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Practice guidelines

Vitamin D and calcium intakes in general pediatric populations: A French expert consensus paper

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ABSTRACT

Objectives: Nutritional vitamin D supplements are often used in general pediatrics. Here, the aim is to address vitamin D supplementation and calcium nutritional intakes in newborns, infants, children, and adolescents to prevent vitamin D deficiency and rickets in general populations.
Study design: We formulated clinical questions relating to the following categories: the Patient (or Population) to whom the recommendation will apply; the Intervention being considered; the Comparison (which may be "no action," placebo, or an alternative intervention); and the Outcomes affected by the intervention (PICO). These PICO elements were arranged into the questions to be addressed in the literature searches. Each PICO question then formed the basis for a statement. The population covered consisted of children aged between 0 and 18 years and premature babies hospitalized in neonatology. Two groups were assembled: a core working group and a voting panel from different scientific pediatric committees from the French Society of Pediatrics and national scientific societies.
Results: We present here 35 clinical practice points (CPPs) for the use of native vitamin D therapy (ergocalciferol, vitamin D_2 and cholecalciferol, vitamin D_3) and calcium nutritional intakes in general pediatric populations.
Conclusion: This consensus document was developed to provide guidance to health care professionals on the use of nutritional vitamin D and dietary modalities to achieve the recommended calcium intakes in general pediatric populations. These CPPs will be revised periodically. Research recommendations to study key vitamin D outcome measures in children are also suggested.

1. Introduction

Vitamin D (vitD) is one of the hormones along with parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) that

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upregulate circulating levels of phosphate and calcium (**Fig. 1**) [1]. VitD deficiency is prevalent worldwide in general populations [2].

VitD and calcium intake prevent rickets in babies, children, and teenagers. Guidelines were published by the Nutrition Committee of the French Society of Pediatrics in 2012 [3] and by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition in 2013 [4].

Based on new data constantly emerging in the field, the present manuscript addresses vitD supplementation and calcium nutritional intakes from birth to teenage years. We present 35 clinical practice points (CPPs) for the use of native vitD therapy in general pediatric populations (**Table 1**).

2. Methods

This consensus document was developed to provide guidance for health care professionals on the use of nutritional vitD in general pediatric populations (indications, dosing, and monitoring). These CPPs reflect the available evidence from clinical studies, expert opinion, and extrapolation from adult studies when appropriate.

2.1. The consensus development group

Two groups were assembled. The core group comprised pediatric nephrologists, endocrinologists, neonatologists, nutritionists, dieticians, research scientists, and a geneticist, all responsible for defining the scope of the project, formulating key questions, performing literature reviews, rating the quality of evidence, grading recommendations, and forming the voting panel. The voting panel included representatives from the French Society of Pediatrics, the French Societies of Neonatology, Pediatric Endocrinology, Pediatric Rheumatology, Pediatric Nephrology, Pediatric Gastroenterology, Hepatology and Nutrition, and the French Association of Primary Care Pediatricians. They also included representatives from the French Board of General Physicians with university positions and a biochemist specialized in vitD. Conflicts of interest are declared.

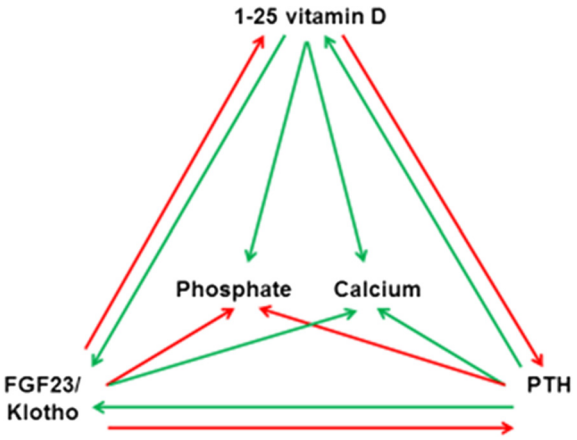

Fig. 1. Overview of phosphate/calcium metabolism, adapted from [119]
Green lines correspond to a stimulating effect
Red lines correspond to an inhibitory effect
FGF23: fibroblast growth factor 23; PTH: parathyroid hormone
Briefly, vitD comes from diet and sun exposure, with a 25-hydroxylation in the liver and a 1-hydroxylation mainly in the kidney, but also in other target cells (see Fig. 3). VitD increases calcium and phosphate intestinal absorption, while inhibiting PTH and stimulating FGF23 synthesis. PTH is synthesized by parathyroid cells, mainly in response to changes in calcium concentrations through the regulation of the calcium-sensing receptor. PTH increases calcium levels, but inhibits tubular phosphate reabsorption, thus inducing hypophosphatemia. PTH stimulates both FGF23 and vitD synthesis. FGF23 is synthesized by osteocytes in the bone, and inhibits both PTH and 1,25(OH)2D while also inhibiting tubular phosphate reabsorption, thus inducing hypophosphatemia. FGF23 increases distal tubular calcium reabsorption, with a mild effect on calcium levels under physiological conditions. Klotho acts mainly as the co-factor of FGF23; it is synthesized by renal and parathyroid cells.

2.2. Developing the PICO questions

To give specific actionable advice, we developed clinical questions to be related to the following categories: the **P**opulation to whom the recommendation will apply, the **I**ntervention being considered, the **C**omparison, and the **O**utcomes affected by the intervention. These PICO elements were arranged into questions to be addressed in the literature searches.

The population covered consisted of children aged 0–18 years in general pediatric populations and premature babies. The intervention was native vitD supplementation and the comparator was placebo or no supplementation, or intra-child comparison using the baseline status, before starting native vitD supplementation. The outcomes addressed were mostly changes in 25 hydroxy-vitD [25(OH)D] levels. Important safety outcomes, including changes in serum and urinary calcium levels, are presented when available. Most of the pediatric studies available did not investigate key patient outcomes such as bone fractures, cardiovascular events, or mortality, and we were unable to discuss these further but consider them as important topics for future research. The overall evidence is not very strong because of vitD supplementation has been used in pediatrics for decades, and because of the nonethical design of a clinical trial against placebo in the field. We addressed statements for indications, contraindications, treatment schedule, monitoring of native vitD supplementation, as well as specific “at-risk” situations in children, neonates, and premature babies.

2.3. Search strategy and selection criteria

The PubMed database was searched until October 2020: articles included were randomized clinical trials (RCTs), prospective uncontrolled or observational studies irrespective of the number of patients, registry data, retrospective studies, and reports with more than five pediatric patients, restricted to human studies in English. The literature search (PubMed) using vitD AND supplement filtered for the past 10 years and from birth to 18 years retrieved 1529 articles, 430 selected as reviews, case series, meta-analyses, or guidelines (Language: English), as summarized in **Supplemental Table 1**. If necessary, papers published before 2010 were also taken into consideration, but not exhaustively.

2.4. Grading system

We applied the grading system of the American Academy of Pediatrics (**Fig. 2**) [5]. The quality of evidence is graded as high (A), moderate (B), low (C), or very low (D). Grading (X) refers to exceptional situations where validating studies cannot be conducted, and benefit or harm clearly predominates.

Voting group members were asked to [1] provide a level of agreement for the 35 CPPs included in this manuscript on a 5-point scale (strongly disagree, disagree, neither agree nor disagree, agree, strongly agree; Delphi method) using an e-questionnaire and [2] suggest rewording if appropriate. A consensus level of at least 70% was achieved for all CPPs.

Table 1
Summary and grading of the 35 consensus statements according to the American Academy of Pediatrics.

