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Review

Daily or intermittent vitamin D supplementation in patients with or at risk of osteoporosis: Position statement from the GRIO

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ABSTRACT

Advantages and disadvantages of intermittent versus daily vitamin D supplementation especially in adults with or at risk of osteoporosis are discussed by the Osteoporosis Research and Information Group (GRIO). The analysis of the literature suggests that intermittent long-term high doses vitamin D supplementation (such as 60,000 IU/month or more), may increase the risk of falls, fracture and premature death in certain populations, while daily doses of 800–1000 IU with calcium decrease falls and non-vertebral fractures in the elderly with vitamin D deficiency. In patients with or at risk of osteoporosis we hence recommend measuring the 25(OH)D concentration prior to supplementation and to provide vitamin D supplementation (with optimization of calcium intake if needed) to obtain a concentration between 30 and 60 ng/mL. We recommend the use of an initial loading dose, especially in those who need a quick repletion of vitamin D store (symptoms of osteomalacia and/or 25(OH)D concentration < 12 ng/mL, patients eligible for treatment with potent antiresorptive therapy), followed by a maintenance dose. A daily supplementation should be the rule when possible. When daily forms are however not available or not reimbursed, we recommend, like other experts, to continue using intermittent dosing with the smallest available dose (≤ 50,000 IU) and the shortest interval between doses as a stopgap until reimbursement or adequate daily pharmaceutical forms (pills or soft capsules of 1000, 2000 IU) are available.

1. Introduction

For the last 15 years, iterative recommendations about vitamin D supplementation in adults have been published. In 2011, the American Institute of Medicine (IOM) first and then the Endocrine Society issued guidelines, but controversies about the recommended dietary allowance (RDAs) of vitamin D and the "normal/optimal" serum 25-hydroxyvitamin D [25(OH)D] rapidly aroused [1,2]. European countries and Australian-New Zealand societies issued also their own guidelines for the general population and for patients with or at risk of osteoporosis. In France, the Osteoporosis Research and Information Group (GRIO) issued

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guidelines concerning patients with bone diseases in 2011 which were updated in 2020 [3,4]. In these updated guidelines, daily doses (1000–3000 IU) of vitamin D were suggested to have advantages over intermittent larger doses. However, considering the low level of evidence in the literature, the lack of head-to-head trials and most of all the non-availability of suitable pharmaceutical forms for daily supplementation in France, GRIO recommendations focused on a reasonable intermittent supplementation using the lowest available doses and shortest possible dosing intervals [4]. Since 2020, new vitamin D formulations have become available in France. In the light of recently published studies, this manuscript discusses the advantages and disadvantages of intermittent versus daily vitamin D supplementation especially in adults with or at risk of osteoporosis.

2. Vitamin D metabolism

The term "vitamin D" covers two molecules: vitamin D2 (ergocalciferol), present in vegetal food (cereals, yeasts. . .) and vitamin D3 (cholecalciferol) produced by the skin when exposed to ultraviolet B radiation (280–320 nm), and also present in foods of animal origin (oily fish, dairy. . .) [5]. Vitamins D2 and D3 can be used in preventive and curative treatment. Although diet is important, vitamin D is primarily a gift of the sun, as 90% of its body store derives from cutaneous sun exposure. Sun exposure (face, arms, hands, legs) is recommended without sunscreen for 5 to 30 minutes at least twice a week or more between the hours of 10am and 4pm [6]. The skin initiates the photochemical conversion of 7-dehydrocholesterol (7-DHC) into cutaneous previtamin D3 that is isomerized to vitamin D3. The term "vitamin D" will be used to designate both vitamins D2 and D3 since their metabolisms are similar except for a faster decline in 25-hydroxyvitamin D2 in blood after supplementation [7]. Vitamin D3 associated to the D-binding protein (DBP) in bloodstream is then activated via two hydroxylations by cytochromes in the liver and the kidney. In the liver, the activation (CYP2R1, CYP3A4, CYP27A1, CYP2J2) at position 25, leads to 25-hydroxyvitamin D3 (25(OH)D3, calcifediol) which half-life ranges from 2 to 3 weeks. A second hydroxylation (CYP27B1) in position 1 alpha, tightly regulated by PTH (stimulating) and fibroblast growth factor-23 (FGF23) (inhibiting) occurs in the proximal tubule of the kidney. This leads to 1 alpha,25-dihydroxyvitamin D3 ($1,25(OH)_2$ D3, calcitriol, half-life 4 hours), the biologically active vitamin D3 that reaches via the blood stream target tissues where it binds to the vitamin D receptor (VDR) to exert genomic and non-genomic effects [8]. The primary function of $1,25(OH)_2$D is the regulation of phospho-calcium metabolism, of normal calcium levels and bone development. The action of a 24-hydroxylase encoded by the *CYP24A1* gene is now recognized as an important step in vitamin D catabolism. This enzyme, which is durably induced by elevated $1,25(OH)_2$ D concentrations, catalyzes the hydroxylation at positions C23 and C24 of both calcidiol and calcitriol and serves as a negative feedback mechanism to prevent hypercalcemia [9]. Vitamin D has also extra-skeletal actions, as the VDR exists in many tissues like prostate, immune cells, central nervous system, pancreas, colon, breast and parathyroid glands. Vitamin D is hence described as a steroid hormone, although it needs to be metabolized to be active and to reach its target tissues, and "vitamin" is a misnomer as it results from an endogenous body production [8].

