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Summary of the new 2022 recommendations of the Italian Society for Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS) for the management of vitamin D deficiency

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INTRODUCTION

In light of new scientific findings, the Italian Society of Mineral Metabolism and Skeletal Diseases (SIOMMMS) believed that there was a need to revise and update its original 2011 recommendations on the definition, prevention, and treatment of vitamin D deficiency in adults using a GRADE/PICO 1 system approach [1].

In recent years, there has been a steady increase in prescriptions for 25(OH)D serum level screening and for the use of vitamin D supplements.

In 2019, AIFA (Italian Medicines Agency), in Note 96, set out to regulate the reimbursement of these prescriptions, in an attempt to curb their consumption and costs, with no appropriate grounds [2,3]. A multidisciplinary task force was set up to provide clinical guidelines with the following main objectives: a) to make the management of vitamin D deficiency appropriate by improving and standardising "clinical practice"; b) to provide patients with indications for the most appropriate treatment, to be followed uniformly at national level; and finally c) to ensure an evidence-based reference for national and regional institutions and agencies. Several key points were addressed. Some of these suggested a marked change in behaviour in clinical practice, including a new definition of vitamin D status with deficiency and optimal values varying depending on the population involved [4]. For methodological aspects related to the search for corroboration and the drafting of levels of evidence and recommendations please see the original publication [4].

QUESTION 1. VITAMIN D STATUS DEFINITION: DEFICIENCY AND OPTIMAL VALUES

Serum levels of 25(OH)D vary widely throughout life, depending on the season, the latitude, the degree of exposure to sunlight, phototype and body mass index (BMI). In addition, one should always consider the high variability linked to chemiluminescent immunoassay screening, which can vary between 10-20% intra-screening and inter-laboratory. On the other hand, there is unanimous agreement that 25(OH)D values < 10 ng/mL are a condition of severe deficiency, which, if prolonged over time, leads to rickets and osteomalacia, whilst consensus on what can be considered "normal" simply does not exist. SIOMMMS recommends a level that can be deemed "optimal" or "desirable", which has been defined as the value that has been shown to be effective in preventing or correcting diseases of the bone such as fragility. A distinction should also be made between the recommendations for the general population and the guidance given to those who are at risk of vitamin D deficiency or who need anti-fracture drug therapy. There is consensus on the association between serum 25(OH)D values <20 ng/mL and increased fracture risk [5] among the general population. Recent meta-analyses have revealed that for values < 20 ng/mL (50 nmol/L) there is a 40 per cent increase in femoral fracture risk for each standard deviation decrease in 25(OH)D levels, whilst for values above 20 ng/mL, supplementation does provide additional benefit [6]. Therefore, among the general population the following definitions for 25(OH) levels have been set out: "defi-

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TABLE I.

a. Definition of vitamin D status in the healthy general population

	Deficient	Insufficient	Optimal
General population	< 10 ng/mL	< 20 ng/mL	Between 20 and 50 ng/mL

b. Definition of vitamin D status in the population at risk of vitamin D deficiency or who are on medication for osteoporosis

	Deficient	Insufficient	Optimal
Population at risk of low vitamin D* or requiring osteoporosis medication	< 10 ng/mL	< 30 ng/mL	Bet 30 & 50 ng/mL

The reported cut-off values must be considered with a margin of variability of ±10%, considering the variability analysis of the 25(OH)D dosage.
Furthermore, due to the seasonal variability of 25(OH)D levels, the value determined in late winter/early spring is indicative. From ng/mL to nmol/L: ng/mL x 2.5. * The population at risk of vitamin D deficiency is shown in Table II.

TABLE II.
Population/condition at risk of vitamin D deficiency.