	No.	Statement	Grade
Physiology and assays	1	We recommend measuring only serum total 25(OH)D concentration in assessing vitD status in children	B
	2	We recommend measuring serum total 25(OH)D concentration in the same lab for a given child	D
	3	We recommend that assays of $1,25(OH)_2D$ or other metabolites should not be used routinely in pediatrics	C
Which children should undergo 25-D level measurement?	4	We do not recommend systematic measurement of serum total 25(OH)D concentration in general pediatric populations	B
	5	We recommend measurement of serum total 25(OH)D levels when there are symptoms of rickets	B
What are the target levels of 25(OH)D?	6	We recommend a 25(OH)D level above 20 ng/mL (>50 nmol/L) in general pediatric populations to prevent rickets	A
	7	We suggest a 25(OH)D level above 30 ng/mL (>75 nmol/L) in general pediatric populations to avoid any mineralization defects and seasonal variability	B
	8	We suggest a 25(OH)D level below 60 ng/mL (<150 nmol/L) in general pediatric populations	C
	9	Toxicity has been described when 25(OH)D levels are above 80 ng/mL (>200 nmol/L) in general pediatric populations	X
What should the supplementation schedule be in general pediatric populations?	10	We recommend supplementing healthy children 0–18 years of age with a minimum of 400 IU of vitD per day	A
	11	We recommend supplementing healthy children 0–18 years of age with a maximum of 800 IU of vitD per day	C
	12	We recommend daily supplementation in children 0–2 years using $vitD_2$ or D_3	A
	13	We suggest preferring daily supplementation in children 2–18 years using D_2 or D_3	C
	14	We suggest intermittent supplementation in the case of nonadherence in children 2–18 years using $vitD_3$ with either 50,000 IU quarterly or 80,000–100,000 IU twice in fall and winter	D
	15	We recommend avoiding 200,000 IU of vitD in one shot	X
	16	We recommend using only licensed pharmaceutical native vitD supplements	X
Which risk factors should increase the vitD dose?	17	We recommend a minimum of 800 IU and a maximum of 1600 IU of vitD per day in children 2–18 years of age in the case of decreased availability of vitD (obesity, black ethnicity, absence of skin exposure to sun) or decreased intake (vegan diet)	D
	18	In such children, we recommend daily supplementation with $vitD_2$ or D_3	D
	19	In such children, we suggest intermittent supplementation in the case of nonadherence using $vitD_3$ with either 50,000 IU every 6 weeks or 80,000–100,000 IU quarterly	D
	20	We recommend considering at increased risk of developing rickets and vitD deficiency children and teenagers with the following conditions: malabsorption, maldigestion, chronic kidney disease, nephrotic syndrome, cholestasis, hepatic insufficiency, cystic fibrosis, secondary bone fragility, chronic inflammatory diseases, anorexia nervosa, skin diseases, anticonvulsant medications, or long-term corticosteroids	B
	21	We suggest that general pediatricians/physicians verify adherence to vitD supplementation in these children	D
Which risk factors should decrease the vitD dose?	22	We recommend that physicians rule out the use of over-the-counter vitD preparations before prescribing native vitD supplementation	X
	23	We suggest monitoring 25(OH)D levels in patients receiving treatment doses above the upper ranges currently recommended	X
	24	We recommend monitoring 25(OH)D levels in the following conditions to adjust vitD supplementation: family history of vitD intoxication, hypercalcemia, hypercalciuria, kidney stones, and/or nephrocalcinosis	B
	25	We suggest preferring daily vitD supplementation in these patients	D
Nutritional calcium	26	We recommend that, from the age of 1–18 years, children and adolescents should consume at least three to four portions of dairy products per day in order to cover calcium needs	B
	27	We recommend prescribing 500–1000 mg per day of calcium supplementation in children and adolescents receiving less than 300 mg adjusted for calcium bioavailability of nutritional calcium per day, especially in those following a vegan diet	C
	28	We recommend evaluating dietary calcium intakes in children with fractures and bone pain	B
	29	Diagnosis of calcium deficiency requires a dietary calcium intake evaluation, radiographs of wrists and knees, and measurement of plasma ALP, PTH, 25(OH)D, calcium and phosphate, and urinary excretion of calcium	B
VitD supplementation in premature babies	30	We recommend optimizing nutritional calcium and phosphate intakes in premature neonates	B
	31	We suggest that, during the initial stay in the NICU, preterm infants receive between 600 IU and 1000 IU per day of vitD, taking into account the content of vitD in milk and parenteral nutrition, vitD supplementation during pregnancy, and birth weight	B
	32	We recommend measurement of 25(OH)D in children born before 32 weeks of gestation or weighing less than 1500 g at 1 month of age	C
	33	We recommend 50 nmol/L as the lower target level and 120 nmol/L as the upper target level of 25(OH)D in premature neonates	D
	34	After discharge from the NICU, we suggest following recommendations in general pediatric populations	D
French overseas territories	35	We suggest the same pattern of supplementation as in Metropolitan France	D

VitD: vitamin D; PTH: parathyroid hormone; NICU: neonatal intensive care unit; ALP: alkaline phosphatase.

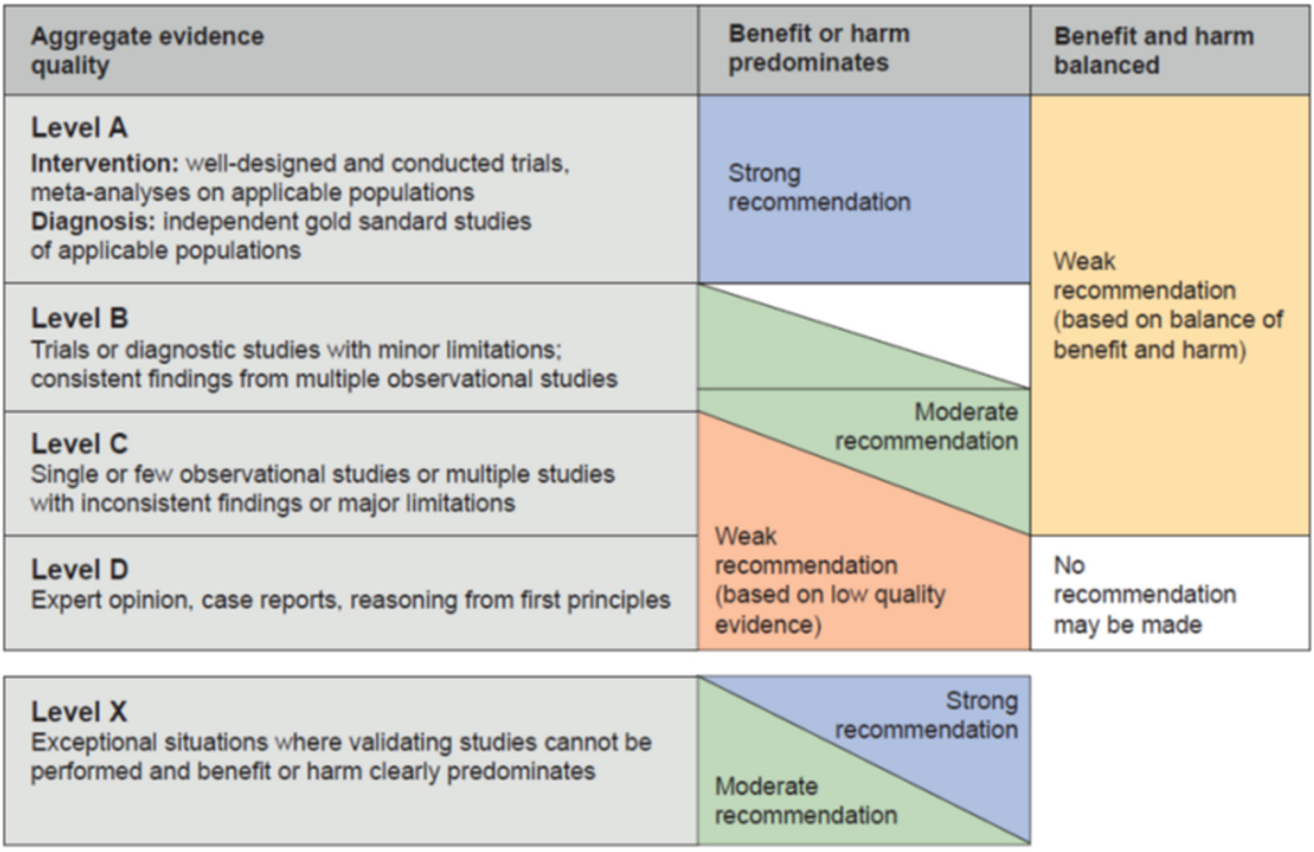

Fig. 2. Grading system for recommendations according to the American Academy of Pediatrics, adapted from [5].