3. Justification of vitamin D supplementation in patients with or at risk of osteoporosis

The concentration of circulating 25(OH)D is considered to reflect vitamin D status, with severe vitamin deficiency < 10–12 ng/mL and optimal concentrations between 20 and 50 ng/mL in the general population. According to the GRIO recommendations, 25(OH)D concentrations should be at or above 30 ng/mL (75 nmol/L) in patients with or at risk of osteoporosis, a level that is not reached by approximately 75–80% of the general French population [4]. Reasons to support vitamin D supplementation in these patients are as follows:

- vitamin D deficiency/insufficiency often causes secondary hyperparathyroidism, especially in those with low calcium intake. Hyperparathyroidism increases bone remodeling which can lead to increased bone fragility. Vitamin D supplements are efficient to curb secondary hyperparathyroidism, with no obvious difference between daily or intermittent doses [10];
- beneficial effects of supplementation with the combination of vitamin D and calcium have been largely shown, with umbrella reviews and meta-analyses of observational and randomized trials: positive multiple health outcomes have been observed including on bone and fracture risk [11]. A recent meta-analysis (in 6 randomized clinical trials with 49,282 participants) showed a 6 and 16% reduction of any fracture and hip fracture respectively, with the association of vitamin D and calcium, five out of six included randomized controlled trials using 800 IU/day vitamin D3 [12]. It is worth noting that, as calcium was co-administered with vitamin D in these studies, the dosing schedule was daily. This meta-analysis also showed (in 11 randomized clinical trials with 34,243 participants) that neither intermittent (weekly, monthly) nor daily dosing with standard doses of vitamin D alone, without calcium, was associated with a reduced risk of fracture;
- an histomorphometry study of 675 post-mortem iliac crest biopsies identified mineralization defects in patients with a serum 25(OH)D below 30 ng/mL suggesting that vitamin D supplementation should ensure that circulating levels of 25(OH)D reach 30 ng/mL to maintain skeletal health [13];
- the role of vitamin D status in response to antiosteoporosis treatments has been discussed in the literature, and it has been shown that by correcting vitamin D levels, we optimize the effect of bisphosphonates, and by extension, probably the effect of other antiosteoporosis treatments [14]. Although vitamin D supplementation should not replace the prescription of antiosteoporosis treatments and should not be considered as an antiosteoporotic treatment on its own, an optimal vitamin D status is required for the treatment of osteoporosis.

4. Daily or intermittent vitamin D doses: clinical outcomes

4.1. Effect of supplementation on falls and fractures

Daily vitamin D plus calcium co-supplementation reduces modestly but significantly the risk of non-vertebral fracture [12]. This supplementation can only be administered daily because of the co-administration of calcium, and thus does not allow to conclude that daily supplementation with vitamin D alone (without calcium) has advantages over intermittent dosing.

