Perspective on the clinical practice management of hypovitaminosis D from a meeting of Italian experts

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Summary

Scientific interest in the clinical aspects surrounding vitamin D has increased exponentially in recent years. Unfortunately, this interest is not currently associated with a proportional level of consensus. Indeed, the large number of studies in this field, which are often of low quality and secondary importance (and have recently been defined as “research waste”), has confused even experts and driven them towards controversial positions. Consequently, there are differences in the currently available guidelines and recommendations on vitamin D supplementation issued by various governments and scientific societies. To shed light on this topic, we arranged a meeting with the aim of collecting the opinions of 50 experts in different specialties (“D Battito Group”), including internists, endocrinologists, rheumatologists, pediatricians, geriatricians, dermatologists, gynecologists and nephrologists. This meeting dealt with specific questions regarding the management of hypovitaminosis D and aimed to investigate the opinions of Italian experts on this topic. Most participants were affiliated with Italian university centers. Six key questions were addressed in the meeting. After a short lecture and a 30 minutes discussion, all the experts expressed their opinions, which were recorded together with any specific commentary. The present paper summarizes the opinions and controversies encountered and addressed during the meeting.

KEY WORDS: vitamin D; supplementation; osteoporosis; fractures.
A search of the PubMed database for “vitamin D” yielded a huge list of papers, of which a large proportion has been published in the last 25 years. From an analysis, we can observe that:

- Fewer than 1000 papers had been published before 1993.
- The number of the published papers exceeded 2000 in 2009.
- The number of published papers doubled in 2014 to more than 4000.
- In 2018 alone, 2500 new manuscripts have been listed in PubMed from January to June.

Clearly, scientific interest regarding vitamin D is strong and rapidly increasing. Unfortunately, this interest is accompanied by some misconceptions and misinterpretations (1, 2). Indeed, the great expansion in published studies, which are often of low quality and secondary importance [and even recently addressed as “research waste”(3, 4)], has led to a certain degree of confusion and controversial positions even among experts (1, 2). For instance, some Authors and opinion leaders strongly support a role for vitamin D and consider its supplementation pivotal in many diseases, nearly to the level of a “panacea” (i.e., overstate the extra-skeletal effects). However, many other Authors endorse vitamin D as playing an exclusive role only in bone diseases (i.e., underestimate the extra-skeletal effects).

These controversial positions largely affect the degree of consensus achieved when comparing the available guidelines and recommendations regarding vitamin D supplementation that have been issued by various governments and scientific societies (5-11). Currently, even the definition of the optimal vitamin D status remains under debate, and the recommended doses and schedule of supplementation vary widely, reflecting the lack of agreement regarding the minimal desirable serum concentration of 25OH-vitamin D (25OHD). The health benefits of vitamin D administration and the serum threshold required to obtain these benefits remain (2).

The current risk is that healthy subjects without any special requirement might be actively receiving vitamin D supplementation, whereas too many fragile subjects who require supplementation fail to obtain it. From a real-life perspective, we allegedly aim to encourage an increase in vitamin D supplementation to prevent clinical conditions beyond skeletal disease; however, this approach is not supported by solid evidence and often disregards the recommendations of the available guidelines.

**Italian meeting: “D Battito”**

Vitamin D is a topic of considerable confusion also in Italy, and the issue involves not only public opinion, but also health authorities and physicians. To shed light on this topic, we arranged a meeting with the aim of collecting the opinions of 50 experts in different specialties, including internists, endocrinologists, rheumatologists, pediatricians, geriatricians, dermatologists, gynecologists and nephrologists. The meeting addressed specific questions regarding the management of hypovitaminosis D and intended to summarize the opinions of Italian experts on this topic. Most participants were affiliated with Italian university centers. Six key questions were addressed in the meeting. During a short lecture (10 minutes), two different opinion leaders summarized the pros and cons of each issue based on evidence available in the literature. After a subsequent thirty minutes discussion, all the experts, who had been previously divided in five groups of 10 participants each, expressed their opinions, which were recorded together without any specific commentary.

**Questions addressed during the debate**

1: **Appropriateness of serum 25OH-vitamin D assay (Figure 1 A)**

Results: 40% (20/50) of the participants agreed that a baseline measurement of serum 25OHD is essential for identifying patients who need supplementation; the remaining 60% (30/50) stated that this assay should be performed only in selected cases. Comments: We must consider that all involved participants were experts who had worked in secondary or even tertiary clinics.

