RATIONALE FOR THE DEFINITION OF THE STATUS OF VITAMIN D: NORMAL AND OPTIMAL VALUES

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Vitamin D levels vary through different stages of life and according to season, latitude, degree of sun exposure, skin color and BMI. In addition, the analytical variability of vitamin D assay currently poses a significant difficulty, both in the field of research and in clinical practice.

Serum levels of 25(OH)D, which includes 25(OH)D2 and 25(OH)D3, are used today to determine vitamin D status, which is interpreted as the expression of the "vitamin D reserve." Serum 25(OH)D is relatively stable with a half-life of 2-3 weeks, while its activated form – 1,25(OH)2D – has a half-life of approximately 15 hours. Today, levels of 25(OH)D are normally determined by chemiluminescence immunoassay (CLIA), which has a variability – between different assays as well as inter-laboratory differences – of between 10 and 20%, such that the need for the standardization of doses is strongly felt, both for proper interpretation of clinical studies and for clinical practice [1].

The definition of normal and deficient vitamin D status is a much debated topic. While there is unanimous agreement that values of 25(OH)D < 10 ng represent a condition of severe deficiency, definitions of "normal" levels vary greatly. This factor has important repercussions both on epidemiological evaluations and on elements of clinical practice, as the question obviously influences prescriptions for vitamin D supplements.

The problem of the definition of a correct vitamin D level requires clarification of what is meant by "normal value" and by "optimal value." To identify a "normal level," reference is made to a statistic datum defined as ± 2 standard deviations (SDs) from the mean of detected values in a given population, a datum that has sparked the interest of researchers and institutions which study phenomena of the general population. In the case of vitamin D, there are different normal values for different geographical areas, age groups and seasons.

Distinct from "normal" values is the "optimal" or "desirable" level, which is defined as the value that has been demonstrated as effective in obtaining prevention of conditions related to vitamin D deficiency, such as fractures, on the basis of evidence provided by ad hoc observational and interventional studies. For this reason, Scientific Society provide a "recommended level" of vitamin D on the basis of the patient's profile and the outcome to be reached.

In 2011, the Institute of Medicine (IOM) defined values of deficiency, insufficiency and sufficiency at < 12 ng/mL, between 12 and 20 ng/mL, and between 20 and 30 ng/mL, respectively [2]. Other Scientific Society have suggested that levels of sufficiency could be represented by values ≥ 30 ng/mL (the Endocrine Society, the National Osteoporosis Foundation and the International Osteoporosis Foundation) [3]. In 2016, the Italian Society for Osteoporosis, Mineral Metabolism and Skeletal Diseases proposed a range of optimal levels at between 30 and 50 ng/mL [4].

There is solid evidence as well as unanimous agreement that 25(OH)D levels < 12 ng/mL (-30 nmol/L) are associated with rickets, osteomalacia and secondary hyperparathyroidism [5], to the extent that researchers are also in agreement that these values constitute a condition of deficiency [2-4].

More controversial, by contrast, is the definition of values of sufficiency. To determine the cutoff of 25(OH)D sufficiency, researchers have analyzed the associations between vitamin D levels and the correction of hyperpara-

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TABLE I.
Population at risk of hypovitaminosis.

- Institutionalized patients
- Conditions associated with inadequate sun exposure
- Pregnancy and breastfeeding
- Vegan diet
- Obesity
- Mineral metabolism and skeletal diseases
- Chronic renal insufficiency
- Tumors (in particular breast, prostate and colon)
- Anorexia nervosa
- Type 2 Diabetes mellitus
- Intestinal malabsorption and bariatric surgery
- Drugs which interfere with absorption or with hepatic metabolism (antiepileptic drugs, glucocorticoids, antiretrovirals AIDS, antifungals, cholestyramine)
- Cystic fibrosis
- Granulomatous diseases and some types of lymphoma

thyroidism, the intestinal absorption of calcium and several outcomes regarding skeletal health – fracture risk in particular. They have further analyzed other cutoff levels, such as those for mortality, tumors and falls.

In reality, data on optimal vitamin D levels with respect to outcomes concerning skeletal health are distributed over a range of values without a precise cutoff. Data relative to optimal 25(OH)D values on extra skeletal outcomes are even less consistent and not definable [6].

The attempt to associate the optimal 25(OH)D value to interaction with PTH does not appear convincing, because studies have found that 25(OH)D values that normalize PTH oscillate between 12 ng/mL (30 nmol/L) and 36 ng/mL (90 nmol/L) [7]. In addition, the interaction curve does not actually seem to have a real plateau point for PTH at 30 ng/mL of 25(OH)D as described; above all it varies considerably by age group and is strongly dependent on the calcium intake [8].

For the definition of an optimal level in the general population, we can take into account the association between vitamin D deficiency and fractures. There is significant consensus on the association between 25(OH)D values less than 20 ng/mL and increased fracture risk [9]. A recent meta-analysis has shown that for levels less than 20 ng/mL there is a 40% increase in femur fracture risk for each SD decrease of 25(OH)D [10]. Similarly, another meta-analysis on prospective cohort studies has reported that fracture risk is linearly reduced up to a 25(OH)D value of approximately 24 ng/mL (60 nmol/L). For values > 24 ng/mL, fracture risk ceases to decrease [11].