4.1.1. Intermittent or daily administration?

The preferable use of 1000–3000 IU daily vitamin D3 doses, particularly in older patients with falls, emerged from studies that showed either no effect or even deleterious effect of high intermittent vitamin D doses on falls and fractures while moderate daily doses decreased the incidence of falls [15–18]. It must be noted, however, that there is no comparative face-to-face studies between daily and intermittent strategies on clinical outcomes and on the risk of fracture or falls.

A large yearly dose of vitamin D3 (500,000 UI/L) increased the incidence of falls and fractures in 2256 women over 70 years old and this was confirmed in a recent meta-analysis of 15 trials that showed that intermittent or single high-dose vitamin D supplementation had no preventive effect on the risk of falls and fractures and might even increase the risk of falls [15,16]. Other studies suggest that intermittent doses may increase the fall risk (monthly 60,000 IU vitamin D3 versus placebo), or that the risk of falls is higher with higher dosages (60,000 IU vitamin D3 monthly) than with lower dosages (24,000 IU vitamin D3 monthly) [18,19]. In another meta-analysis which included 32 studies, daily administration of vitamin D was associated with a reduced risk of falls, while intermittent dose was not [17].

4.1.2. Daily administration and optimal dose

It is worth noting that only vitamin D supplementation with daily dose of 800 to 1000 IU was associated with lower risks of osteoporotic fracture and fall (pooled relative risk [RR], 0.87; 95% confidence interval [CI], 0.78 to 0.97 and RR, 0.91; 95% CI, 0.85 to 0.98), especially in patients with vitamin D deficiency, while doses < 800 or > 1000 IU/day were not [17]. A 12-month trial with 7 different daily oral doses of vitamin D or placebo showed that the faller rate over one year described a U-shaped curve with a maximum decrease on 1600–3200 IU doses (or serum 25(OH)D of 32–38 ng/mL [80–95nmol/L]) [10]. However, high vitamin D doses of 4000–4800 IU increased the incidence of falls in those with previous fall history [10]. In another study with 688 participants aged 70 years and older, elevated fall risk and vitamin D3 supplementation at doses of 1000 IU/day or 2000 IU/day, the risk of fall was similar compared to 200 IU/day vitamin D3; furthermore, safety concerns (first serious fall and first fall with hospitalization) with higher than 1000 IU/day vitamin D3 doses were raised [20]. In an older meta-analysis, which concluded that vitamin D reduces falls, doses lower than 700 IU/day appeared to be ineffective on fracture risk reduction [21].

4.2. Extraskeletal effects

Patients with or at risk of osteoporosis may often present with some other conditions related to aging or fragility that could be influenced by vitamin D supplementation. Even if it is not the primary topic of the GRIO, and thus of the present paper, we cannot ignore the results of the many intervention studies that tested the effect of vitamin D supplementation on numerous extra skeletal outcomes. As these studies have been extensively reviewed elsewhere, we only summarize the main beneficial extra-skeletal effects of daily vs intermittent vitamin D supplementation [22–24]. A multitude of RCTs have been conducted, and their results present a somewhat inconclusive picture. While some RCTs demonstrated beneficial effects of vitamin D, most did not find significant difference between vitamin D and placebo. In rare cases, vitamin D was even found to be harmful compared to a placebo. The intent-to-treat analysis of recent mega-trials which mostly included vitamin D-sufficient patients, and meta-analyses, commonly conclude that vitamin D lacks significant effects. Beneficial effects of vitamin D have been however reported in prespecified post-hoc analyses of subgroups of vitamin D-deficient subjects who received daily vitamin D supplementation but not in those who received intermittent high doses. In brief, a reduction of the risk of respiratory infections, of cancer mortality (though not incidence) and a significant decrease of blood pressure in hypertensive, but not in normotensive persons were reported [25–29]. While mortality was increased in the vitamin D group of recent mega-trials of monthly supplementation (60,000 IU/month) in patients at risk of cardiovascular disease and cancer [30,31], this finding is not universal. Additionally, daily vitamin D supplementation may mitigate the progression from a prediabetes state to type 2 diabetes, decrease the risk of autoimmune diseases and of pregnancy pathologies like preeclampsia or gestational diabetes [32–34].