However, none of those who favored the 25OHD testing agreed on a whole-population screening, given the high cost of this strategy. In their opinion, this measurement should be selectively recommended in all the patients affected by the most severe form of bone metabolic diseases, including severe osteoporosis. On the contrary, the majority (60%) considered the test indicated only in selected cases, such as those involving conditions with a potential risk of toxicity (e.g., primary hyperparathyroidism, granulomatosis) in subjects who developed fractures despite effective pharmacological treatment, and in those with bone diseases, musculoskeletal symptoms or other conditions (e.g., myopathy, osteomalacia or rickets) attributable to vitamin D deficiency that would be likely to improve with adequate supplementation.

Given the high prevalence of hypovitaminosis D, especially in the elderly, a broad consensus was reached concerning to measure serum 25OHD a few months (i.e. 3-6 months) after starting the supplementation, with the intent to gain feedback regarding the adequacy of the administered dosage and/or the adherence to treatment. Most participants considered the high variability of the adopted laboratory assay to be a major limitation to the broadest assessment of 25OHD, as this variability could potentially bias the interpretation of the results. A standardization of the available 25OHD assays was considered to be strongly needed.

2: **Ideal threshold of serum 25OHD for bone health to be achieved: 30 ng/ml or 20 ng/ml? (Figure 1 B)**

Results: 62% (31/50) of the participants agreed that a threshold of 30 ng/ml (75 nmol/L) should be considered ideal for bone health, while the remaining 38% (19/50) recommended levels above 20 ng/ml (50 nmol/L) as adequate.

Comments: although vitamin D deficiency and its consequences are well known worldwide, the optimal concentration of serum 25OHD, even for skeletal health, remains controversial. In addition, the optimal serum levels for extra-skeletal health are far from established. Among all guidelines, a substantial consensus indicates that serum 25OH-vitamin D concentrations below 10-12 ng/ml (25-30 nmol/l) should be avoided in all age groups, as such a low level is a risk factor for rickets and osteomalacia. Worldwide, most experts agree that levels lower than 20 ng/ml (50 nmol/L) are suboptimal for skeletal health (2).

Italian experts were also divided regarding this issue. The majority (62%) considered the threshold of serum 25OHD
of 30 ng/ml (75 nmol/l) to be adequate. This is in line with the guidelines of the Endocrine Society (5) and appears to be necessary especially in patients already stratified for disease severity. Conversely, the remaining experts (38%) suggested that a concentration of 20 ng/ml (50 nmol/l) would be sufficient for healthy subjects.

3: The preferred compound for supplementation: cholecalciferol or calcifediol? (Figure 1 C)
Results: 86% (43/50) of the participants considered cholecalciferol the most suitable molecule for supplementation. The remaining 14% (7/50) considered calcifediol to be more advantageous.
Comments: there was an expected consensus regarding the use of inactive vitamin D compounds (cholecalciferol or calcifediol) for the management of hypovitaminosis D. Most participants supported cholecalciferol as the first-choice in common clinical practice. This choice was driven not only by the various treatment schedules available (daily, weekly, monthly, or less frequently), but also because correction of cholecalciferol deficiency itself is the aim of the supplementation. However, during the discussion, some experts highlighted some potential advantages of calcifediol administration. For example, oral calcifediol may produce a more rapid increase in serum 25OHD levels when compared to oral cholecalciferol, and consequently a lower dosage of the former may be required. In addition, calcifediol seems to have a higher intestinal absorption, which might guarantee significant advantages as initial treatment in patients with severe deficiency or subjects with impaired intestinal absorption due to a variety of diseases (i.e. obesity, severe liver dysfunction and concomitant use of drugs at risk for 25-hydroxylase inhibition).

4: Preferred dosing schedule for vitamin D supplementation: frequent administration (daily or weekly) or boluses (beyond weekly)? (Figure 1 D)
Results: 62% (31/50) of the participants supported the bolus approach. By contrast, 24% (12/50) preferred the frequent administration schedule. Another 14% had not a strong opinion on this issue and suggested a different schedule expressed their indifference to this question and adjusted their recommendation depending on the patients’ preferences.
Comments: during the discussion, a general agreement was reached regarding the more physiological role of the daily schedule. However, daily administration may induce compliance issues, especially in elderly patients who are often taking several drugs. This represented the main justification for supporting the intermittent administration. Commonly, a daily schedule is recommended only for infants and children. For some colleagues, especially those who declared their indifference regarding this topic, the patient’s preference was the main driver behind their decision. All participants confirmed that they would avoid doses exceeding 100,000 IU administered more often than at monthly intervals.

