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► To cite this version:

Jean-Claude Souberbielle, Catherine Cormier, Etienne Cavalier, Véronique Breuil, Françoise Debiais, et al.. Vitamin D Supplementation in France in patients with or at risk for osteoporosis Recent data and new practices. *Joint Bone Spine*, 2020, 87 (1), pp.25-29. 10.1016/j.jbspin.2019.04.004 . hal-02152873

HAL Id: hal-02152873

<https://univ-rennes.hal.science/hal-02152873>

Submitted on 21 Jun 2019

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Vitamin D Supplementation in France in Patients with or at Risk for Osteoporosis:**Recent Data and New Practices**

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Graphical Abstract

In patients with or at risk for osteoporosis

Until daily dosing becomes feasible, intermittent dosing should remain standard practice, with the lowest available dosages and shorter dosing intervals. This strategy probably improves adherence compared to daily dosing.

- Start with a **loading phase**

50 000 IU of vitamin D3 per week for 8 weeks in patients whose **25OHD** is **<20 ng/mL**

50 000 IU of vitamin D3 per week for 4 weeks in patients whose **25OHD** is between **20 and 30 ng/mL**

- After this loading phase, prescribe **long-term supplementation**:

50 000 IU of vitamin D3 per month

- After **3-6 months** of this **long-term supplementation**, repeat the **25OHD assay**

If **25OHD** is still **<30 ng/mL**

- either shorten the dosing interval (e.g., **50 000 IU every 2 weeks**)
- or increase the dosage (e.g., to **80 000** or **100 000 IU each month**)

If **25OHD** is **>60 ng/mL** (extremely rare)

- The only possibility contradicts the recommendations above:
- increase the dosing interval (e.g., **50 000 UI every 2 months**) until lower dosages become available

Abstract

With intermittent vitamin D supplementation, serum 25-hydroxyvitamin D (25OHD) levels may remain stable only if the dosing interval is shorter than 3 months, the ideal perhaps being about 1 month. Recent data support moderate daily vitamin D doses instead of high intermittent doses, notably in elderly patients prone to falls. The level of evidence is low, however, with no head-to-head comparisons of clinical outcomes such as fractures and falls in groups given identical dosages daily versus intermittently. A challenge to daily vitamin D supplementation in France is the absence of a suitable pharmaceutical formulation. In addition, daily dosing carries a high risk of poor adherence. Until suitable vitamin D3 formulations such as tablets or soft capsules each containing 1000 or 1500 IU become available, we suggest intermittent supplementation according to 2011 GRIIO guidelines. Among the available dosages, the lowest should be preferred, with the shortest possible interval, e.g., 50 000 IU monthly rather than 100 000 every two months.

Keywords: Vitamin D. Osteoporosis. Muscle. Falls. Bone metabolism. Fractures.

1. Introduction

In 2011, the French Osteoporosis Research and Information Group (*Groupe de Recherche et d'Information sur l'Ostéoporose*, GRIO) issued recommendations about vitamin D supplementation in adults [1]. Since then, new data have emerged, causing changes to former concepts. Thus, 24-hydroxylation is now recognized as a major vitamin D-inactivation pathway, new clinical definitions of vitamin D deficiency and vitamin D insufficiency have been developed, and technical advances have been achieved including the development of a reference standard procedure for assaying 25-hydroxy-vitamin D (25OHD). Furthermore, the French statutory health insurance system no longer reimburses serum 25OHD assays under all circumstances. However, the main reason for this update explaining recent changes in our approach is that new evidence challenges current vitamin D supplementation modalities, notably the intermittent administration of high dosages.

Vitamin D contributes to regulate calcium and phosphate metabolism and makes a key contribution to musculoskeletal health. Effects of vitamin D include increased intestinal absorption of calcium and phosphate; stimulation of fibroblast growth factor 23 (FGF23) expression; regulation, in synergy with parathyroid hormone (PTH), of distal renal tubule calcium reabsorption and bone turnover; and regulation of PTH release via a feedback loop. Profound vitamin D deficiency results in defective bone mineralization, rickets, osteomalacia, and diffuse muscle pain. In several randomized placebo-controlled trials, vitamin D supplementation, usually given in conjunction with calcium supplementation, decreased the risk of nonvertebral fractures in patients older than 65 years [2] and the risk of falls in those older than 70 years [3], provided the daily vitamin D intake was at least 20 μg (800 IU) and the serum 25OHD level was about 30 ng/mL. Furthermore, osteoporosis medications that act

by inhibiting bone resorption, such as bisphosphonates, are fully effective only in patients whose serum 25OHD is at least 30 ng/mL [4].