3. Physiology and assays: relevance for clinical practice

3.1. Rationale

3.1.1. VitD as fat-soluble secosteroid

$VitD_2$ and D_3 derive from ergosterol in plants and fungi, and from cholesterol in animals, respectively. VitD produced endogenously through the skin via sunlight accounts for 50–90% of circulating 25(OH)D [1]. The activities of $VitD_2/D_3$ are similar, but the pharmacokinetics and bioavailability of D_3 are greater [6]. Apart from supplements, vitD content in the human diet is limited. Both 25(OH)D (half-life 2–3 weeks) and $1,25(OH)_2D$ (half-life 4 h) levels result from a series of hydroxylations (**Fig. 3**) [7]. Bioactive vitD activities are mediated through binding to the vitD receptor (VDR) (**Fig. 4**) [1].

3.1.2. VitD skeletal and extraskeletal effects

Rickets and hypocalcemia are caused by vitD deficiency, and by loss-of-function mutations in the VDR or in the vitD hydroxylases CYP27B1 and CYP2R1 [8,9]. Conversely, hypercalcemia occurs because of vitD excess or CYP24A1 loss-of-function mutations [10].

The 25(OH)D levels provide information on the availability of bioactive precursors for target tissues, while $1,25(OH)_2D$ levels reflect the activity of renal CYP27B1, the enzyme involved in the rate-limiting step of $1,25\ (OH)_2D$ synthesis. Both 25(OH)D and $1,25\ (OH)_2D$ are able to bind VDR and control biological processes, albeit with different affinities and potency [8]. VitD also has anti-inflammatory and anti-proliferative activities [11].

3.1.3. Assays for 25(OH)D and $1,25(OH)_2D$

Circulating levels of 25(OH)D result from recent vitD intake and endogenous production. The gold standard technique for measurement of 25(OH)D uses the HPLC-tandem mass spectrometry (HPLC-MS/MS) technology. Automated techniques are now available at low cost [7], measuring total $25(OH)D_{2/3}$, unless mentioned otherwise in reports. A few assays are not standardized, justifying always referring patients to the same laboratory [12]. Some assays cross-react with the epimer-C3 forms, overestimating the amount of effective 25(OH)D, especially in preterm infants and neonates [13,14]. A major staging effort was initiated during the last decade to move references from "normal values" to "recommended thresholds."

The assay of $1,25(OH)_2D$ is used to explore specific genetic, infectious, or inflammatory diseases [15].

3.2. Consensus statements

1. We recommend measuring only serum total 25(OH)D concentration in assessing vitD status in children.
2. We recommend measuring serum total 25(OH)D concentration in the same lab for a given child.
3. We recommend that assays of $1,25(OH)_2D$ or other metabolites should not be used routinely in pediatrics.

4. Which children should undergo 25(OH)D level measurement?

4.1. Rationale

Total 25(OH)D levels are usually measured in children with chronic diseases or with a combination of risk factors for vitD deficiency (**Table 2**) [16]. This assay is not reimbursed in the absence of medical justification [17]. If an underlying abnormality of phosphate/calcium metabolism is suspected (hypo- or hypercalcemia), 25(OH)D levels should be measured.

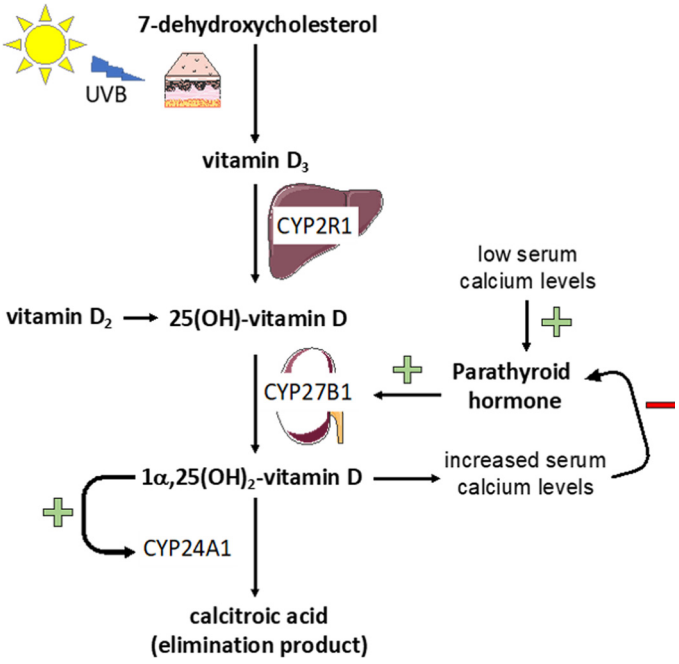

Fig. 3. Circulating $1,25(OH)_2D$ levels are controlled by a tightly regulated network

Upon sun exposure, $vitD_3$ is formed by spontaneous isomerization of pre-$vitD_3$, a precursor obtained by photo-isomerization of 7-dehydroxycholesterol in the skin. VitD enters the circulation after binding to the VitD binding protein (DBP), and therefore there is no specific storage in the liver [120]. Of note, $vitD_3$ as well as its vegetal form $vitD_2$ can be obtained from diets enriched in fish and fungi, respectively, or from supplements. Once in the liver, vitD is hydroxylated at the carbon 25 by CYP2R1. Then a second hydroxylation step at carbon 1 by CYP27B1 in the kidney, the limiting reaction step, leads to the bioactive form of vitD, 1alpha-25-dihydroxy-vitD (1,25D). Importantly, the expression of these hydroxylases is controlled by the parathyroid hormone (PTH). Parathyroid glands (PTG) sense any variation of serum calcium levels, and in response to low levels, will produce and secrete PTH that in turn increases the expression of CYP2R1 and CYP27B1. In addition, 1,25D3 induces the expression of CYP24A1, a 24-hydroxylase, its main catabolic enzyme that converts it into calcitroic acid, an inactive hydrophilic degradation product eliminated by urine [121], thus completing the regulatory feedback loop of $1,25D_3$ circulating levels. Of note, the metabolism of vitD in preterm infants and neonates is marked by an increase of a 25 OHD C3 epimer [122]. In addition, 1,25D can be 3-epi hydroxylated. 3epi-1,25D can bind the DBP with a modest affinity (36–46%) and the VDR with a low affinity (2–3%) compared to 1,25D. It is as effective as 1,25D in inhibiting PTH secretion or inducing phospholipid surfactant synthesis, but is less effective on CYP24A1 induction. Importantly, C3 epimer levels increase during the first 2 months of life and then decrease. Therefore, amounts of C3 epimers seem more relevant in preterm than in term newborns. However, the exact physiological role of these 3-epi vitD metabolites remains to be determined.

4.2. Consensus statements

4. We do not recommend systematic measurement of serum total 25(OH)D concentration in general pediatric populations.

5. We recommend measurement of serum total 25(OH)D levels when there are symptoms of rickets.

5. What are the target levels for circulating 25(OH)D levels?

5.1. Rationale

Today, there is no definitive consensus on the normal range for circulating 25(OH)D levels. We propose the following cut-off points: sufficiency 30–60 ng/mL (75–150 nmol/L), insufficiency 20–29 ng/mL (50–74 nmol/L), deficiency below 20 ng/mL (<50 nmol/L), severe deficiency below 10 ng/mL (<25 nmol/L), excess above 60 ng/mL (>150 nmol/L), and risk of toxicity above 80 ng/mL (>200 nmol/L). The lower cut-offs are based on the PTH feedback threshold, calcium intestinal absorption, and bone health.

PTH levels usually increase for 25(OH)D levels <20 ng/mL, reaching a plateau between 30 and 40 ng/mL [18,19]. The risk of rickets is major when 25(OH)D levels are <10–15 ng/mL, whatever the calcium intake [20]. The American Academy of Pediatrics and the Pediatric Endocrine Society define sufficiency as 25(OH)D >20 ng/mL and 30 ng/mL, respectively [21,22].