By contrast, there is no evidence that 25(OH)D values > 20 ng/mL are beneficial for skeletal health (BMD or fractures) in the general population. In a large randomized controlled study on healthy adults, elevated doses of cholecalciferol (equal to 100,000/IU per month) for approximately 4 years did not provide any benefit in terms of risk of fall and fracture with respect to the control group. Since 80% of the studied population had baseline values of > 25 ng/mL (60 nmol/L), these results indicate that this value is sufficient and adequate in the general population. Consequently, there is no reason for or advantage to supplementation in these subjects [12].

A recent meta-analysis on the musculoskeletal effects of vitamin D supplementation confirms these findings. Researchers have indeed concluded that there is no significant effect on BMD (bone mineral density) and fractures. Yet 55% of the studies included in the meta-analysis recruited patients with base values > 20 ng/mL (50 nmol/L), and only 6% looked at patients with levels < 10 ng/mL (25 nmol/L), again indicating that supplementation in subjects with values ≥ 20 ng/mL does not bring any benefit; this 25(OH)D level can therefore be considered adequate in the general population [13].

Another relevant aspect to be emphasized is that optimal 25(OH)D values ≥ 20 ng/mL (50 nmol/L) – that is, levels at which supplementation does not seem to produce benefits – refer to the normal population, in other words, to healthy subjects outside of institutional settings, persons who do not show the classic conditions of high risk of hypovitaminosis (Table I). These "healthy" persons often represent the majority of subjects included in prospective population studies and randomized trials in which supplementation with cholecalciferol did not produce clinically significant results. In a wide-ranging meta-analysis of 9 randomized controlled trials (RCTs) on healthy adult subjects – who were indeed selected because they did not have osteoporosis, fractures or a risk of fall and did not use osteopenia drugs – cholecalciferol supplementation with doses from 700 to 3,000 IU/day did not have any effect on fractures, mortality or morbidity [14].

The definition of a correct target of 25(OH)D values and of the categories of subjects in which supplementation is appropriate is therefore fundamental in order to prevent an excessive use of supplements in a broad sector of the population, which in particular will not receive any benefit from them [15]. The lack of such definitions has had the harmful result that vitamin D has been uncritically included among overused drugs and supplements and has attracted the attention of national regulatory agencies [16].

There is also general agreement as well as evidence that vitamin D supplementation is indispensable in subjects at risk of hypovitaminosis (Table I) and in those being treated with drugs able to reduce fracture risk (antiresorptive and anabolic).

In the RCT meta-analysis in which the overall effect of vitamin D supplements (with or without calcium) on fractures seems negative, researchers observed a significant benefit in terms of fracture risk reduction in the subgroup of patients who were either institutionalized or had previous fractures [13], a conclusion also supported by ESCEO and IOF [17].

In the RCT meta-analysis on vitamin D supplementation, those trials which showed an outcome of reduced femur and non-vertebral fracture risk saw significant reductions – 20% for non-vertebral and 18% for femur fractures – in subjects that reached 25(OH)D values > 30 ng/mL (75 nmol/L) [18, 19].

Today, we are paradoxically witnessing widespread vitamin D supplementation in population sectors that receive no advantage from it, while supplementation is not used by subjects who by contrast would benefit greatly, such as those at risk of fracture undergoing therapy with drugs for osteoporosis. Drugs for fracture risk reduction (which in Italy appear on the *Nota 79* list) were always associated with vitamin D supplements in the observational RCTs. A lack of vitamin D supplementation in association with these drugs significantly reduces the latter's anti-fracture effect, therefore worsening the cost-benefit relationship of the drugs themselves [20, 21]. Failure to combine anti-fracture drug therapies with vitamin D intake is the major cause of repeated fractures [22]. For this reason, it is crucial to assure that cholecalciferol supplementation accompanies any type of specific therapy for osteoporosis and also to guarantee that levels reach at least the optimal value of ≥ 30 ng/mL.

The upper limit of optimal values in the general population has been defined at 50 ng/mL (125 nmol/L) on the basis of some data that show a "U-shaped" tendency on several outcomes, such as falls and mortality,

TABLE II.
Definition of vitamin D status.

	Deficiency	Insufficiency	Optimal
General population	< 10 ng/mL	< 20 ng/mL	20-50 ng/mL
At-risk population*	< 10 ng/mL	< 30 ng/mL	30-50 ng/mL

*At-risk population for hypovitaminosis is shown in Table II. These values also apply to those subjects who are to begin or are undergoing anti-fracture therapy for osteoporosis. Multiply ng/mL by 2.5 to obtain values in nmol/L.

suggesting that beyond these values pathological events could reoccur. Thanks to the standardization of 25(OH)D doses, a recent study has shown that the curve between vitamin D levels and mortality is not U-shaped by rather flat ("J-shaped"). The plateau occurs at values of approximately 18-20 ng/mL (40-44 nmol/L) [23]. This finding indicates that in the general population reaching 25(OH) D levels far above 30 ng/mL is not particularly useful, even if it is relatively safe.

In conclusion, the definition of optimal 25(OH)D levels is fundamental, as it has repercussions not only on epidemiological estimates but also on daily clinical practice. In the general population, including in elderly subjects who are substantially healthy, a 25(OH)D value ≥ 20 ng/mL (50 nmol/L) should be considered adequate, while in patients with osteoporosis especially if they are undergoing therapy with a *Nota 79* drug, a value ≥ 30 ng/mL (75 nmol/L) should be considered optimal (Tab. II).

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