In addition to these well-demonstrated effects, vitamin D may have other benefits. Thus, numerous observational and experimental studies suggest that vitamin D may prevent a range of health conditions including diabetes, cardiovascular disease, certain types of cancer, age-related cognitive decline, infections, and autoimmune diseases [5]. However, controlled interventional studies usually failed to confirm these nonclassical effects of vitamin D, except in patients who were vitamin D-deficient at baseline [6] and in those who achieved the target serum 25OHD levels defined for the study [7]. Here, we will confine our discussion to the musculoskeletal effects of vitamin D in an attempt to define the optimal vitamin D status and adequate vitamin D intake.

2. Defining the optimal vitamin D status

The optimal vitamin D status is defined based on the serum 25OHD level. Reference ranges for laboratory parameters are usually defined as the range that includes 95% of the values found in a healthy population. This method cannot be used for serum 25OHD levels, however: as 25OHD levels are significantly lower in winter than in summer, two different normal ranges would have to be defined. Consequently, experts agree that a better approach consists in determining 25OHD cutoffs below and above which deleterious effects may occur, as well as the 25OHD levels associated with beneficial effects, based on the available interventional studies. Various cutoffs have been put forward in recommendations about managing patients with vitamin D stores. A consensus exists about defining vitamin D deficiency as a serum 25OHD level below 10-12 ng/mL, whereas some uncertainty continues

to surround the definition of vitamin D insufficiency. It is useful to distinguish two main situations depending on the risk of osteoporosis.

2.1. Patients with osteoporosis or at high risk for osteoporosis

In patients who have osteoporosis or are at high risk for osteoporosis due to treatments with potentially deleterious bone effects (e.g., high-dose glucocorticoids, aromatase inhibitors, and GnRH analogs) or to health conditions (e.g., primary hyperparathyroidism or other endocrinopathies; or malabsorption related to celiac disease, cystic fibrosis, or bypass bariatric surgery), patients with chronic kidney disease, and older patients at high risk for falls, many experts believe that the serum 25OHD level must be kept at or above 30 ng/mL (75 nmol/L) to optimize musculoskeletal strength [1;8-11]. Serum 25OHD assays are warranted, before starting the supplementation then during follow-up to adjust the dosage. In this patient subset, the GRIO has recommended a loading phase to allow the rapid and accurate interpretation of parameters reflecting the calcium and phosphate status, notably the serum PTH level. Importantly, a calcium intake of about 1 g/day should be provided in these patients.

2.2. The general population of apparently healthy individuals

For this patient population, the Institute of Medicine in the US recommends supplying the vitamin D dose that will allow most individuals to achieve a serum 25OHD level of 20 ng/mL (50 nmol/L), which is deemed sufficient in this situation [12]. No prior serum 25OHD assay is required.

The upper limit of the desirable serum 25OHD range is currently set at 60 ng/mL, which is approximately the highest value found in populations exposed to generous amounts of UVB radiation from sunlight year-round [13]. The 60 ng/mL value is also markedly

different from the lowest value at which vitamin D poisoning may occur, i.e., 150 ng/mL [14]. Another point of interest is that a few observational studies found an upside-down J-shaped relationship between the 25OHD level and the relative risk of disease: the risk was higher not only in patients with low values, but also, to a lesser extent, in those with values above 60 ng/mL [15]. Although these observational studies cannot supply information about causality, their findings support the choice of 60 ng/mL as the highest desirable serum 25OHD level.

Studies in the general population in France have found serum 25OHD levels below 20 ng/mL (50 nmol/L) in about 40%-50% of individuals and below 30 ng/mL (75 nmol/L) in 80% of individuals [16-18].

3. Vitamin D supplementation

The goals of vitamin D supplementation are to ensure that serum 25OHD levels are between 20 and 60 ng/mL in most individuals in the general population and between 30 and 60 ng/mL in patients with osteoporosis, chronic kidney disease, or malabsorption. Until very recently, standard practice consisted in obtaining a serum 25OHD assay to guide selection of the vitamin D dose. Thus, higher doses were given to patients with lower serum 25OHD values. This practice made sense but resulted in a large number of 25OHD assays, at considerable cost to the healthcare system. The French National Authority for Health (HAS) therefore decided to reimburse serum 25OHD assays only for individuals meeting specific criteria (http://www.has-sante.fr/portail/jcms/c_1356838/fr/utilite-clinique-du-dosage-de-la-vitamine-d-rapport-d-evaluation). Many experts feel that these criteria are overly restrictive [19].