Children with chronic diseases accumulate risk factors for both 25(OH)D and calcium deficiency, which is why the target threshold of 25(OH)D level should be >30 ng/mL. Autopsy studies in adults showed that the threshold of 30 ng/mL was required to avoid mineralization defects [23]. Two large epidemiological studies in adults associated increased mortality and 25(OH)D levels either >60 ng/mL or <20 ng/mL [24,25]. In children, persistently elevated levels of 25(OH)D likely increase the risk of hypercalciuria and subsequent nephrolithiasis and/or nephrocalcinosis [26,27]. Thus, the American Endocrine Society and the Canadian Pediatric Society have proposed a target range of 30–60 ng/mL in children, to prevent both rickets and nephrolithiasis/nephrocalcinosis [16,28].

5.2. Consensus statements

6. We recommend a 25(OH)D level >20 ng/mL (50 nmol/L) in general pediatric populations to prevent rickets.

7. We suggest a 25(OH)D level >30 ng/mL (75 nmol/L) in general pediatric populations to avoid any mineralization defects and seasonal variability.

8. We suggest a 25(OH)D level <60 ng/mL (150 nmol/L) in general pediatric populations.

9. Toxicity has been described when 25(OH)D levels are above 80 ng/mL (200 nmol/L) in general pediatric populations.

6. Native vitD supplementation in children

6.1. Rationale

Countries of the northern hemisphere recommend universal vitD supplementation in infants, toddlers, and adolescents to optimize 25(OH)D levels and prevent nutritional rickets, despite the absence of large trials proving safety or efficacy for any disease outcome [3,4,21,29].

6.1.1. Effects in infants

VitD deficiency is common in mothers and infants, though the prevalence in diverse populations may depend upon sun exposure behaviors and supplementation during pregnancy [30]. The persistence of maternal vitD deficiency/insufficiency during pregnancy/breastfeeding irrespective of season and supplementation suggests that current vitD supplementation during pregnancy is inadequate [31]. Human breast milk for healthy full-term newborns contains very little vitD even in vitD-repleted mothers [32]. As such, exclusively breastfed infants, especially those born to vitD-deficient mothers, are at higher risk for rickets [33]. **Table 3** summarizes the RCTs of native vitD supplementation performed in infants [34–36]. Briefly, the dose of 400 IU/day (1 μg = 40 IU) in healthy breastfed term babies prevents rickets but also ensures adequate bone health [37,38]. Higher doses (1200 IU/day) are not associated with better outcomes [35]. VitD supplementation ranging from 400 to 800 IU/day in healthy newborns is recommended in North America and Europe to maintain 25(OH)D levels of 10–20 ng/mL (25–50 nmol/L) [4].

6.1.2. Effects in healthy children and adolescents

Table 4 summarizes the RCTs on native vitD supplementation performed in healthy children and adolescents [39–49]. A daily supplementation of 400 IU (vs. 1000, 2000, and 4000 IU) is sufficient to prevent the 3-ng/mL physiological decrease in 25(OH)D concentrations over winter [39], so as to maintain 25(OH)D within the target

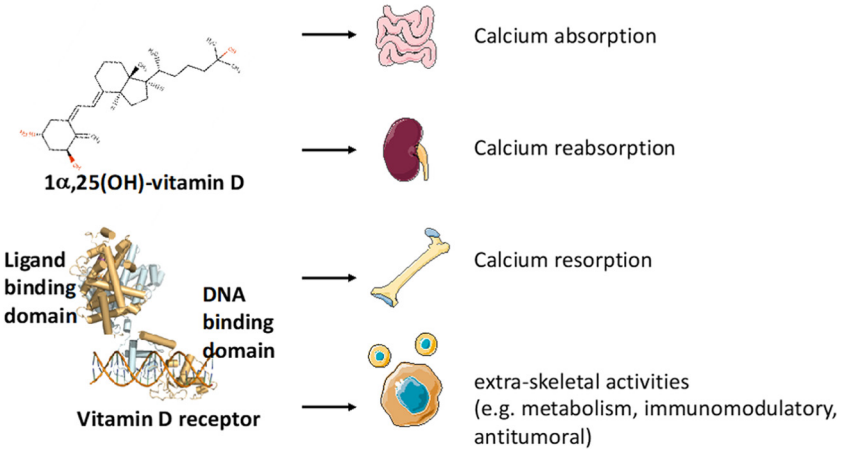

Fig. 4. 1,25$(OH)_2$D activities are mediated by the vitD receptor

The main physiological roles of bioactive vitD are to control calcium absorption in the intestine and calcium reabsorption in kidney, and under certain circumstances to promote calcium mobilization from bones [123]. Such a tightly regulated network is principally controlled by the levels of vitD receptor (VDR) in the intestine, highlighting the importance of the 1,25$(OH)_2$D/VDR signaling pathway in this tissue [87], In addition, several preclinical and clinical studies have highlighted the important extraskeletal role of 1,25$(OH)_2$D and its potential therapeutic potency for the treatment of autoimmune disorders and various cancers. 1,25$(OH)_2$D activities are mediated through its binding to VDR (also known as NR1I1), a ligand-dependent transcription factor and member of the nuclear receptor superfamily. VDR is composed of a ligand-binding domain (LBD) and a DNA-binding domain (DBD) separated by a disorganized hinge region [10]. Upon 1,25$(OH)_2$D binding, VDR conformational changes allow VDR to translocate into the nucleus. Then VDR heterodimerizes with its partner retinoid X receptor to bind with high affinity to specific DNA sequences, called vitD response elements (VDRE), in the regulatory regions of 1,25$(OH)_2$D/VDR target genes. After DNA binding, VDR conformational changes of helix 12 of the LBD favor the recruitment of coregulatory proteins to regulate the transcription of its target genes. Importantly, recent studies have demonstrated that in the absence of ligand, VDR is mainly cytosolic, but the residual VDR nuclear fraction is able to bind to VDRE and repress the expression of its target genes ((8,9), opening new avenues of the physiological consequences of low circulating 1,25$(OH)_2$D levels.

range continuously. The mineralization peak is delayed as compared to the growth peak, thus providing a rationale to maintain supplementation throughout puberty [50]. In healthy children, vitD repletion does not modify bone density, heart and vascular function, immune defense and infection, IGF1 levels, muscle strength, and physical performance [41,43,44,46–48,51–55].

6.1.3. *Diet, daily intake, or single high-dose oral vitD (STOSS) therapy*

In the absence of convincing evidence of efficacy and safety, daily vitD supplementation should be preferred in children, as proposed in other European countries [4], mainly to avoid increased urinary calcium following vitD administration, and to prevent nephrolithiasis. A recent RCT in children with chronic kidney disease and vitD deficiency showed that the time until 25(OH)D normalization and the number of children with 25(OH)D levels <30 ng/mL were similar after oral cholecalciferol for 3 months at various regimens, i.e., 3000 IU daily, 25,000 IU weekly, or 100,000 IU monthly [56].

The main risk for a daily regimen is likely noncompliance over the long term [57]; as such, given vitD pharmacokinetics, even though it has not been published yet in healthy children, one may consider weekly supplementation instead of daily supplementation, as proposed in particular populations [56]. Still, because a significant number of children are at risk of rickets [58], administration of 50,000 −100,000 IU at regular intervals may also be considered in some children. However, the use of megadoses above 200,000 IU in a single shot should be avoided to prevent hypercalcemia/hypercalciuria and renal consequences [59–61]. In any case, this rationale should be explained to parents, to provide them with the better choice for their child: intermittent supplementation will be preferred to no supplementation at all.

Table 2
Risk factors of vitD deficiency in children.