5. Physiological explanations for the superiority of daily over intermittent dosing on clinical outcomes

It has been shown that high intermittent intakes of vitamin D stimulate at least 2 inactivation pathways that may be considered as natural defense against an excess of vitamin D (reviewed in [35,36]). The first pathway is the 24 hydroxylation that leads to inactive metabolites ($24,25(OH)_2D$ and $1,24,25(OH)_3D$). Recent studies showed that after a large intake of vitamin D, the serum concentration of $24,25(OH)_2D$ will remain high longer than 25(OH)D. The intracellular synthesis of calcitriol is decreased in favor of the synthesis of $1,24,25(OH)_3D$. High intake of vitamin D may thus lead to a paradoxical intracellular deficiency in calcitriol. Secondly, high doses of vitamin D may also induce a long-term increase in the secretion of FGF-23, a key regulator of phosphate and vitamin D metabolism that would diminish the synthesis of $1,25(OH)_2D$. FGF 23 is also linked to an increase in all-cause mortality, in particular in case of kidney failure [37].

The liver and kidney hydroxylation are not the only pathways for the production of active vitamin D, and it has been shown that vitamin D may enter into cells that express both 25 hydroxylase and 1-alpha hydroxylase and thus be directly activated in an autocrine way. Cholecalciferol half-life is however relatively short (12–24 hours) and will thus quickly disappear from the bloodstream in case of intermittent high dose supplementation; the activation of this autocrine pathway may therefore be impaired with high intermittent rather than daily regular vitamin D intake [38].

6. Daily or intermittent vitamin D doses for optimal 25(OH)D blood concentration

An objective attitude to guide towards one or the other strategy is to focus on a biological parameter, the optimal serum 25(OH)D concentration as it is considered the most significant indicator for vitamin D status, and several studies have evaluated the concentrations reached with different dosages. It is however important to distinguish the situation where bolus administration and intermittent doses will be limited in time, from the daily long-term intake.

Doses of 100,000 or 200,000 IU of oral cholecalciferol every 3 months were not capable of stabilizing 25(OH)D levels in a randomized study with 60 women aged 75.0 ± 2.9 years suggesting that the interval between boluses had to be shorter [39]. A recent Bayesian network meta-analysis using Cochrane methodological quality assessment, explored in 116 randomized clinical trials, 11,376 participants, whether intermittent (weekly or monthly) vitamin D supplementation is as effective as daily supplementation in improving serum 25(OH)D levels [40]. They showed that the efficacy of intermittent vitamin D supplementation was similar to daily supplementation. Daily administration or monthly administration of vitamin D allows to reach similar levels of 25(OH)D. Daily administration is however more physiological as regards to the endogenous synthesis of vitamin D and should be preferred as it allows to reach a steady state in a more stable way.

7. Daily or intermittent dosing for a better adherence to vitamin D supplementation

The rationale for prescribing intermittent vitamin D supplementation is to optimize adherence to supplementation. According to

a recent consensus paper, however, there is no scientific evidence that intermittent bolus vitamin D enhance adherence compared to daily dosing, especially in high-risk osteoporosis patients [41]. In the very recent clinical guideline on vitamin D published by an expert panel of the Endocrine Society, no studies indicating better adherence to intermittent versus daily vitamin D supplementation were identified [42]. Although the authors clearly recommend daily dosing, they nonetheless, based on the preference of most osteoporosis patients for an intermittent bisphosphonate schedule, assumed that intermittent vitamin D supplementation may be more acceptable for some patients and thus improve adherence. Considering bisphosphonates as a model, to promote intermittent vitamin D has some limitation in our opinion. Indeed, bisphosphonates had to be taken after overnight fasting, and, after taking the drug, patients were required to remain upright for at least 30 min to minimize gastroesophageal reflux, and refrain from food, medications and liquids other than poorly mineralized water for at least 30–45 min to optimize absorption. Such a constraint easily explains the preference for intermittent dosing but is not transposable to vitamin D. Many patients with or at risk of osteoporosis often take daily medications for other diseases. Those who are adherent to these treatments may have no problem with daily vitamin D if acceptable pharmaceutical forms are available. Data on adhesion of patients to daily intake are however still missing.