Whereas calcium supplements must be taken every day, vitamin D supplements can be taken at far wider intervals, due to the long half-life of 25OHD. In France, preparations are

available for either daily or intermittent administration. Drops for supplying small daily doses (300-400 IU of vitamin D per drop) are chiefly used for infants. Tablets and sachets combining vitamin D3 and calcium are also available. For intermittent administration, the dosages available in France are 50 000, 80 000, 100 000, and 200 000 IU for vitamin D3 and 600 000 IU for vitamin D2. Patient adherence to daily vitamin D supplementation, notably in combination with calcium, is often low [20]. Consequently, intermittent administration is currently the preferred method in France. With intermittent administration, two rules must be scrupulously followed: only vitamin D3 should be used, as it maintains an optimal vitamin D status for far longer than does vitamin D2 [21]; and very high doses at widely spaced intervals should not be used, particularly in older women. The second rule is based on several studies. In women older than 80 years, a single annual dose of 500 000 IU of vitamin D3 given for 4 consecutive years increased the risk of both fractures and falls compared to a placebo [22]. The excess fractures and falls was significant only during the first 3 months after each annual dose. Although surprising, these findings confirm those of a previous study in which men and women older than 75 years had a higher hip fracture rate when given annual intramuscular injections of 300 000 IU of vitamin D2 instead of a placebo [23].

In France, when prescribing intermittent vitamin D supplementation in doses of 80 000 or 100 000 IU, the usual dosing interval is 2 to 3 months, in keeping with earlier recommendations [1]. Recent data, however, suggest that a shorter interval may be preferable. A randomized controlled trial done in postmenopausal women in Finland compared 25OHD levels before and 7 days after treatment with either a placebo or with vitamin D3 in a dosage of 100 000 IU or 200 000 IU [24]. Each treatment was given at 3-month intervals. The 25OHD levels 7 days after dosing were higher in the 200 000 IU group than in the 100 000 IU group, as expected, but the 25OHD levels just before the next dose were the same in the two vitamin D3 groups. The key messages from this study are that a steeper rise in vitamin D

levels induced by supplementation is followed by a steeper decline, and a 3-month interval between 100 000 IU or 200 000 IU doses may allow marked fluctuations in 25OHD levels, suggesting that a shorter interval may be preferable. This last point is important, as recent studies have shown that fluctuations in 25OHD levels are associated with variations in the opposite directions in serum levels of PTH and CTX: PTH and CTX levels increase when 25OHD levels decrease, indicating increased bone resorption that probably adversely affects bone health [25].

In several studies, 25OHD levels remained similarly stable with daily and monthly dosing [26]. A recent randomized trial, however, calls this finding into question. The participants were 200 elderly individuals (67% of females) with at least one fall during the past year [27]. The treatments were given once a month. One group received 60 000 IU (the theoretical equivalent of 2 000 IU/day) of vitamin D3 and another only 24 000 IU of vitamin D3. The mean number of falls was significantly higher in the group given the higher dose. One possible explanation is that the excess falls were caused by the higher vitamin D3 doses and/or higher 25OHD levels. However, a randomized controlled trial done a few years earlier by the same group suggests that the intermittent dosing schedule may be the culprit [28]. Mean age and proportion of female participants were similar to those in the subsequent study, and the inclusion criterion was a recent hip fracture. The fall risk was similar in the groups given 800 IU/day and 2000 IU/day. In contrast, readmissions and complications of falls were significantly less common in the group given the higher dose.

Although definitive data are still lacking, the available studies raise many questions regarding the best vitamin D supplementation regimen, notably in older individuals. Daily dosing instead of the monthly administration of higher doses has been advocated in an editorial [29] and a position paper [30]. Several older publications also recommended daily dosing [31;32]. Furthermore, metaanalyses assessing the effects of vitamin D supplementation

on muscle strength [33] or on the risk of respiratory tract infections [34] found that vitamin D supplementation was beneficial when given daily but not when given in high doses at wide intervals.