5: Does the available evidence sufficiently support a role of vitamin D for extra-skeletal health: yes or no? (Figure 1 E)
Results: 60% (30/50) of the participants agreed that vitamin D might have extra-skeletal effects, whereas the remaining 40% (20/50) did not consider the available evidence to be sufficient.
Comments: based on the available data, a majority of the experts supported the concept of potential extra-skeletal benefit of vitamin D supplementation, particularly in deficient states.
However, there was a general agreement on the need of further studies to support the benefits of vitamin D supplementation beyond the skeletal health. Furthermore, there is a pressing need to define the threshold of serum 25OHD concentration to be reached to achieve these benefits. For these reasons, no recommendations can be made currently regarding the use of vitamin D supplementation for the prevention and treatment of extra-skeletal chronic diseases, consistent with a recent statement by the European Society for the Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (12).

6: Efficacy of vitamin D for bone health: are observational studies sufficient or are RCTs needed? (Figure 1 F)
Results: 78% (39/50) of the participants expressed the need for RCTs, while the remaining 22% (11/50) considered the available observational studies sufficient to justify vitamin D supplementation for improving bone health.
Comments: most experts expressed the need for additional high-quality studies supporting of vitamin D supplementation in the setting of bone metabolic diseases such as osteoporosis and rickets/osteomalacia. None of the participants denied the fundamental role of vitamin D supplementation to prevent and treat rickets and osteomalacia. Rather, RCTs are needed to establish the possibility of any role for the correction of a mild or moderate deficiency for improve and/or maintain bone health in otherwise healthy adult subjects. The discussion also raised relevant doubts regarding the clinical utility of some recent studies [i.e. VIDA (13)] who mostly enrolled healthy subjects with an adequate vitamin status as defined by serum 25OHD concentration, and also of a recent meta-analysis from Bolland (14), in which trials including vitamin D-deficient patients (i.e. 25OHD <25 nmol/L) only accounted for 831/39485 (21%) of patients. Of note, this paradox has been underscored from Bolland himself, in a paper published few days after the publication of the meta-analysis (3). As vitamin D is a nutrient, its administration would be expected to produce positive effects only in deficient subjects.

Conclusions
The Italian meeting demonstrated the presence of insufficient agreement on many key questions regarding the management of vitamin D deficiency, even among clinical experts. The meeting asked the participants to make binary choices regarding some topics. However, this dichotomy likely excluded, or at least significantly reduced, the possibility of identifying specific conditions and exceptions for which the experts might have made different choices and thus favored possible further controversies. Nevertheless, this approach demonstrated that it is easy to understand which of the two answers was considered the best choice in the most common conditions. The aim of the meeting was to present a view of the Italian state-of-the-art regarding this topic, rather than to produce a position paper. The results may therefore seem a bit discouraging, as they confirm the lack of a solid consensus even among experts, regarding...
fundamental questions such as i) who should be treated?; ii) which dosages of vitamin D should be used?; iii) which is the target of serum levels of 25OHD to be reached?; iv) which are the most appropriate treatment schedule?; v) when should the serum 25OHD assay be performed? Given the growing evidence apparently questioning the usefulness for vitamin D supplementation for musculoskeletal health (14, 15), we feel the strong need to address the issue in a proper manner to avoid further confusion, and especially to avoid dangerous misinterpretation of the available data by fellow practitioners even by public health organizations. It has to be noted that most studies evaluating vitamin D supplementation to date might be considered “research waste” (3, 4). Therefore, there is also the risk that meta-analyses stemming from these studies may be tainted to a similar extent.

In conclusion, adequate and well-designed studies are needed to provide new answers to these old and yet unsolved questions. Unsurprisingly, the available data seem to point out that vitamin D supplementation in non-deficient subjects is useless; currently, no one is wishing for yet another guideline. On the other hand, the need for well-aimed and conducted studies is strongly felt, in order to finally clarify the extent of skeletal and extra-skeletal benefits of hypovitaminosis correction (and not of random widespread supplementation).

We hope that the various scientific societies will recognize and analyze the inconsistencies in their own positions and reach adequate consensus, especially on the tenets required for conducting proper and useful investigations on the topic, and that the results of these future new studies will be able to shed the needed light.

Conflict of interest

Luisella Cianferrotti has received personal fees from: Abiogen Pharma, Bruno Farmaceutici, Shire. Davide Gatti reports personal fees from: Abiogen, Amgen, Janssen-Cilag, Mundipharma, Pfizer. Angelo Fassio reports personal fees from: Abiogen Pharma, Novartis. Andrea Giusti has received research support and/or honoraria from vitamin D manufacturers: Abiogen Pharma & Internis Pharma.

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All the other Authors have no conflict of interest to declare.

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