8. Is there a place for calcifediol?

Two pharmaceutical preparations of calcifediol, drops for daily supplementation (5 μg/drop) and higher dose soft capsules (266 μg/capsule) for intermittent dosing, are available and reimbursed in France. By far, most of the trials that have evaluated the effects of vitamin D supplementation have focused on vitamin D3. Recent studies have shown that calcifediol, given daily, weekly, or monthly is faster and more effective than cholecalciferol in raising serum 25(OH)D levels [7,43]. Indeed, it is rapidly and better absorbed by the intestine and transported through the portal vein contrary to cholecalciferol which is transported more slowly by chylomicrons via the lymphatic system. Calcifediol is less lipophilic than cholecalciferol and is thus less sequestered in fat. Based on 9 RCTs, 1 μg calcifediol is 3.2 times more potent than 1 μg vitamin D3 in raising 25(OH)D concentration [44]. One must be cautious however as this conversion factor was found only in studies where daily vitamin D3 doses $\leq$ 25 μg (1000 IU) were tested. In the few studies where much higher vitamin D3 doses were used, calcifediol appeared more potent in its capacity to increase 25(OH)D level (up to 10 times). Note that there were no studies that used intermediary vitamin D3 doses (> 1000–4000 IU/day) [44]. The relationship between the dose of calcifediol and the increase in 25(OH)D concentration is linear contrary to cholecalciferol which induces a rise in 25(OH)D that is inversely related to the basal 25(OH)D level (for a given vitamin D3 dose, the lower the basal 25(OH)D concentration, the higher the increase in 25(OH)D concentration). In other words, if a given calcifediol dose rises the 25(OH)D concentration by X ng/mL in an individual, twice this dose would rise 25(OH)D concentration by (approximately) 2X ng/mL. This may be an advantage for calcifediol over cholecalciferol when the 25(OH)D concentration is measured, as knowing the 25(OH)D concentration before and after supplementation with calcifediol allows to predict with a certain degree of confidence how the 25(OH)D concentration would change if the posology is modified. This phenomenon may however become a disadvantage if the 25(OH)D concentration is not known (remember that 25(OH)D measurement is not recommended nor reimbursed in the general population in France) with a significant risk of inducing too high 25(OH)D concentration in persons who are vitamin D sufficient before supplementation. A few studies have evaluated the effect of calcifediol given monthly during one or two years on the elevation of 25(OH)D level [45,46]. They reported that long-term administration of calcifediol maintains stable and sustained 25(OH)D concentrations, with no safety concerns. A continuous significant increase in mean 25(OH)D values from basal 20.9 ng/mL during the 2-year study was observed with the mean value at 2 years (36.7 ng/mL) not significantly different from the mean value at 1 year (41.2 ng/mL), suggesting an equilibrium was reached [46]. The maximum 25(OH)D concentration reached among the whole studied group was 79.7 ng/mL at month 24, in a patient whose basal value was 26.3 ng/mL. It must be noted that neither the concentration of 24-hydroxylated vitamin D compounds nor FGF23 levels were reported in these studies so that it is not possible to know whether monthly calcifediol or cholecalciferol present similar or different inactivating effects.

While it seems premature to recommend supplementation with calcifediol instead of cholecalciferol, especially when the 25(OH)D concentration is unknown, there are some situations where calcifediol should logically be preferred to cholecalciferol. This is the case for the situation of inhibition of hepatic 25-hydroxylase, linked to a genetic mutation in the *CYP2R1* gene or to specific long-term medications such as antiepileptics or corticosteroids. Calcifediol could also be an interesting option in conditions for which a rapid normalization of 25(OH)D levels is needed, as well as in managing vitamin D supplementation in patients with hepatic insufficiency, or in case of fat malabsorption [47]. Obesity may also be a target for calcifediol supplementation which may be less sequestered in fat mass due to its more hydrophilic nature compared to cholecalciferol. Furthermore, experimental data obtained in mice suggest that expression of CYP2R1 is reduced in obesity and accounts in part for the decreased circulating 25(OH)D [48]. Bypassing the liver hydroxylation may be an advantage in obese patients. It could also be an interesting option in chronic kidney disease in an extended-release formulation, to help the management of secondary hyperparathyroidism in non-dialysis CKD patients [49].