- Elderly (≥ 75 years)
- Institutionalised subjects or conditions associated with inadequate exposure to sunlight
- Obesity
- Pregnancy and breastfeeding
- Metabolic bone diseases and other skeletal disorders
- Vegan diet
- Anorexia nervosa
- Chronic renal insufficiency
- Cancer (especially breast, prostate and colon)
- Diabetes mellitus type 2
- Intestinal malabsorption and bariatric surgery
- Drugs that interfere with the absorption or liver metabolism of vitamin D (antiepileptics, glucocorticoids, AIDS antivirals, anti-fungal agents, cholestyramine)
- Cystic Fibrosis

cient" <10 ng/mL, "insufficient" if < 20 ng/mL and "optimal" if between 20-50 ng/mL [4] (Tab. Ia). Conversely, among patients with osteoporosis, especially those treated with drugs for osteoporosis therapy, as well as among individuals at risk of vitamin D deficiency (shown in Table II), a value of at least 30 ng/mL is indicated as being "optimal" This value has been associated with significant reductions in femoral fracture risk among women who are institutionalised and a 4.5-fold improved response among subjects treated with bisphosphonates [7] (Tab. Ib).

QUESTION 2. WHO ARE THE SUBJECTS AT RISK OF VITAMIN D DEFICIENCY?

There are many clinical and lifestyle conditions that expose individuals to much higher risks of vitamin D deficiency than are found in the general population. These are listed in Table II. With respect to the classic risk conditions indicated in other international guidelines, SIOMMMS has updated its list to include subjects who maintain a vegan diet or those with anorexia nervosa. Whilst those patients with cancer of the breast, prostate or colon, and those with diabetes [4] are especially at risk. The categories of subjects included in this list should all have "optimal" levels of 25(OH)D that are at least 30 ng/mL.

QUESTION 3. IS IT APPROPRIATE TO GIVE THE GENERAL POPULATION 25(OH)D ASSAYS?

Assays of serum levels of 25(OH)D have shown a dramatic increase over the last decade worldwide. Clearly, this has increased healthcare expenditures inappropriately. Currently, there is no evidence that "universal" vitamin D level screening is useful, nor has it been shown to be helpful in ensuring greater success in vitamin D supplementation [8,9]. Therefore, at this stage, it is being recommended that extensive screening of 25(OH)D levels in the general population not be implemented, since there is, as yet no evidence that this represents any benefit,4 which is in agreement with most of the guidelines in this field.

QUESTION 4. ARE 25(OH)D LEVEL ASSAYS APPROPRIATE AMONG POPULATIONS AT RISK FOR VITAMIN D DEFICIENCY OR WHO ARE TO BEGIN OSTEOPOROSIS DRUG THERAPY?

Although most guidelines highly recommended serum 25(OH)D level screening among individuals who have been defined as being at risk for vitamin D deficiency, there is no direct evidence to support this recommendation [4]. Furthermore, there is no evidence that basal assessment of 25(OH)D levels is a predictor of the risk of toxicity during supplementation or that it can be used to determine the dosage of vitamin D to be administered [10]. At the same time, many studies have shown that supplementation with high doses of vitamin D is safe even in subjects with 25(OH)D levels > 20 ng/mL. Therefore, it has been suggested that among patients with conditions or diseases at risk of vitamin D deficiency, 25(OH)D levels should not be measured indiscriminately. It has also been proposed that basal 25(OH)D levels should not be measured routinely in patients who are candidates for bone fragility drug treatment, since this is mandatory regardless of basal values. If anything, it would be useful to check whether "optimal" 25(OH)D levels have been achieved once supplementation has begun [4].

QUESTION 5. HOW SHOULD VITAMIN D BE SUPPLEMENTED?

There is no single fixed supplementation dose for everyone who needs vitamin D. For supplementation, an oral dose between 800 IU and 2,000 IU/day of cholecalciferol is recommended [11].
A supplementation programme is suggested, which may be daily, weekly, or monthly, adjusting the dose to be administered to the time interval of the schedule adopted.
It is recommended that divided doses not be used beyond 30 days. The bolus dose of 100,000 IU of cholecalciferol in one day (in a monthly schedule) should not be exceeded. The dose of cholecalciferol administered to obese subjects should be increased by about 30 per cent compared to the dose administered to individuals with a normal BMI.
An adequate intake of calcium (800-1,000 mg/day) through the diet or supplements

TABLE III.
Synopsis of recommendations, degree of evidence and strength of recommendation.