Inadequate cutaneous vitD synthesis
• Dark skin
• Obesity
• Physical blocking of ultraviolet-B exposure: clothing, use of sunscreens, etc.
• Geographic factors: higher latitude, winter season, lower altitude, etc.
Inadequate dietary intake of vitD
• Unbalanced diet
• Vegetarians, eating disorders: anorexia nervosa, bulimia nervosa, etc.
• Malabsorption syndrome
• Intestinal malabsorption: celiac disease, Crohn's disease, ulcerative colitis, etc.
• Pancreatic insufficiency: cystic fibrosis
• Cholestasis syndrome: biliary atresia, etc.
• Following gut resection: short bowel syndrome
Perinatal factors
• Maternal vitD deficiency during pregnancy
• Prematurity
• Child exclusively breastfed beyond 3–6 months of age
Chronic metabolic disorders
• Chronic liver/renal diseases
• Hyperparathyroidism, growth hormone deficiency, diabetes mellitus
• Hereditary resistance of vitD
Medications
• Anticonvulsants: carbamazepine, phenytoin, phenobarbital, topiramate
• Antiretroviral agents for treating human immunodeficiency virus infection
• Azole antifungal agents: ketoconazole, fluconazole
• Glucocorticoids

VitD: vitamin D.

6.1.4. *Novel concerns regarding vitD supplementation*

A recent alert from the French Drug Agency (ANSES) reported the occurrence of severe hypercalcemia in neonates receiving food complements enriched in vitD instead of drug formulations [62], as previously reported [63]. Particular attention should be given to food supplements containing vitD at concentrations sometimes seven to ten times that of licensed pharmaceutical formulations, significantly increasing the risk of overdose.

Some parents' concern is the presence of excipients in the licensed formulation of vitD, leading parents and some physicians to propose food supplements instead of drug formulations. To date, there is no established link between the presence of certain flavors/excipients in the licensed preparations of vitD and the occurrence of diseases. The excipients vary according to the different forms, but each physician should have the free choice of

Table 3
RCTs of vitD supplementation in infants.

Authors	Year	Population	Methods	Results
Gallo et al.	2013	132 healthy term infants, breastfed, from Canada	Randomization 400/800/1200/1600 IU/day, follow-up 11 months.	The only dose that puts more than 97.5% of infants above 75 nmol/L of 25(OH)D was 1600 IU/day, but there was a significant proportion of hypercalcemia. The 400 IU dosage maintained 25(OH)D levels in all but one subject.
Rosenthal et al.	2018	975 healthy term infants at a maternity hospital in Helsinki, Finland. 854 were breastfed.	Randomization 400 vs 1200 IU/day, follow-up 24 months.	400 IU per day is sufficient. Note that daily dietary intake at 1 year was 248±148 IU/day
Specker et al.	1992	256 term infants from two northern and two southern cities in China	Randomization 100 versus 200 versus 400 IU/day, follow-up 6 months	400 IU per day was sufficient. Note that food was not enriched in vitD in this trial. No cases of rickets were observed.

VitD: vitamin D; RCTs: randomized clinical trials.

the prescribed specialty, if it is a licensed form of vitD, subject to manufacturing processes and controls performed by pharmaceutical companies.

VitD can be given any time during the day, and parents/patients should be warned that it may stick to glass or plastics.

6.2. Consensus statements

10. We recommend supplementing healthy children 0–18 years of age with a minimum of 400 IU of vitD per day.

11. We recommend supplementing healthy children 0–18 years of age with a maximum of 800 IU of vitD per day.

12. We recommend daily supplementation in children 0–2 years using D_2 or D_3.

13. We suggest preferring daily supplementation in children 2–18 years using D_2 or D_3.

14. We suggest intermittent supplementation in the case of non-adherence in children 2–18 years using $vitD_3$ with either 50,000 IU quarterly or 80,000–100,000 IU twice in fall and winter.

15. We recommend avoiding of 200,000 IU of vitD in one shot.

16. We recommend using only licensed pharmaceutical native vitD supplements.

7. RISK factors leading to increased native vitD supplementation

7.1. Rationale

Many factors contribute to 25(OH)D deficiency, including increased bone turnover during periods of rapid skeletal growth, sun

Table 4
RCTs of vitD supplementation in healthy children and teenagers.

Authors	Year	Population	Methods	Results
Lewis et al.	2013	323 healthy children aged 9–13 years (50% male, 51% black)	Randomization placebo/400/1000/2000/4000 IU/day, follow-up 12 weeks in winter	Supplementation with 400 IU/day was sufficient to maintain wintertime 25(OH)D concentrations >20 ng/mL in healthy black, but not white, children.
Rajakumar et al.	2015	157 healthy children aged 8–14 years (53% black)	Randomization placebo/1000 IU/day, follow-up 6 months	VitD supplementation with 1000 IU/day in children with mean baseline 25(OH)D concentration <20 ng/mL effectively raised mean 25(OH)D level to ≥20 ng/mL but failed to reach 30 ng/mL.
Ferira et al.	2016	323 healthy children aged 9–13 years (50% male, 51% black)	Randomization placebo/400/800/1000/2000/4000 IU/day, follow-up 12 weeks	No impact on insulin resistance (fasting glucose, insulin, HOMA)
Mortensen et al.	2016	119 healthy white children aged 4–8 years (mean age, 6.7 years)	Randomization placebo/400/800 IU/day, follow-up 20 weeks	VitD intakes between 400 and 800 IU/day were required to maintain serum 25(OH)*D* >30 and 50 nmol/L, respectively
Aglipay et al.	2017	703 healthy children aged 1–5 years (mean age, 2.7 years, 58% male)	Randomization 400/2000 IU/day, minimum follow-up 4 winter months	Higher doses of vitD did not reduce overall wintertime upper respiratory tract infections
Ohlund et al.	2017	206 healthy children aged 5–7 years (48% dark skin)	Randomization placebo/400/1000 IU/day, follow-up 3 winter months	Children with fair and dark skin required vitD intakes of 400 and 1000 IU/day, respectively, to maintain 25(OH)*D* ≥ 50 nmol/L during winter.
Marwaha et al.	2018	216 healthy prepubertal girls aged 6–12 years	Randomization 600/1000/2000 IU/day, follow-up 6 months	Serum 25(OH)D levels of ≥20 ng/mL were seen in 91% in 600 IU group, 97% in 1000 IU group, and 100% in 2000 IU group.
Hauger et al.	2018	119 healthy children aged 4–8 years (6.7 ± 1.5 years, 36% male, 82% normal weight)	Randomization placebo/400/800 IU/day, follow-up 20 weeks	No effect on cardiometabolic risk markers (BMI, waist circumference, blood pressure, serum lipids, fasting glucose and insulin, HbA1c)
Hauger et al.	2019	119 healthy children aged 4–8 years	Randomization placebo/400/800 IU/day, follow-up 20 weeks	No effect on respiratory infection
Mortensen et al.	2019	117 healthy children aged 4–8 years	Randomization placebo/400/800 IU/day, follow-up 20 weeks	No effect on muscle strength
Ohlund et al.	2020	206 healthy children aged 5–7 years	Randomization placebo/400/1000 IU/day, follow-up 3 winter months	No effect on cardiometabolic risk markers (blood pressure, serum lipids, CRP)

VitD: vitamin D; RCTs: randomized clinical trials; HOMA: homeostasis model assessment; BMI: body mass index; CRP: C-reactive protein.

Table 5
RCTs of vitD supplementation in obese children.

