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Recommendations for the administration of vitamin D. National and international guides

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Introduction

The D hormone system, in spite of having been known for more than a century, has been ignored until relatively recent years. Proof of this is its still erroneous naming as vitamin D. Since the end of the 1990s, and with the turn of the century, the interest and the potential beneficial effects of its supplementation and/or replacement has increased enormously, moving from a recommendation of a dose which empirically avoids infantile rickets to a recommendation of mega-dosage.

The better knowledge of its beneficial effects and its potential risks resulted in recommendations of limited intake by the Institute of Medicine in 2010 clearly lower than those recommended by other scientific societies. Since then, the controversy persists without a clear response, which we try to resume in this article.

Spanish declaration on vitamin D in the management of osteoporosis of March 9th 2006

The interest in the the effects of vitamin D and its deficit status in broad sections of the population, both osteoporotic and apparently healthy, started in our country with a generic declaration on the part of various scientific societies involved in the management of osteoporosis, brought to a consensus in 2006 and published in 2007¹. In this document were proposed measures to understand its impact and correct its deficit.

Position document of the IOF (International Osteoporosis Foundation) on recommendations for vitamin D in older adults

In a document published in 2010, the IOF

(International Osteoporosis Foundation) recommended levels higher than 30 ng/ml (75 nmol/L) of 25(OH) vitamin D, with supplements of between 800 and 1,000 UI/day (20-25 µg/day) being required to achieve this threshold in most of the population, although it was thought that vitamin D supplementation could reach 2,000 UI/day in certain individuals, among others, those who were obese, osteoporotic, with limited exposure to sunlight (for example, institutionalised), or with absorption problems, etc².

Position document on the necessities and optimum levels of vitamin D

Some years after the earlier declaration, and this time led by the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) and including representatives from up to 11 other scientific societies involved in the management of this issue (Spanish Association for the Study of the Menopause [Asociación Española para el Estudio de la Menopausia], Hispanic Foundation for Osteoporosis and Bone Metabolic Diseases [Fundación Hispana de Osteoporosis y Enfermedades Metabólicas Oseas], Spanish Society for Orthopaedic Surgery and Traumatology [Sociedad Española de Cirugía Ortopédica y Traumatología], Spanish Society for Endocrinology and Nutrition [Sociedad Española de Endocrinología y Nutrición], Spanish Society for Osteoporotic Fractures [Sociedad Española de Fracturas Osteoporóticas], Spanish Society for Geriatrics and Gerontology [Sociedad Española de Geriátría y Gerontología], Spanish Society for Primary Care Doctors [Sociedad Española de Médicos de Atención Primaria], Spanish Society for Family and Community Medicine [Sociedad Española de Medicina Familiar y Comunitaria], Spanish Society for

Internal Medicine [Sociedad Española de Medicina Interna], Spanish Society for Rheumatology [Sociedad Española de Reumatología], Spanish Society for Rehabilitation and Physical Medicine [Sociedad Española de Rehabilitación y Medicina Física] and the IberoAmerican Society for Osteoporosis and Mineral Metabolism [Sociedad Iberoamericana de Osteoporosis y Metabolismo Mineral]) produced a document in which were recommended optimum concentrations of 25(OH) vitamin D of between 30 and 75 ng/ml, and which considered as clearly pathological levels those below 20 ng/ml. The existence of insufficient levels in wide sections of the population were recognised (from 30% in young people to 87% in institutionalised older people) in the absence of supplementation in food commonly consumed and with limited exposure to sun. In this document, supplements of vitamin D₂ or D₃ of 800-1,000 UI/day were recommended for older people and those with osteoporosis (600-800 UI/day for postmenopausal women)³.