It is worth noting that, contrary to cholecalciferol, very few clinical trials have tested the effects of calcifediol on clinical outcomes apart from the (nonetheless encouraging) recent open-label studies (no placebo groups) in Covid-19 patients [50].

9. Are there limitations to adopt a daily therapeutic strategy in vitamin D supplementation in France?

Daily rather than intermittent vitamin D supplementation has been unequivocally recommended by several independent groups of vitamin D experts, as well as in very recent international consensus statements and clinical guidelines [22,35,36,41,42,51–54]. We concur with this approach. Indeed, as indicated above, daily supplementation is more physiologic, and has been shown to exert various beneficial effects in vitamin D deficient/insufficient patients that are not found in studies where intermittent supplementation schedules have been tested. In addition, several recent trials of intermittent vitamin D supplementation (60,000 IU/month) have reported worse outcomes (increased fractures, falls, cancer mortality) in the vitamin D group than in the placebo group. Furthermore, explanations underlining clinical advantages of daily supplementation have been proposed, especially avoiding the strong stimulation of vitamin D inactivating pathways after intermittent high vitamin D doses. Even the reasons that have been hypothesized to be in favour of an intermittent supplementation (i.e. better adherence to supplementation, and quicker increase in 25(OH)D serum concentration) have not been demonstrated. In our opinion, the only reason to favour intermittent vitamin D supplementation in France is the lack of pharmaceutical forms compatible with a simple and well-accepted daily supplementation that are reimbursed by

Table 1
List of vitamin D pharmaceutical preparations available in France.

Cholecalciferol, vitamin D3	200,000 IU	Soft capsule, drinkable ampoule, ampoule for intramuscular injection
	100,000 IU	Soft capsule, drinkable ampoule
	80,000 IU	Drinkable ampoule
	50,000 IU	Soft capsule, drinkable ampoule
	20,000 IU	Soft capsule
	10,000 IU	Oral drops
	1000 IU	Soft capsule (not reimbursed in France)
	300 and 100 IU	Drops prescribed generally to infants
Ergocalciferol, vitamin D2	15 "A" 600,000 IU/1,5 mL	Drinkable ampoule
	15 "H" 600,000 IU/1,5 mL	Ampoule for intramuscular injection
	400 IU	Oral drops provided in 2,000,000 IU/100 mL flask
Calcifediol, 25(OH) vitamin D3	5 µg	Oral drops provided in 15 mg/100 mL flask
	266 µg	Soft capsule
Combinations vitamin D3 with calcium	1000 IU + 500 mg calcium	Tablets

the French Health insurance (with the exception of cholecalciferol drops (300 IU/drop) usually prescribed to babies and calcifediol drops (5 µg/drop), drops being difficult to use in older persons) (Table 1). Several unlicensed vitamin D preparations are also available in France like in other countries. The GRIO however does not recommend these preparations until evidence of the pharmaceutical quality provided by independent bodies is available. A study by Wan et al. supports this caution: the authors measured the vitamin D content of 2 pharmaceutical preparations and 11 food supplements [54]. The 11 food supplements showed a vitamin D content ranging from 41% to 165% of the labelled claim, with 8 of them failing to comply with the food supplement specification, while both the pharmaceutical forms were in accordance with the labelled claim.