Question and Recommendation	Level of evidence
1. Should biochemical assessment of serum 25(OH)D levels be conducted in the general population?	
It is recommended that the 25(OH)D screening in the general population not be done	⊕
2. Should serum 25(OH)D levels be determined in the population at risk of vitamin D deficiency?	
It is suggested that 25(OH)D levels not be indiscriminately measured in patients with conditions or diseases at risk of vitamin D deficiency	⊕⊕
It is recommended that 25(OH)D levels be measured only when it has been deemed necessary for the patient's clinical management (i.e., when osteomalacia is suspected)	⊕⊕
3. Should a determination of serum 25(OH)D levels be made in specific categories of subjects/patients at risk (Table II)?	
It is suggested that baseline 25(OH)D levels should not be routinely assessed in patients who are candidates for pharmacological treatment for osteoporosis or other metabolic bone disorders (which are perforce associated with vitamin D supplementation), unless osteomalacia is suspected	⊕⊕
4. How should vitamin D be supplemented in individuals with vitamin D deficiency or candidates for pharmacological treatment with anti-fracture drugs?	
A supplementation dose of cholecalciferol between 800 IU/day and 2,000 IU/day is suggested. There is no single fixed dose for all subjects to be supplemented	⊕
A daily, weekly, or monthly schedule based on the dose administered is suggested. The maximum single daily dose to be administered must not exceed 100,000 IU.	
An adequate intake of calcium (800-1,000 mg/day) should always be ensured	⊕
An initial loading dose followed by a maintenance dose is suggested in patients with symptomatic osteomalacia and/or 25(OH)D levels < 10 ng/mL or in patients starting intravenous bisphosphonate therapy or denosumab with 25(OH)D < 20 ng/mL	⊕⊕⊕
We suggest, as a loading dose, cholecalciferol 3,000-10,000 IU/day (average 5,000 IU/day) for 1-2 months, or cholecalciferol in a single dose of 60,000 to 150,000 IU followed by the maintenance dose (2,000 IU/day)	⊕⊕⊕
Alternatively, calcifediol 20-40 mcg/day (4-8 drops/day) for 20-30 days is suggested, before switching to the maintenance dose with cholecalciferol**	
5. Should vitamin D be supplemented in the general population?	
It is recommended that vitamin D supplements not be administered to the general population, as there is no definite evidence of favourable cost-effectiveness, either on mortality or on skeletal and extra-skeletal effects	⊕⊕⊕
6. How should vitamin D be supplemented in patients with impaired renal function?	
It is recommended that patients with CKD-MBD correct vitamin D deficiency with cholecalciferol in the same manner as in the general population with normal renal function	⊕⊕⊕⊕
It is recommended that the use of active vitamin D compounds (calcitriol or synthetic analogues) be limited to individuals on dialysis or to patients with CKD stages G4 and G5 with severe and progressive hyperparathyroidism	
7. How should vitamin D be supplemented in subjects suffering from severe liver failure or therapies that interfere with vitamin D metabolism in the liver?	
Supplementation with at least 2,000 IU/day of cholecalciferol is suggested patients with severe liver failure or in the case of chronic therapies that interfere with vitamin D metabolism in the liver. The use of calcifediol is a possible alternative	⊕

* The recommendation is restricted to achieving a more rapid normalisation of serum 25(OH)D levels.
Strength of the recommendation: suggested/not recommended: positive/negative weak; recommended/not recommended: positive/negative strong.
Level of evidence: ⊕ very low, ⊕⊕ low, ⊕⊕⊕ moderate, ⊕⊕⊕⊕ high.

should always be ensured. An initial loading dose followed by a maintenance dose is recommended for patients requiring rapid normalisation of vitamin D levels (symptomatic osteomalacia or in those who are to start using zoledronic acid or denosumab). As a loading dose, we recommend 3,000-10,000 IU/day (mean 5,000 IU/day) of cholecalciferol for 1-2 months or a single dose of 60,000 to 150,000 IU of cholecalciferol followed by a maintenance dose (2,000 IU/day) [4,12]. Alternatively, calcifediol 20-40 mcg/day (4-8 drops/day) for 20-30 days may be considered before switching to the maintenance dose with cholecalciferol.