Recommendations of the Institute of Medicine (IOM)

Amid growing interest in the beneficial effects of the D hormone in bone, muscular and even extra-skeletal health, in which progressively larger doses of dietary supplements were being proposed – reaching an intake of 2,000 UI/day or more – the body responsible for setting the reference levels for dietary intake in the United States, the Institute of Medicine (IOM) published recommendations which were clearly restrictive and which cooled the general euphoria associated with vitamin D. These were based on the estimated average requirements (EAR) to achieve a concentration of 25OH vitamin D of 16 ng/ml, which would be sufficient for the needs of 50% of the population, and the recommended dietary allowance (RDA) to achieve 20 ng/ml of 25OH vitamin D which would be sufficient to meet the needs of 97.5% of the apparently healthy population of the USA^{4,6}. The IOM's recommended dietary allowance to reach such levels was only 600 UI/day for most of the American population, reaching 800 UI/day for people over 70 years of age, while recognising that the maximum tolerable intake was 4,000 UI/day. These recommendations were based on the absence of proven benefits of blood concentrations of 25OH vitamin D above 20 ng/ml and the potential risks – nephrolithiasis and tissue damage – putting an end to the theory “more is better” which prevailed at that time⁴.

In terms of the daily necessary intake to reach these sufficient blood levels the IOM indicated a dose response curve between intake and associated blood levels which are summarised in the following formulae^{4,7,8}:

$$25\text{OH vitamin D in the blood (nmol/l)} = 9.9 \times \ln(\text{total intake of vitamin D [UI/day]})$$

$$25\text{OH vitamin D in the blood (ng/ml)} = 24.75 \times \ln(\text{total intake of vitamin D [UI/day]})$$

Which means that 100 UI/day of vitamin D₂ (ergosterol) or D₃ (colecalciferol) would raise the concentration of 25OH vitamin D by approximately 3.25

ng/ml, and 800 UI/day of vitamin D₂ or D₃ would raise concentrations of 25OH vitamin D by 26 ng/ml.

Recommendations and guide to clinical practice of the North American Endocrine Society

Only a few weeks before the report of the IOM referring to apparently healthy people, the North American Endocrine Society released a guide to clinical practice which was much more interventionist and more favourable to supplementation when looking for benefits for the skeleton⁹. They recommended supplements of vitamin D₂ (ergosterol) or D₃ (colecalciferol) – after measuring 25OH vitamin D with a reliable test – in all deficient subjects. For adults over 18 years of age an intake of at least 600 UI/day of vitamin D₂ or D₃ was recommended in order to maximise bone and muscle function. However, optimum levels of 25OH vitamin D were considered to be those above 30 ng/ml, for which an intake of at least 1,500-2,000 UI/day of vitamin D would be necessary¹⁰. From the age of 70, the Endocrine Society would recommend at least 800 UI/day, recognising that to reach its objective of 25OH vitamin D above 30 ng/ml, 1,500 to 2,000 UI/day of vitamin D₂ or D₃ could be required. In special populations such as those who are obese, or using anticonvulsants, glucocorticoids, antifungals or antivirals for HIV, the requirements could be 2 to 3 times higher.

The aforementioned guide⁹ recommends as therapy for people deficient in vitamin D the following doses:

- Babies up to 1 year old deficient in vitamin D: 2,000 UI/day of vitamin D₂ or D₃, or 50,000 UI of vitamin D₂ or D₃ weekly over 6 weeks to reach the target levels of 25OH vitamin D, followed by a maintenance dose of 400-1,000 UI/day.
- For children from 1 to 18 years of age deficient in vitamin D: 2,000 UI/day of vitamin D₂ or D₃, or 50,000 UI of vitamin D₂ or D₃ weekly over 6 weeks to reach the target levels of 25OH vitamin D, followed by a maintenance dose of 600-1,000 UI/day.
- For adults deficient in vitamin D: 50,000 UI of vitamin D₂ or D₃ weekly over 8 weeks to reach the target levels of 25OH vitamin D, followed by a maintenance dose of 1,500-2,000 UI/day.
- For those with obesity, patients with malabsorption and patients treated with drugs which affect vitamin D metabolism: 6,000 to 10,000 UI/day of vitamin D₂ or D₃ to reach the target levels of 25OH vitamin D, followed by a maintenance dose of 3,000-6,000 UI/day.
- The maximum tolerable maintenance dose of vitamin D₂ or D₃ – which ought not be exceeded without medical supervision – would be 1,000 UI/day for babies up to 6 months, 1,500 for children of 6 to 12 months, at least 2,500 UI/day for children between 1 and 3 years, 3,000 UI/day for children between 4 and 8 years and 4,000 UI/day for those older than 8 years of age. However, the guide itself recognises that a dose of 2,000 UI/day may be required in children up to 1 year, 4,000 UI/day for those