Authors	Year	Population	Methods	Results
Kelishadi et al.	2014	43 Iranian adolescents (10–16 years of age), obese (median BMI 28); 25(OH)D level at baseline **17**–**18** ng/mL	Triple masked controlled trial comparing **300,000 IU/week** vs. placebo for 12 weeks	Group treated with 300,000 IU/week showed 25(OH)D level increased significantly to 32 ng/mL (vs. 19 in placebo group); significantly decreased serum insulin and triglyceride concentrations
Nader et al.	2014	58 adolescents (12–18 years of age; median 15 years), obese (median BMI Z score 2.2); 25(OH)D level at baseline **24**–**25** ng/mL. Most were Caucasian	Double-blind, randomized controlled trial comparing **2000 IU/day** vs. placebo for 12 weeks	Group treated with 2000 IU/day showed modest but significant increase of 25(OH)D level (+6 ng/mL) after 12 weeks. No effects were observed on lipid profile, markers of insulin resistance or inflammation
Javed et al.	2015	46 Caucasian adolescents (15±1.9 years), obese (median BMI, 98perc), 25(OH)D level at baseline **23**–**24**±8 μg/L	Double-blind, randomized trial comparing **400 vs. 200 IU/day** for 12 weeks	Modest but significant increase of 25(OH)D level in the 2000 IU/day group (+3.1) but not in the 400-IU group, no change in β cell function or insulin action
Talib et al.	2016	183 vitD-deficient adolescents (mean 25(OH)D, **13.7 ± 3.9** ng/mL; mean age, 16.6 ± 2.2 years), obese (median BMI, 27–28), 88% identified as either Hispanic or black	Prospective, open-label, randomized clinical trial comparing **50,000 IU/week; 5000 or 1000 IU/day** for 8 weeks	80% of patients of the groups treated with 5000 IU/day or 50,000 IU/week reached a 25(OH)D level >20 ng/mL
Rajakumar et al.	2020	225 adolescents (mean age, 13.6 ± 2.3 years), obese (median BMI, 95.8perc±3.8), level of 25(OH)D at baseline **14.3 ± 3.7** ng/mL; 94% identified as black	Randomized, double-masked controlled trial of **600 vs. 1000 vs. 2000 IU/day** for 6 months	25(OH)D level >20 ng/mL in the three groups, >30 ng/mL only in the group treated with 2000 IU/day; no effect on endothelial function or stiffness, systemic inflammation or lipid profile, but reductions in BP and fasting glucose concentration and in improvements in insulin sensitivity

VitD: vitamin D; RCTs: randomized clinical trials; BMI: body mass index.

exposure, epidermal melanin composition, and obesity (**Table 2**). Cutaneous vitD$_3$ synthesis depends on body location, extent of clothing, cultural factors, topical screen, latitude, altitude, season, pollution, and time of day for sun exposure [18,22]. Levels of 25(OH)D and the increment in response to vitD supplementation are negatively influenced by adiposity [64,65]. **Table 5** summarizes the RCTs on vitD supplementation in obese children [66–70].

Because of current trends in dietary habits, the risk of vitD deficiency in individuals adopting a vegan diet should be emphasized. Since dietary vitD comes almost exclusively from fatty fish and fortified dairy products, subjects following a vegan diet excluding all animal products are at high risk of calcium/vitD deficiency and nutritional rickets [71,72].

Many chronic pediatric conditions involving intestinal malabsorption, inflammation, liver diseases, and kidney insufficiencies may also reduce vitD production and/or absorption. Drugs affect vitD metabolism through different mechanisms: enhanced catabolism (anticonvulsants), inhibition of intestinal calcium absorption (glucocorticoids), or induction of liver enzymes (nifedipine, spironolactone, clotrimazole, and rifampin) [73]. To adjust vitD supplementation in these conditions, there are specific international guidelines [74–76].

7.2. Consensus statements

17. We recommend a minimum of 800 IU and a maximum of 1600 IU of vitD per day in children 2–18 years of age in the case of decreased availability of vitD (obesity, black ethnicity, absence of skin exposure to sun) or decreased intake (vegan diet).

18. In such children, we recommend daily supplementation with vitD$_2$ or D$_3$.

19. In such children, we suggest intermittent supplementation in the case of nonadherence using vitD$_3$ with either 50,000 IU every 6 weeks or 80,000–100,000 IU quarterly.

20. We recommend considering at increased risk of developing rickets and vitD deficiency children and teenagers with the following conditions: malabsorption, maldigestion, chronic kidney disease, nephrotic syndrome, cholestasis, hepatic insufficiency, cystic fibrosis, secondary bone fragility, chronic inflammatory diseases, anorexia nervosa, skin diseases, anticonvulsant medications, or long-term corticosteroids.

21. We suggest that general pediatricians/physicians verify adherence to vitD supplementation in these children.

8. Conditions where vitD supplementation should be suspended

8.1. Rationale

Overstimulation of VDR following vitD intoxication leads to acute hypercalcemia (manifesting as polyuria, hypertension, or acute kidney injury), and/or chronic hypercalciuria, nephrocalcinosis, and nephrolithiasis. Levels of 1,25(OH)$_2$D are elevated or nonadjusted to hypercalcemia. PTH is always suppressed [77]. The causal mechanisms are exogenous (iatrogenic excessive intake of native vitD) or endogenous (overproduction or lack of degradation of the bioactive vitD: paraneoplastic syndrome, systemic diseases, lymphoproliferative syndromes, rare genetic diseases including loss-of-function mutations in *CYP24A1* or *SLC34A1/A3*) [78].

VitD intoxication is mainly caused by inappropriate prescription or administration of native vitD, and/or the use of high-dose over-the-counter unlicensed preparations, whether or not they are purchased on the internet [62,63]. Circulating 25(OH)D levels are usually above 150 ng/mL (375 nmol/L) [16,63].

8.2. Consensus statements

22. We recommend that physicians rule out the use of over-the-counter vitD preparations before prescribing native vitD supplementation.

23. We suggest monitoring 25(OH)D levels in patients receiving treatment doses above the upper ranges currently recommended.

24. We recommend measuring 25(OH)D levels in the following conditions to adjust vitD supplementation: family history of vitD intoxication, hypercalcemia, hypercalciuria, kidney stones, and/or nephrocalcinosis.

Table 6
Calcium absorption efficiency depending on the type of food.

Foods	Mean calcium content (mg/100 g or mL)	Absorption efficiency
Breast milk	33	65%
Infant formulas	60	30–40%
Follow-up formulas	71	30–40%
Growing-up milks	76	30–40%
Cow's milk	115	30–40%
Cooked pressed cheeses	935	30–40%
Soft cheeses	523	30–40%
White cheeses	122	30–40%
Rocket	160	40%
Cress	87	40%
Kale	72	40%
Green cabbage	70	40%
Broccoli	43	30–40%
Rhubarb	145	5%
Spinach	140	5%
White bean	120	15–20%
Red bean	55	10–20%
Sweet potato	33	5–10%
Bran	74	15–25%
Mineral waters	1–500	30–40%
French tap water	7	30–40%

25. We suggest preferring daily vitD supplementation in these patients.

9. Nutritional calcium

9.1. Evidence and rationale

9.1.1. Calcium content and absorption efficiency of some foods

Calcium is absorbed in the intestine through nonsaturable passive paracellular absorption and by active transcellular absorption, respectively; absorption is greater in the duodenum and jejunum. In food, most of calcium is released from complexes with other dietary constituents to be absorbed [79]. Increased growth velocity, dietary components, and a calcium-deficient diet improves the efficiency of calcium absorption. Calcium bioavailability results from the net calcium retention in bones and organs, the calcium absorption, and urine losses.

Dairy products are the major source of calcium due to an efficient absorption (30–40%), because of the lactose content [80]. Fat (except in steatorrhea) and protein contents of the diet do not affect calcium absorption.

Many dietary components affect calcium absorption [79,81]. Oxalate and phytate, through the formation of unabsorbable complexes, reduce the absorption of calcium when present in large amounts in some leafy green vegetables. Phytate is mainly present in whole wheat products. Conversely, oxalate content in brassica vegetables is very low, allowing efficient absorption of calcium. Insoluble fibers of fruits and vegetables (hemicellulose and lignin) impair calcium absorption because of their content of uronic acids [82]. Some mineral waters are rich in calcium, their absorption efficiency being very close to that of dairy products (**Table 6**) [83].

Table 7
Calcium population reference intake depending on age according to the 2017 EFSA recommendations.

	Population reference intake
7–11 months	280 mg/day
1–3 years	450 mg/day
4–10 years	800 mg/day
11–17 years	1150 mg/day

EFSA: European Food Safety Authority.