QUESTION 6. SHOULD THE GENERAL POPULATION BE SUPPLEMENTED?

The rationale for potential supplementation of all subjects with cholecalciferol is based on considering subjects with values < 30 ng/mL as "deficient", over the potential extra-skeletal effects, the safety profile, and the low cost.

However, based on recent evidence sufficient conclusions for an advantage in supplementation among the general population cannot currently be drawn (among subjects excluded from Table II) [13]. Therefore, it is recommended that the general population not at risk of vitamin D deficiency not receive supplements.

QUESTION 7. SHOULD SUBJECTS WITH RENAL IMPAIRMENT BE SUPPLEMENTED WITH VITAMIN D AND HOW?

In renal impairment, reduced 25(OH)D levels limit the availability of the substrate for renal hydroxylation to calcitriol, thus exacerbating the effects of reduced hydroxylation to $1,25(OH)_2D$. This results in secondary hyperparathyroidism. Vitamin D supplementation can normalise 25(OH)D levels and reduce PTH levels whilst improving bone mineralisation in renal impairment. The same supplementation indications suggested for the general population [14] are suggested for these cases.

The use of cholecalciferol is recommended, whereas the evidence is limited for calcifediol. [14] It is recommended that the use of active vitamin D compounds (calcitriol or synthetic analogues) be limited to individuals on dialysis or for patients with CKD stages G4 and G5 with severe and progressive hyperparathyroidism [14].

QUESTION 8. HOW TO SUPPLEMENT PATIENTS WITH LIVER FAILURE OR THOSE IN THERAPY WITH DRUGS THAT INTERFERE WITH VITAMIN D METABOLISM IN THE LIVER?

Reduced 25(OH)D levels are common in patients with chronic liver disease (CLD) not only due to a deficiency in 25-hydroxylation or to increased catabolism of calcifediol, but due to multiple conditions, including malnutrition, reduced sun exposure, malabsorption, and reduced D-Binding Protein synthesis [4].

The importance of reduced 25-hydroxylation seems to be limited to the more advanced stages of liver failure [15]. Vitamin D supplementation is also necessary in the case of the administration of many drugs that interact with vitamin D metabolism in the liver, such as antiepileptics (carbamazepine, phenobarbital, dintoin), but also glucocorticoids, anti-neoplastic agents, antiretrovirals, and anti-tubercular antibiotics. Supplementation with at least 2,000 IU/day of cholecalciferol is recommended for patients with severe liver failure or in the case of chronic therapies that interfere with vitamin D metabolism in the liver. The use of calcifediol is a possible alternative although evidence of any advantage is limited [4].

QUESTION 9. WHAT IS ITS SAFETY PROFILE AND LEVEL OF TOXICITY?

The "classic" manifestations of vitamin D intoxication, such as hypercalcaemia and hypercalciuria, are to be considered exceptional with the administration of cholecalciferol and may only occur with 25(OH)D levels around or above 150-200 ng/mL [16]. Toxicity may occur more frequently, even with recommended dosages, with calcitriol or alfacalcidiol (per SPC). Among the "non-classical" toxicity effects, the risk of falling has been indicated in some studies. Though the data are contradictory and limited to high bolus doses and in institutionalised subjects, in those subjects deficient in vitamin D, the effect of normalisation (to 30 ng/mL) appears to be protective against falls [17].

CONCLUSIONS

These recommendations on how to manage vitamin D deficiency in Italy have been based on the most solid scientific findings currently available. This advice, which was generated through the use of rigorous methodology, is mainly directed at physicians so that they can address this widespread issue with evidence-based appropriateness, whilst perhaps being able to offer some improvement on the standard of approach to the problem. Though some of these recommendations are consistent with other guidelines there are some points that offer a new approach, such as the personalisation of optimal levels. These recommendations have focused on the skeletal effects of vitamin D in at-risk populations. Extra-skeletal effects were deliberately not addressed, whilst the lack of clear benefits in supplementation of healthy populations can, for now, be confirmed.

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