between 1 and 18 and up to 10,000 IU/day in those over 18 in order to correct vitamin D deficiency.

These recommendations are based on the assumption that the relationship between the dose received of vitamin D₂ and/or D₃ and the response of blood 25OH vitamin D fits a regression line with a constant relationship in which for every 100 IU/day vitamin D intake, vitamin D increases 25OH 1 ng/ml (2.5 nmol/L)^{9,11}.

The controversy between the recommendations of the Endocrine Society and the Institute of Medicine

In the months following the appearance of the recommendations of the IOM and the Endocrine Society an argument commenced which still remains and which centres on the values of 25OH vitamin D recommended as targets, and on the recognition, or not, of the extra-skeletal effects of higher intakes of vitamin D^{5,11,12}.

The fundamental difference between the two associations is in reference to the populations for which the recommendations are made, which for the Institute of Medicine are apparently healthy people without pathologies or known deficient in whom there is little proof of benefits, especially extra-skeletal, of a high intake of vitamin D, while the Guide to Clinical Practice of the Endocrine Society focuses on patients with osteoporosis or other conditions of risk of vitamin D deficit for whom it seems reasonable that the targets and doses are higher. The Endocrine Society, furthermore, interprets more favourably the evidence of the bone, muscle and extra-skeletal benefits, while recognising that the proof of the last is not sufficient to recommend vitamin D supplements in the prevention or treatment of conditions such as arterial hypertension, diabetes, different cancers or multiple autoimmune diseases.

Recommendations subsequent to the Institute of Medicine-Endocrine Society controversy

In 2012, many of the signatories of the guide to clinical practice of the Endocrine Society published a new revised version of their recommendations¹³ in which was discussed the best parameter for defining the optimum concentration of 25OH vitamin D – probably the better the concentrations in populations maintaining ancestral lifestyles such as the Aborigines or the Masai, the lower the osteoid volume that the values of PTH highly dependent on age, sex and renal function, among others – the benefits for the skeleton, muscle and to health in general of concentrations of 25OH vitamin higher than 30 ng/ml, and indicated the differences between recommendations for the general healthy population and those for osteoporotic patients.

Subsequent to the exchange of the aforementioned articles, a recommendation related to the use of calcium and vitamin D was made by the US Preventive Services Task Force (USPSTF)¹⁴. The USPSTF is the North American body responsible for making recommendations on the efficacy of preventative services specifically for patients without signs or

symptoms of these pathologies. Its recommendations, based on systematic reviews of publications available and their meta-analysis for people with neither osteoporosis nor known vitamin D deficit, are that:

- There is no proof of the efficacy of calcium or vitamin D supplements in preventing fractures.
- Nor is there proof for the recommendation of doses higher than 400 IU/day of vitamin D₂ or D₃ combined with a gram of calcium in the primary prevention of fractures, except in older people admitted to residential homes for chronic patients.

Rules for the calculation of the replacement dose for vitamin D

As has already been said, the IOM and the Endocrine Society base their recommendations for the replacement of vitamin D on different assumptions about the relationship that exists between the dose of vitamin D received and the response of 25OH vitamin D in the blood (see above). In a study with low intakes of vitamin D (800 IU/day) administered to institutionalised older people over 16 months with severe hypovitaminosis D, the dose response curve found was 3.6 ng/ml per each 100 IU/day, nearly 4 times higher than that predicted by the Endocrine Society. Using the IOM's regression equation, the predicted value was 26 ng/ml for an intake of 800 IU/day, similar to that observed, of 31.9 ng/ml, and clearly higher than that predicted by the Endocrine Society rules (an increase of 8 ng/ml)^{7,8}.