In conclusion, our opinion is that, by contrast with the general population for whom a measurement of serum 25(OH)D is not a prerequisite for vitamin D supplementation, vitamin D must remain a medication in response to a need identified by 25(OH)D serum measurement in patients with or at risk of osteoporosis. In these patients (Fig. 1), we recommend measuring the 25(OH)D concentration prior to supplementation and to provide vitamin D supplementation (with optimization of calcium intake if needed) to obtain a concentration between 30 and 60 ng/mL [55]. We recommend the use of an initial loading dose, especially in those who need a quick repletion of vitamin D store (symptoms of osteomalacia and/or 25(OH)D concentration < 12 ng/mL, patients eligible for treatment with potent antiresorptive therapy), followed by a maintenance dose. As indicated above, we consider that a daily supplementation should be the rule. Due to the scarcity of available pharmaceutical forms, it is however probable that, even if informed by their physician about the superiority of daily dosage, some patients may be reluctant to take drops every day and/or to pay for their vitamin D supplementation. Thus, like several experts, we emphasize the importance of pragmatism and suggest, in these patients, to continue using intermittent dosing with the smallest available dose (not exceeding 50,000 IU, and preferably lower doses), and the shortest interval between doses as a stopgap until reimbursed pharmaceutical preparations adequate for a simple and well-accepted daily supplementation (i.e. pills or soft capsules of 1000, 2000 IU) become available and reimbursed in France [48,52,53].

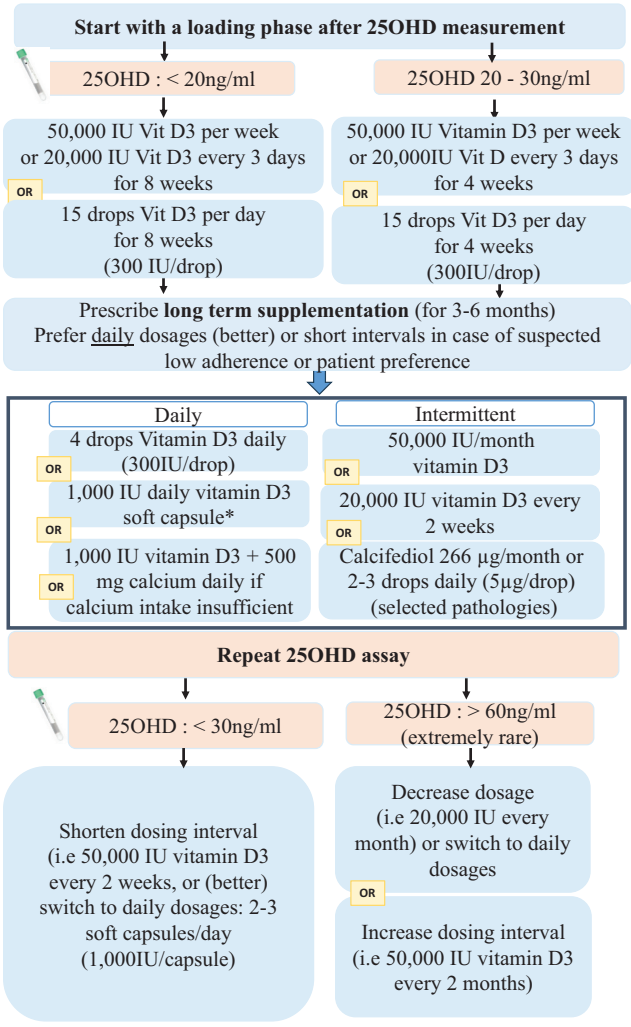

Fig. 1. Proposition for updated modalities of vitamin D supplementation in patients with or at risk of osteoporosis, according to the pharmaceutical forms available in France, January 2025 (adapted from Souberbielle et al., 2020). *Note that 1000 IU soft capsules are not reimbursed in France.

Disclosure of interest

MEP, AB, RMJ and EK declare that they have no competing interest.

JCS: Viatris, Crinex, DiaSorin, Roche Diagnostics, Amgen.

VB: Amgen, Lilly, UCB, Theramex, Besin, IBSA.

KB: ALEXION, Amgen, Besins, Kyowa Kirin.

RC: Amgen, UCB, Abbvie, Mereo, Alexion, Kyowa-Kirin, Medac, Nordic, Alfasigma, Galapagos, Novartis, Pfizer, Lilly.

PF: Amgen, Arrow, Besins, Expanscience, FAES, Fresenius, Innothera, Lilly, Mylan, UCB, Theramex, X.O, Kyowa Kirin.

BC Alexion, Amgen, Aptissen, Besins, Expanscience, Lilly, Kyowa-Kirin, Novartis, Theramex, UCB, Viatris.

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