, Jodar E, Sanchez R, Guadalix S, Hawkins F. Prevalencia de concentraciones deficientes e insuficientes de vitamina D en una poblacion joven y sana. Endocrinol Nutr 2009;56:164-9.
30. González Padilla E, García Santana S, González Rodríguez E, Groba Marco MV, Mirallave Pescador A, Soria López A, et al. Prevalencia de insuficiencia de vitamina D en estudiantes de Medicina canarios. Rev Multidisciplinar Gerontol 2009;19(Supl.1):16.
31. Mata-Granados JM, Luque de Castro MD, Quesada Gomez JM. Inappropriate serum levels of retinol, alpha-tocopherol, 25 hydroxyvitamin D_3 and 24,25 dihydroxyvitamin D_3 levels in healthy Spanish adults: simultaneous assessment by HPLC. Clin Biochem 2008;41:676-80.
32. Aguado P, del Campo MT, Garces MV, González-Casaús ML, Bernad M, Gijón-Baños J, et al. Low vitamin D levels in outpatient postmenopausal women from a rheumatology clinic in Madrid, Spain: their relationship with bone mineral density. Osteoporos Int 2000;11:739-44.
33. Mezquita-Raya P, Munoz-Torres M, Luna JD, Luna V, Lopez-Rodriguez F, Torres-Vela E, et al. Relation between vitamin D insufficiency, bone density, and bone metabolism in healthy postmenopausal women. J Bone Miner Res 2001;16:1408-15.
34. Larrosa M, Gratacos J, Vaqueiro M, Prat M, Campos F, Roque M. Prevalencia de hipovitaminosis D en una poblacion anciana institucionalizada. Valoracion del tratamiento sustitutivo. Med Clin (Barc) 2001;117:611-4.
35. Perez-Llamas F, Lopez-Contreras MJ, Blanco MJ, Lopez-Azorin F, Zamora S, Moreiras O. Seemingly paradoxical seasonal influences on vitamin D status in nursing-home elderly people from a Mediterranean area. Nutrition 2008;24:414-20.
36. Quesada Gómez J, Mata Granados J, Delgadillo J, Ramírez R. Low calcium intake and insufficient serum Vitamin D status in treated and non-treated postmenopausal osteoporotic women in Spain. J Bone Miner Metab 2007;22:309.
37. Lips P, Duong T, Oleksik A, Black D, Cummings S, Cox D, et al. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab 2001;86:1212-21.
38. Quesada Gómez JM, Díaz Curiel M. Vitamin D Deficiency and Consequences for the Health of People in Mediterranean Countries (capítulo 23). En: Holick MF (Editor). Nutrition and Health: Vitamin D. Nueva York. Ed. Humana Press (Springer Science+Business Media, LLC); 2010. p. 303-9. DOI 10.1007/978-1-60327-303-9_23
39. Binkley N, Novotny R, Krueger D, Kawahara T, Daida YG, Lensmeyer G, et al: Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab 2007;92:2130-5.
40. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Calcium, phosphorus, magnesium, vitamin D and fluoride. Washington, DC: National Academy Press;1999:250-87.
41. Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, et al. The urgent need to recommend an intake of vitamin D that is effective. Am J Clin Nutr 2007;85:649-50.
42. Ginde AA, Liu MC, Camargo CA. Demographic differences and trenes of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 2009;169:626-32.
43. Rajakumar K, Thomas SB. Reemerging nutricional rickets: a historical perspectiva. Arch Pediatr Adolesc Med 2005;159:335-41.
44. Wagner CL, Creer FR, for the American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Comité on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children and adolescents. Pediatrics 2008;122:1142-52.
45. Burger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. Vitamin D and its major metabolites: serum levels alter graded oral doses in healthy men. Osteoporos Int 1998;8:222-30.
46. Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. Altern Med Rev 2008;13:6-20.
47. Mosekilde L. Vitamin D requirement and setting recommendation levels: long-term perpective. Nutr Rev 2008;66:170-7.
48. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A: Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370:657-66.
49. Bischoff-Ferrari H. Vitamin D: what is an adequate vitamin D level and how much supplementation is necessary? Best Pract Res Clin Rheum 2009;23:789-95.
50. Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010;340:b5664. doi:10.1136/bmj.b5664.
51. Norman AW, Bouillon R, Whiting SJ, Vieth R, Lips P. 13th Workshop Consensus for vitamin D Nutricional Guidelines. J Steroid Biochem Mol Biol 2007;103:204-5.
52. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. Am J Clin Nutr 2007;85:6-18.
53. Heaney RP. Barriers to optimizing vitamin D3 intake for the elderly. J Nutr 2006;136:1123-5.
54. Brown SE. Vitamin D and fracture reduction: an evaluation of the existing research. Altern Med Rev 2008;13:21-33.
55. Bacon CJ, Gamble GD, Horne AM, Scout MA, Reid IR. High.dose oral vitamin D_3 supplementation in the elderly. Osteoporos Int 2009;20:1407-15.
56. American College of Rheumatology. Recommendations for the prevention and treatment of Glucocorticoid-induced osteoporosis. Arthr Rheum 2001;44:1496-503.
57. Van Staa TP. The patogénesis, epidemiology and management of glucocorticoid-induced osteoporosis. Calcif Tissue Int 2006;79:129-37.

58. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caayers N, et al. EULAR evidence-based recommendations on the manegements of systemic glucocoticoid therapy in rheumatic diseases. Ann Rheum Dis 2007;66:1560-7.
59. Weng MY, Lane NE. Medication-induced osteoporosis. Curr Osteoporos Rep 2007;5:139-45.
60. Doga M, Mazziotti G, Bonadonna S, Patelli I, Bilezikian JP, Cannalis E, et al. Prevention and treatmen of glucocorticoid-induced oteoporosis. J Endocrinol Invest 2008;31(Suppl.17):53-8.
61. Stoch SA, Saag KG, Greenwald M, Sebba AI, Cohen S, Verbruggen N, et al. Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: a 12-month randomized, placebo-controlled clinical trial. Rheumatol 2009;36:1705-14.
62. Compston J. Management of glucocorticoid-induced osteoporosis. Nat Rev Rheumatol 2010;6:82-8.
63. Guía de prevención y tratamiento de la osteoporosis inducida por glucocorticoides. Coordinador: Manuel Sosa Henríquez. Grupo de Trabajo en Osteoporosis de la Sociedad Española de Medicina Interna. Madrid. Ed. Medical and Marketing Communications. 2007. ISBN: 84-690-3296-8.
64. Ceglia L. Vitamin D and its role in skeletal muscle. Curr Opin Clin Nutr Metab Care 2009;12:628-33.
65. Houston DK, Cesari M, Ferrucci L, Cherubini A, Maggio D, Bartali B, et al. Association between vitamin D status and physical performance: the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2007;62:440-6.
66. Stewart JW, Alekel DL, Ritland LM, Van Lan M, Gertz E, Genschel U. Serum 25-hydroxyvitamin D is related to indicators of overall physical fitness in healthy postmenopausal women. Menopause 2009;16:1093-101.
67. Campbell PM, Allain TJ. Muscle strength and vitamin D in older people. Gerontology 2006;52:335-8.
68. Bunout D, Barrera G, Leiva L, Gattas V, de la Maza MP, Avendaño M, et al. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. Exp Gerontol 2006;41:746-52.
69. Janssen H, Samson M, Verhaar H. Vitamin D deficiency, muscle function, and falls in elderly people. Am J Clin Nutr 2002;75:611-5.
70. Annweiler C, Schott AM, Beirut G, Fantino B, Beauchet O. Vitamin-related changes in physical performance: a systematic review. J Nutr Health Aging 2009;13:893-8.
71. Dhesi J, Jackson S, Bearne L, Moniz C, Hurley M, Swift C, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age and Aging 2004;33:589-95.
72. Moreira-Pfrimer LD, Pedrosa MA, Teixeira L, Lazzaretti-Castro M. Treatment of vitamin D deficiency increases coger limb muscle strength in institutionalized older people independently of regular physical activity: a randomized double-blind controlled trial. Ann Nutr Metab 2009;54:291-300.
73. Lips P, Binkley N, Pfeifer M, Recker R, Samanta S, Cohn DA, et al. Once-weekly dose of 8400 UI vitamin D_3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. Am J Clin Nutr 2010;91:985-91.
74. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D_3) on the risk of fall and fracture: a meta-analysis. Q J Med 2007;100:185-92.
75. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009:339:3692.
76. Gillespie LD, Robertson MC, Gillespie WJ, Lamb SE, Gates S, Cumming RG, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2009;15:CD007146.