Following this observation, and with the aim of confirming the appropriateness of the rules for the dose-response relationship from the two associations, 41 available works have been studied in which the daily doses administered were lower than 2,000 IU/day, with a duration greater than 3 months and with baseline and final measurements of 25OH vitamin D. The changes in these levels were compared with those predicted by the IOM and Endocrine Society formulae (see above), as well as the regression equation for Vitamin D Supplementation in Older Subjects (ViDOS) ($25\text{OHD (nmol/l)} = 54.5 + 24.6 \times \text{dose}/1,000 - 2.5 \times \text{dose}^2/1,000^2$)¹⁵. The constant for the relationship observed was 2.12 (1.76-2.48) ng/ml (5.3 nmol/l) for each 100 IU/day of intake. This is, on average, double that predicted by the rule of the Endocrine Society. The differences in percentages between the expected and observed values were: IOM -7%; ViDOS + 2% and ES - 21%, which is why the authors propose that the Endocrine Society rule should be doubled (an increase of 2 ng/ml for each 100 IU/day)¹⁶.

In any case, most of the recommendations for the replacement of vitamin D make mention of the use of daily, weekly or monthly doses, given that recent evidence has shown that the administration of annual mega-doses of vitamin D (500,000 IU/annually of colecalciferol) is associated with an increase in the risk of falls of 15% and of fractures of 26% in women over 70 years of age¹⁷. Similar data have been published for apparently healthy older men¹⁸.

Most of the available data, and the recommendations of the scientific societies, are based on the administration of oral supplements of vitamin D₃ (colecalciferol).

ciferol) or D₂ (ergocalciferol). However, the formulations available in each country are different. A study in the general population has evaluated the efficacy and safety of the administration of 50,000 UI/monthly of vitamin D₃. In the group of patients the vast majority achieved concentrations higher than 20 ng/ml, and in more than ¾ of them, values of between 20 and 50 ng/ml. In this study, no significant adverse effects were identified¹⁹. On the other hand, in healthy subjects it has been confirmed that calcifediol is between 4 and 5 times more effective than vitamin D₃ in increasing blood concentrations of 25OH vitamin D²⁰, which means that in cases where calcifediol is chosen doses between 4 and 5 times lower should be given. It should be remembered that in order to obtain health benefits from vitamin D supplements it is indicated that treatment with vitamin D₂, D₃ or calcifediol should be sustained while factors which predispose to the development of this deficit persist, which in most cases means indefinite treatment.

On the other hand, if vitamin D is being treated, we should understand the response to the treatment, with a view to changing the regimen or its intensity. It is necessary to take into account the seasonal variation and the use of drugs which may alter the rate of response (such as corticoids or hepatic inductors). An annual review is indicated in order to adjust the treatment regime. It has also been recently reported that there may be a greater risk of lithiasis, and greater than expected hypercalcemia²¹.

In summary, although there is general agreement in terms of the high prevalence of vitamin D deficit, especially in some populations such as those who are osteoporotic, and older people, there are wide differences in terms of the recommended doses for replacement and for its supplementation. As a reasonable general rule, 800-1,000 UI/day of ergocalciferol or colecalciferol daily, or its weekly or monthly equivalent may be recommended. Calcifediol at doses 4 to 5 times less is also a reasonable approximation. Taking into account the fact that there is a correlation between the number of UIs administered and the blood levels of 25OH vitamin D achieved, the highest dose of this range (1,000UI/day) could increase the probability that those individuals achieve levels higher than 30 ng/ml. Furthermore, the administration to certain individuals and/or certain circumstances of supplementary doses of up to 2,000 UI/day could be considered.

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