9.1.2. Population reference intakes

The most recent European recommendations are from the EFSA (**Table 7**) [84]. For infants 0–6 months, the EFSA published only mean calcium intakes based on breast milk: 200 mg/day [84]. The previous 2011 American Dietary Reference Intakes (DRI) were higher; those of the French FSA in 2001 were intermediate.

9.1.3. Practical dietary modalities to evaluate and meet calcium requirements

Table 8 illustrates food equivalences necessary to ensure a calcium intake of 150 mg [83]. The evaluation of calcium intakes should also consider the efficiency of calcium absorption (as compared to that of dairy products). Practical dietary modalities to meet calcium intake requirements according to age are illustrated in **Table 9**. Thus, from the age of 1 to 18 years, three or four dairy products are needed daily to meet calcium requirements. Consumption of mineral waters rich in calcium should be encouraged, especially when daily dairy product intake is insufficient. Replacing one or more dairy products with plants rich in calcium seems unreasonable since the amounts necessary to provide enough calcium would be too high, particularly at these ages or with plants rich in components affecting calcium absorption.

In exclusively breastfed or bottle-fed infants, calcium needs are covered. However, in case of vegan diets, only rice protein-based or soy protein-based infant formulas, whose composition complies with European regulations for infant formulas, cover calcium needs. All other plant-based beverages do not contain enough calcium to ensure adequate intake [71].

Table 8
Food equivalents for calcium content.

150 mg of calcium ingested (and not absorbed) =	450 mL of breast milk
	250 mL of infant formula
	210 mL of follow-up formula
	200 mL of growing-up milk
	130 mL of cow's milk
	16 g of cooked pressed cheese
	29 g of soft cheese
	125 g of white cheese
	125 g of yoghurt
	95 g of rocket
	170 g of cress
	210 g of kale
	215 g of green cabbage
	350 g of broccoli
	100 g of rhubarb
	110 g of spinach
	125 g of white beans
	270 g of red beans
	450 g of sweet potatoes
	200 g of bran
	50 g of sardines with bones
	300 mL of mineral water with 500 mg/L of Ca (i.e., Contrex)
	600 mL of mineral water with 250 mg/L of Ca (i.e., Vittel)
	1.5 L of mineral water with 100 mg/L of Ca (i.e., Evian)
	2.1 L of French tap water

The evaluation of calcium intakes should take into account the efficiency of calcium absorption (as compared to that of dairy products). For example, the efficiency of calcium absorption is seven-fold lower in spinach and rhubarb than in dairy products. The amount of calcium provided by these plants should therefore be divided by 7 when evaluating dietary calcium intakes.

Table 9
Practical dietary modalities to ensure whole daily recommended calcium intakes.

In infants from 7 to 11 months	In toddlers from 1 to 3 years	In children from 4 to 10 years	In adolescents from 11 to 17 years
390 mL of follow-up formula, a volume easily reachable by at least two bottles daily	250 mL (one usual bottle) of growing-up milk + 1 yoghurt (125 g) + 10 g of cooked pressed cheese	200 mL of cow's milk + 1 yoghurt (125 g) + 30 g of cooked pressed cheese + 250 mL of mineral water with 500 mg/L of calcium	350 mL of cow's milk + 1 yoghurt (125 g) + 30 g of cooked pressed cheese + 600 mL of mineral water with 500 mg/L of calcium

These amounts could be reduced if plants rich in calcium with good bioavailability are consumed.

9.1.4. Calcium deficiency

Calcium deficiency is defined by a prolonged calcium intake below the recommended intake for age. Its consequences are like those of vitD deficiency, namely insufficient intestinal calcium absorption to cover the needs of the organism despite reduced renal calcium excretion. However, dietary calcium deficiency is associated with secondary increased $1,25(OH)_2D$ levels, which inhibits bone formation and redirects calcium towards the serum. This contributes to the maintenance of serum calcium when calcium transport is deficient, at the expense of bone mineralization [85–87].

A low calcium diet is associated with increased PTH levels in children with 25(OH)D levels >50 nmol/L [88]. A chronic deficit in dietary calcium and increased PTH/$1,25(OH)_2D$ impair cartilage and bone mineralization [89]. Furthermore, increased PTH levels inhibit tubular phosphate reabsorption, thus contributing to hypophosphatemia and further bone mineralization defect.

9.1.5. Criteria of calcium deficiency

Serum calcium levels are not a marker of calcium deficiency [58,87], but low urinary calcium (urinary Ca/creat <0.2 mmol/mmol) may be associated with low calcium intake [74]. Assessment of daily dietary calcium intakes in toddlers, children, and adolescents leads to the three following categories [90]: sufficiency (>500 mg/day), insufficiency (300–500 mg/day), and deficiency (<300 mg/day). Such subjects with calcium deficiency should receive calcium supplementation from 250 to 1000 mg/day according to age, the total daily calcium dose not exceeding the population reference intake (PRI) for age. Diagnosis of calcium deficiency requires a dietary calcium intake evaluation, radiographs of wrists and knees, and measurement of plasma ALP, PTH, 25(OH)D, calcium and phosphate levels, and urinary calcium excretion.

9.2. Consensus statements

26. We recommend that, from the age of 1 to 18 years, children and adolescents should consume at least three to four portions of dairy products per day to cover calcium needs.

27. We recommend prescribing 500–1000 mg per day of calcium supplementation in children and adolescents receiving less than 300 mg adjusted for calcium bioavailability of nutritional calcium per day, especially in those following a vegan diet.

28. We recommend evaluating dietary calcium intakes in children with fractures and bone pain.

29. Diagnosis of calcium deficiency requires a dietary calcium intake evaluation, radiographs of wrists and knees, and measurement of plasma ALP, PTH, 25(OH)D, calcium and phosphate, and urinary excretion of calcium.

10. VitD supplementation in premature babies

10.1. Evidence and rationale

Preterm infants are prone to vitD deficiency due to incomplete transplacental transfer during the third trimester, low body stores, low vitD in parenteral nutrition, decreased absorption, and negligible sun exposure during the hospital stay [91]. At birth, 25(OH)D levels in infants are highly correlated with maternal levels [92]. It is common for preterm infants to have low 25(OH)D levels [91,92]; respiratory distress syndrome [93], bronchopulmonary dysplasia [94], and enterocolitis [95] were associated with lower 25(OH)D levels at birth. **Table 10** summarizes RCTs on native vitD supplementation in preterm infants [96–103]. VitD intake through feeds varies greatly in preterm infants, from 2 (unfortified human milk) to 250 IU per day depending on the formula or the human milk fortifier chosen [104]. Despite supplementation and nutritional support, rickets and metabolic bone disease are still observed in 8–50% of preterm infants at term corrected age (CA) [105–108].

Various results have been described in response to vitD supplementation of preterm babies: with 400 IU/day, 25(OH)D at term CA was <50 nmol/L in 65% of infants in India [90,99], while it was only 14% at 7 weeks CA in Ireland [109]. With 800–1000 IU/day supplementation, 25(OH)D deficiency was less frequent but still present [96,103,110].

Beside preventing rickets, the challenge is also to avoid the onset of hypercalciuria and subsequent nephrocalcinosis, which is multifactorial in this particular population [111]. About 8% of children who received 400 IU/day had 25(OH)D levels >125 nmol/L at 6 weeks CA [109]. The majority of infants born before 28 weeks who received 1000 IU/day displayed 25(OH)D levels >150 nmol/L at 28 days of life [97]. Lastly, despite serial measurements and therapeutic adjustment of doses, 25(OH)D levels were found to be >125 nmol/L in 19% of preterm infants at 34 weeks CA [112]. A retrospective study found the threshold of 120 nmol/L for hypercalciuria and/or hypercalcemia [113], which was further confirmed prospectively (submitted data). Even though the level of evidence is low for optimal upper 25(OH)D levels in premature babies, and notably between 120 and 150 nmol/L, we suggest using 120 nmol/L in regards to the risk of hypercalciuria.