4. Conclusion and perspectives

A few recent studies suggest that moderate daily doses of vitamin D may be preferable over larger doses given intermittently in patients who fall. The level of evidence underlying this suggestion is low, however. More specifically, no head-to-head comparisons of clinical outcomes such as fractures and falls with daily versus intermittent administration of the same dosages has been published to date. In addition, daily dosing is challenging given the lack of a suitable pharmaceutical formulation and high risk of nonadherence. Similar doses of vitamin D given daily or intermittently seem to induce the same decrease in PTH release, an effect that is central to the efficacy of vitamin D in improving bone health. A reasonable suggestion at present is intermittent supplementation using the lowest available doses and shortest possible dosing intervals. For instance, in patients with falls and/or osteoporosis, for whom the target is a 25OHD level above 30 ng/mL, the dosage could be determined according to the baseline 25OHD level, namely, 50 000 IU/week for 8 weeks if below 20 ng/mL and 50 000 IU/week for 4 weeks if between 20 and 30 ng/mL (Figure 1). This loading phase can be followed by the long-term administration of 50 000 IU/month. A 25OHD assay after 3-6 months is then necessary to determine whether the dosage needs to be adjusted, given the huge interindividual variability in the 25OHD response to vitamin D₃, which ranges from minimal to very considerable [35]. If the 25OHD level remains below 30 ng/mL, the dosing interval can be shortened or the dosage increased to 80 000 or 100 000 IU each month. If the 25OHD level is above 60 ng/mL, the only available strategy to date, despite being in

contradiction to the comments above, consists in lengthening the dosing interval (e.g., 50 000 IU every 2 months), until lower dosages (e.g., 25 000 IU) become available.

Should pharmaceutical forms suitable for daily supplementation become available (e.g., tablets or soft capsules containing 1000 or 1500 IU of vitamin D3), patients displaying good treatment adherence could take a daily dose determined based on the 25OHD level. Thus, for patients with 25OHD levels below 20 ng/mL, 3000 to 5000 IU/day for about 3 months could be followed by long-term supplementation with 1000 to 3000 IU/day, with adjustments based on follow-up 25OHD assays. These suggested treatment regimens are consistent with previous recommendations issued by the GRIIO [1], which also include intermittent.

Disclosure of interest

Souberbielle JC: fees for occasional interventions as an expert or speaker for Diasorin, Roche Diagnostics, Abbott, Amgen, Shire, MSD, Lilly, and Mylan

Cormier C: fees for occasional interventions as an expert or speaker for Amgen, Lilly, and Shire

Cavalier E: fees for occasional interventions as an expert or speaker for Diasorin, IDS, Roche, Abbott, and Amgen

Breuil V: fees for occasional interventions as an expert or speaker for Amgen, Lilly, and UCB

Debiais F: fees for occasional interventions as an expert or speaker for Abbot, Alexion, Amgen, Lilly, MSD, Pfizer, Roche, Novartis, and Theramex

-Fardellone P: fees for occasional interventions as an expert or speaker for Amgen, Expanscience, Lilly, Novartis, Mylan, MSD, Pfizer, Théramex, and UCB; indirect financial ties: funding for research projects or as an investigator from Roche-Chugai, Biogen, and Abbvie

Guggenbuhl P: fees for occasional interventions as a speaker or attendee at conventions from Amgen, Lilly, and Novartis

Javier RM has no conflicts of interest to declare.

Legrand E: fees for occasional interventions as an expert or speaker for Amgen and Lilly

Lespessailles E: fees for occasional interventions as an expert or speaker for Amgen, Celgène, Expanscience, Lilly, MSD, Novartis UCB, and Amgen; indirect financial ties: funding for research projects or as an investigator from AbbVie, Amgen, Celgène, Eli Lilly, MSD, and UCB

Paccou J: fees for occasional interventions as an expert or speaker for Amgen, Lilly, Janssen, MSD, Pfizer, UCB, and Novartis

Thomas T: occasional interventions for Amgen, Chugai, Expanscience, Gilead, HAC-Pharma, LCA, MSD, Novartis, Pfizer, Thuasne, UCB, Abbvie, BMS, Lilly, TEVA, and Medac

Cortet B: fees for occasional interventions as an expert or speaker for Amgen, Expanscience, Ferring, Lilly, Medtronic, MSD, Mylan, Novartis, Roche Diagnostics, and UCB

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Figure 1: Modalities of vitamin D supplementation for patients with vitamin D deficiency or insufficiency