77. Cameron ID, Murray GR, Gillespie LD, Robertson MC, Hill KD, Cumming RG, Kerse N. Interventions for preventing falls in older people in nursing care facilities and hospitals. Cochrane Database Syst Rev 2010; 20:CD005465.
78. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women. A randomized controlled trial. JAMA 2010;303:1815-22.
79. Schwalfenberg G. Improvement of chronic back pain or failed back surgery with vitamin D repletion: a case series. J Am Board Fam Med 2009;22:69-74.
80. McBeth J, Pye SR, O'Neill TW, Macfarlane GJ, Tajar A, Bartfai G, et al. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. Ann Rheum Dis 2010;69:1448-52.
81. Pierrot-Deseilligny C. Clinical implications of a possible role of vitamin D in multiple sclerosis. J Neurol 2009;256:1468-1479.
82. Ascherio A, Munger KL, Simon KC. Vitamin D and multiple sclerosis. Lancet Neurol 2010;9:599-612.
83. D Hooghe M, Nagels G, Bissay V, De Keyser J. Modificable factors influencing relapses and disability in multiple sclerosis. Mult Scler 2010;16:773-85.
84. Soilu-Hänninen M, Laaksonen M, Laitinen I, Erälinna JP, Lilius EM, Mononen I. A longitudinal study of serum 25-hydroxyvitamin D and intact parathyroid hormone levels indicate the importance of vitamin D and calcium homeostasis regulation in multiple sclerosis. J Neurol Neurosurg Psychiatry 2008;79:152-7.
85. Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. Mult Scler 2008;14:1220-4.
86. Burton JM, Kimball S, Vieth R, Bar-Or A, Dosch HM, Cheung R, et al. A phase I/II dose-escalation trial of vitamin D and calcium in multiple sclerosis. Neurology 2010;74:1852-9.
87. Lyons RA, Johansen A, Brophy S, Newcombe RG, Phillips CJ, Lervy B, et al. Preventing fractures among older people living in institucional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int 2007;18:811-8.
88. The DIPART group. Patient level pooled analysis of 68500 patients from seven major vitamin D fracture trials in US and Europe. BMJ 2010;340:5463.
89. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effects of annual intramuscular vitamin D on fracture risk in elderly men and women -a population based, randomized, double-blind, placebo-controlled trial. Rheumatology 2007;46:1852-7.
90. Avenell A, Gillespie WJ, Gillespie LD, O Connell DL. Vitamin D and vitamin D analogues for preveting fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2009; 15:CD000227.
91. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren P, Haentjens D. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab 2007;92:1415-23.
92. Bergman GJ, Fan T, McFetridge JT, Sen SS. Efficacy of vitamin D_3 supplementation in preventing fractures in elderly women: a meta-analysis. Curr Med Res Opin 2010;26:1193-201.
93. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr 2007;86;1780-90.
94. Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fracture. Osteoporos Int 2008;19:1119-23.
95. Bischoff-Ferrari HA, Rees JR, Grau MV, Barry E, Gui J, Baron JA.Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. Am J Clin Nutr 2008;87;1945-51.
96. Nakamura K, Kurahashi N, Ishihara J, Inoue M, Tsugane S. Calcium intake and the 10-year incidence of self-reported vertebral fracture in women and men: the Japan Public Heath Centre-based Prospectuve Study. Br J Nutr 2009;101;285-94.

97. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al. Prevention on nonvertebral fractures with oral vitamin D and dose dependency. Arch Int Med 2009;169:551-61.
98. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B: Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293:2257-64.
99. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008;19:399-428.
100. National Osteoporosis Foundation.Clinician's guide to prevention and treatment of osteoposis. http://www.nof.org/professionals/Clinicians_Guide.htm.
101. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;322:1265-71.
102. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-41.
103. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344-52.
104. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83-91.
105. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40.
106. Chesnut IC, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241-9.
107. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
108. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637-45.
109. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
110. Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med 2007;146:326-39.
111. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90:2816-22.
112. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004;350:459-68.
113. Chesnut CH, 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109:267-76.

Rules for publication

Revista de Osteoporosis y Metabolismo Mineral is the official scientific organ of the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM). It will publish scientific articles in this field in two languages, Spanish and English, every four months, with the third issue each year consisting of a monographic edition bringing together the material presented at the annual conference of SEIOMM. In addition, supplements of a monographic nature may also be published.

General rules

-All works to be submitted in A4 format
-Font: Arial
-Font size: 12 point
-30 lines per page (1.5 spaced)
-The first page should consist of: title of work; names and surname(s) of author or authors, and the work place of each of them; contact details of the author responsible for correspondence: complete address with post code, telephone number, e-mail address and fax.

Type of articles

1. Original articles: These should be works of research on themes related to bone mineral metabolism in whatever form: basic research, epidemiological studies, clinical studies… etc. On the first page should be shown the authors' names and surname(s) and the place of work of each of them, and name and contact details of the author who is responsible for correspondence: complete address with post code, telephone number, e-mail address and fax. It is advisable that the number of authors should not be greater than 6. Next should be presented a summary, which should occupy a maximum of one page and be structured in the following sections: Background, Material and Method, Results, and Conclusions. A list of key words should follow. The number of tables and figures, combined, should be fewer than 6. It is not necessary to present the summary in English as the Journal has a translation service. The maximum number of pages may not exceed 20, including the bibliography, tables and figures. It is advisable that the number of bibliographical citations not exceed 30.

2. Clinical notes: Research articles, which are of shorter length and with somewhat less content may be presented. It is advisable that the maximum number of authors should not exceed 5, and that the article should have a maximum length of 15 pages, including the bibliographical citations, which should not number more that 15.

3. Discussion of clinical cases: In this section those clinical cases will be published and discussed which, by their originality or curiosity, could be of interest to the readers. The maximum number of authors is 4, and the bibliographical citations should not exceed 15. With a maximum length of 15 pages, these cases should be accompanied by adequate illustrations.

4. Editorials: These will be in the charge of the Director of the Journal. They should be of a maximum length of 3 pages. The number of bibliographic citations should not exceed 10, and may be accompanied by a table or a figure.

5. Reviews: This section will bring together reviews carried out on a current topic in bone mineral metabolism. The maximum length of the manuscript should not exceed 20 pages, including the bibliography, and the maximum number of authors should not be more than 4. It is advisable to consult the management of the *Revista de Osteoporosis y Metabolismo Mineral* before submitting the original.

6. Other special articles: Special articles, which are considered of interest by the management of the Journal, and which fall outside the aforementioned sections, may be published.

Sending Articles

Manuscripts may be submitted by e-mail to the following address: revistadeosteoporosisymetabolismomineral@ibanezyplaza.com accompanied by a brief covering letter in which the authors highlight those aspects they consider most important to bring to the reviewers' attention. In addition, if desired, at least 3 possible external reviewers may be proposed, of whom, in addition to name and surname(s), should be included their e-mail address and the reasons why the authors consider them able to evaluate the article objectively. Authors may also indicate which reviewers they wish not to evaluate the manuscript, a view which should be justified. However, authors should be assured that this matter will be dealt with in absolute confidence by the Journal's management team.

Bibliographical references

Bibliographical references should be included in the text as numbers and listed in the bibliography in the same order in which they appear in the text. The Vancouver style should be followed in this respect: the name of the first six authors, followed by "et al" (if this number is exceeded); year; volume: first and last page numbers.

Drawings, Tables, Photographs

Images and illustrations should be sent in compatible formats (preferably JPEG or TIFF) and of adequate resolution (300ppi). They should be citied in the text in order of their appearance and with the denomination of "Figure nº" or "Table nº".

Acceptance and publication

The Journal will ensure that anonymous peer review is for evaluation, and promises to have evaluated and to have given a decision on all articles submitted, within a maximum period of 45 days.

Relation of companies and laboratories advertisers who have sponsored this number:

Companies	Product
Amgen/GSK	Institutional
Faes Farma	Bondenza®
Ferrer	Adrovance®
Gebro Pharma/Novartis	Aclasta®
Italfarmaco	Natecal D®
Lilly	Forsteo®
MSD	Institutional
Nycomed	Preotact®
Pfizer	Combriza®
Servier	Protelos®