Data are scarce to establish post-discharge recommendations. Normal 25(OH)D levels have been characterized in 6-month-old infants who received supplementation of 1000 IU/day [114]. One study suggested a lower incidence of wheezing before 12 months in babies who were randomly assigned to 400 IU/day of supplementation [115]. For infants with abnormal 25(OH)D levels at NICU discharge, personalized supplementation may be discussed.

10.2. Consensus statements

30. We recommend optimizing nutritional calcium and phosphate intakes in premature neonates.

31. We suggest that, during the initial stay in the NICU, preterm infants receive between 600 IU and 1000 IU per day of vitD, taking into account the content of vitD in milk and parenteral nutrition, vitD supplementation during pregnancy, and birth weight.

32. We recommend measurement of 25(OH)D in children born before 32 weeks of gestation or weighing less than 1500 g at 1 month of age.

33. We recommend 50 nmol/L as the lower target level and 120 nmol/L as the upper target level of 25(OH)D in premature neonates.

Table 10
RCTs of vitD supplementation in preterm neonates.

Authors	Year	Population	Methods	Results
Natarajan et al.	2014	96 infants 28–34 weeks GA, India	400/800 IU/day	VitD deficiency less frequent in the 800-IU group at 40 weeks CA (38.1% vs. 66.7%) and at 3 months (12.5% vs. 35%), no difference at 3 months in bone mineral content, no nephrocalcinosis
Fort et al.	2016	100 infants 23–27+6/7 weeks GA, USA	200/400/1000 IU/day	25(OH)D above 150 nmol/L at 28 days of life in the majority of 1000-IU infants (median, 25(OH)D 212 nmol/L), 0% under 50 nmol/L, versus 41% in the group with 200 IU/D and 16% with 400 IU/day
Backström et al.	1999	39 infants born below 33 weeks GA, Finland	200 IU/kg to a maximum of 400 IU/day vs. 960 IU/day	25(OH)D higher at 6 weeks in the 960-IU group, more respiratory distress syndrome in the 200-IU/kg group. No difference in bone mineral content at 3 and 6 months
Mathur et al.	2016	50 infants with BW <1500 g, GA<37 weeks, 90% IUGR, India	400 vs. 1000 IU/day	25(OH)D and blood calcium significantly higher and alkaline phosphatase significantly lower at 6 weeks in the 1000-IU group. Increased weight and length, less skeletal hypomineralization
Alizadeh Taheri et al.	2014	60 infants born below 2000 g and below 37 weeks GA, Iran	200 vs. 400 IU/day	No significant difference in 25(OH)D or in radiological evidence of rickets
Tergestina et al.	2016	99 infants born between 27 and 34 weeks GA, India	400 IU/1000 IU	VitD deficiency 65% versus 2%, 9.8% in the 1000-IU group had 25(OH)D above 70 ng/mL
Anderson-Berry et al.	2017	32 infants 24–32 weeks GA, USA	400 vs. 800 IU/day + parenteral vit D and milk content	25(OH)D is higher in the 800-IU/d group at 4 weeks, BMC is more frequently below the 10th percentile in the 400-IU group (56 vs. 16%)
Al-Beltagi et al.	2020	96 infants born between 28 and 36 weeks GA with respiratory distress syndrome, Egypt	Milk or parenteral content only/400 IU/800 IU	Duration of hospitalization shorter and complications less frequent in the group supplemented with 800 IU
Bozkurt et al.	2017	121 born before 32 weeks GA, Turkey	400 vs. 800 vs. 1000 IU/day	Average 25(OH)D concentrations at 36 weeks CA significantly higher in 800 IU (40±21 ng/mL) and 1000 IU groups (43±19 ng/mL) when compared to 400-IU group (29±13 ng/mL).

VitD: vitamin D; RCTs: randomized clinical trials; CA: corrected age; GA: gestational age; BW: birth weight; IUGR: intrauterine growth retardation; BMC: bone mineral content.

Table 11
Key research questions.

	Research questions
Physiology and assays	- What are the molecular and cellular mechanisms underlying 1,25D3-dependent calcium homeostasis? - Are extraskeletal effects observed in adults also applicable in children? - Is CYP27B1 regulated in the same way in children as in adults in all the target cells? - What other metabolites of vitD are interesting to evaluate?
What are the target levels of 25-D levels?	- Are adult data adaptable to children?
What should the supplementation schedule be in general pediatric populations?	- How should data be adapted from RCTs conducted in vitD-deficient subjects in general pediatric populations? - Could the weekly supplementation be used in general pediatric populations? - What are the real-life data (insurance database)?
Which risk factors increase vitD dose?	- What would be the ideal vitD supplementation protocol in obese children, depending on their ethnicity? - How should data be adapted from RCTs conducted in vitD-deficient subjects in general pediatric populations?
Which risk factors decrease vitD dose?	- What is the optimal schedule of vitD supplementation and monitoring in children and teenagers with hypercalciuria and nephrolithiasis?
Nutritional calcium	- How should the variability of calcium absorption be evaluated in children? - Is there a reliable laboratory parameter to assess calcium status and to recommend calcium supplementation in the case of deficiency?
VitD supplementation in premature babies	- What is the role of C3 epimerization in neonates and pregnant women? - What is the optimal schedule of vitD supplementation and monitoring in premature babies? - What is the ideal upper target of 25(OH)D levels in premature babies for bone outcomes but also global outcomes? - What is the exact frequency of vitD deficiency and overdose in very preterm infants?
Overseas territories	- Establish data on vitD status and needs for supplementation in overseas territories

VitD: vitamin D.

34. After discharge from the NICU, we suggest following recommendations in general pediatric populations.

11. Vitamin D supplementation in French overseas territories

11.1. Evidence and rationale

There are no data on vitamin D status and supplementation of children from French overseas territories, whether from northern (e.g., Saint Pierre et Miquelon) or southern (e.g., Guiana, Antilles, Reunion Island, Tahiti, Mayotte) territories. Requirements for vitD supplementation notably depend on sunlight exposure, skin coloration, food contents, and individual genetic factors. Nutritional factors (such as calcium intake and phytate content), obesity, exclusive breastfeeding, and socioeconomic background may vary between Metropolitan France and the different overseas territories.

The current recommended dietary allowance for vitD (600 IU/day) may be inadequate in children residing in higher latitudes during winter to maintain 25(OH)D concentrations ≥20 ng/mL [40]: vitD intakes needed to maintain serum 25(OH)D concentrations at 12, 16, and 20 ng/mL in 90% of the children were 581, 1062, and 1543 IU/day, respectively. Systematic enrichment by vitamin D in food should also be taken into account, for example in Saint Pierre et Miquelon.

Skin pigmentation and genetic factors are also crucial for vitD metabolism, with a poor vitD status in many African-American children [116,117], with significantly decreased free and bioavailable 25

(OH)D [118]. In southern areas, two situations carry a risk of 25(OH)D deficiency: either children with dark skin or Caucasian/Asian children using sunscreen to protect their skin against the risk of melanoma and skin cancer.

11.2. Consensus statements

35. We suggest the same pattern of supplementation as in Metropolitan France.

12. Conclusion

We propose 35 CPPs on vitD/calcium supplementation in general pediatric populations. The overall policy of vitD supplementation must remain the prevention of nutritional rickets, but the "neither too much nor too little" rule should also avoid renal toxicity in the long term. Like other national and European guidelines, we propose daily supplementation of vitD. However, in case of poor adherence, we also propose an alternative protocol with intermittent administrations. New behaviors favoring the use of "more natural" over-the-counter forms of native vitD increase the risk of intoxication and misuse. Nevertheless, to prevent rickets and optimize bone health and peak bone mass, it is critical to provide all children aged 0–18 years with native vitD and adequate nutritional calcium intake, and to promote physical activity, in the setting of a shared clinical decision with the child and his/her parents. In the long term, it remains to be demonstrated whether vitD supplementation in children also has beneficial extraskeletal effects. Lastly, suggestions for research in the field are proposed (**Table 11**).

Supplemental Table 1: Literature review

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Data sharing statement

Data sets and systematic literature review analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declaration of Competing Interest

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Supplementary materials

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