Vitamin D: nothing new under the sun

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Even if present in small quantities, a vitamin plays an indispensable role in the normal functioning of one or more physiological processes. In general, the body is not able to synthesize these substances by itself, meaning that they have to be regularly introduced into our diets. This definition of a vitamin, in reality, largely fits the characterization of vitamin D. The heat and action of ultraviolet sun rays are in fact able to transform the 7-dehydrocholesterol present on our skin into vitamin D3 (Fig. 1). For this reason, vitamin D becomes a "true vitamin" only when humans (and any other mammals) are not adequately exposed to sunlight and therefore need to supply themselves with it through diet [1].

Another interesting point is that vitamin D (both in its endogenous form synthesized by the body in the skin and in its exogenous state through consumption) is an inactive biological composite.

Since the discovery of vitamin D last century, it has never been doubted that sunlight is able to correct and prevent rickets precisely through the production of this molecule. Yet the real mechanism with which this substance acts – even when it is taken as supplement – remained unknown for many years. Only in the 1960's and 70's was it finally understood that vitamin D actually acts as a substrate for a complex metabolic process which gives rise to a great number of metabolites through different phases of hydroxylation and the involvement of several organs (mainly the liver and kidneys) (Fig. 1). Soon after, it was shown that the hydroxylated metabolite in the 1 and 25 positions (calcitriol) was over 400 times more powerful than vitamin D (the substrate) in inducing the active transport of calcium into the intestine. It thus became clear that it indeed represented the final metabolic and biologically active stage of vitamin D (Fig. 1) [2].

Even so, the story did not come to an end at that point: the identification of the existence of a specific binding protein and therefore a receptor (the vitamin D receptor, or VDR) [3] opened new and unexpected fields of inquiry. It in fact soon became clear that the VDR receptor was practically ubiquitous. Actually, two types of VDRs have been identified. The first is located in the cell nucleus and is able to directly stimulate gene transcription and hence the *ex-novo* synthesis of proteins (the genomic mechanism). The second, meanwhile, is located on the cell membrane and acts by inducing the formation of second messengers (such as cyclic AMP and arachidonic acid) and by the phosphorylation of some cellular proteins. The latter mechanism is the non-genomic type and assures a very rapid cellular response [4]. At this point, if we consider that calcitriol has the structure of a steroid hormone and that its receptor is distributed in a great number of tissues, we can't help applying the "endocrinological" paradigm, according to which if a cell expresses a hormonal receptor, that cell must necessarily possess the ability to produce biological effects resulting from its binding hormone-receptor (in this case, then, calcitriol-VDR).

All of this explains why interest in vitamin D was no longer limited to bone metabolism only, but expanded to include the so-called extra-skeletal effects, which are linked to the important physiological role that it plays in numerous other functions in the body.

If we take a look at PubMed to search for the term "vitamin D," we notice that the quantity of published works is great indeed and that the annual total of works has grown rapidly over the last 25 years. Until 1994, fewer than 1000 works a year were published on vitamin D; over the next 15 years, this number doubled, reaching over 2000 works annually in 2009. Following that, it took only another 5 years for this figure to double again: since 2014, more than 4000 articles have appeared on this topic each year! In only the first six months of 2018, the number has already reached 2500.

Nonetheless, this great interest has not – as so often happens – created a shared culture

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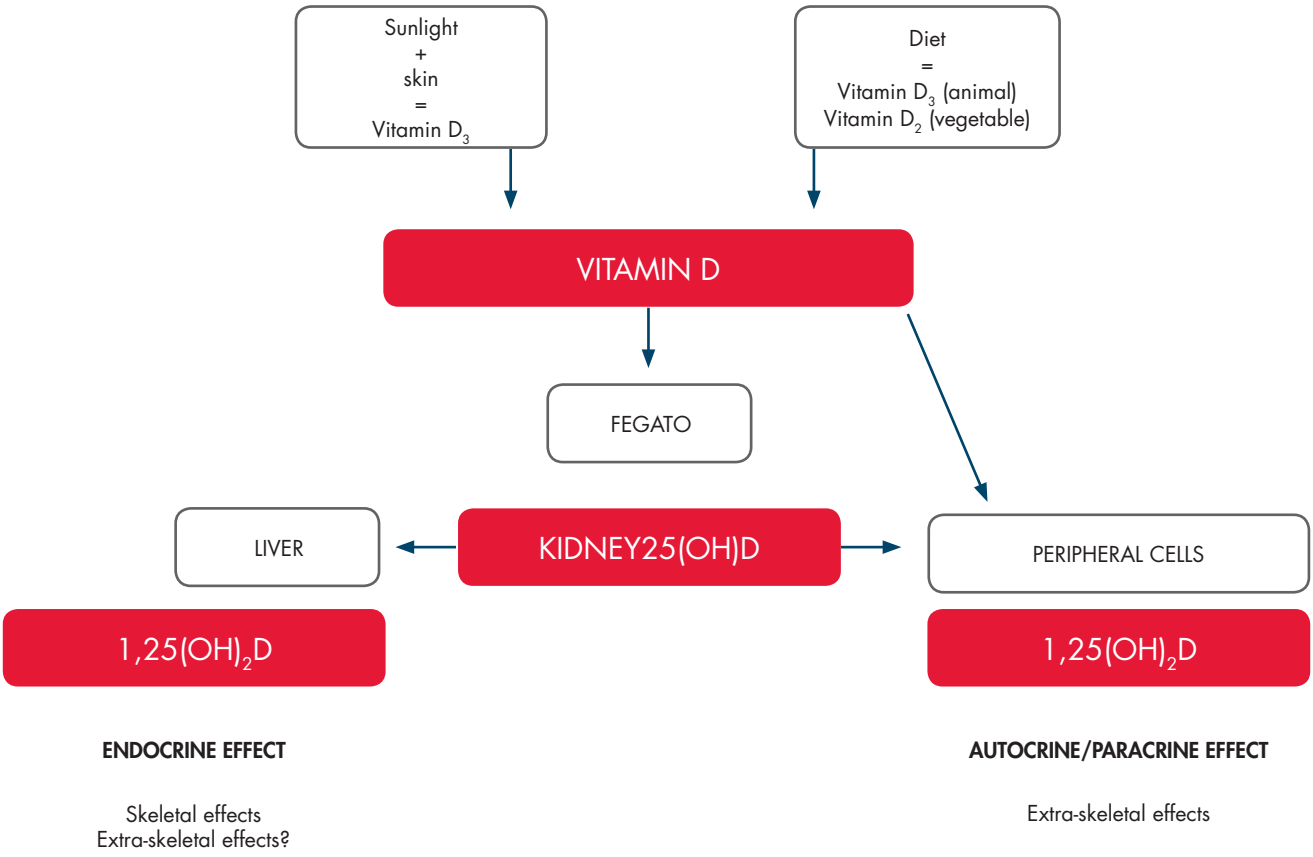

VITAMIN D: inactive substrate; 25(OH)D: inactive metabolite; vitamin D status marker.
1,25(OH) 2D: active metabolite that produces its biological effects by binding to VDR.

FIGURE 1.
Metabolic steps of vitamin D activation and biological effects.

based on objective data. This proliferation of studies, which are often of poor quality and focus on marginal questions, has ended up producing even more confusion, creating positions which are often contradictory, even among experts and scientific societies. Unfortunately, we often find ourselves having to accommodate positions based on biases, which can be extreme and quite contrasting, between those who wish to see this vitamin as a panacea for all illnesses (overestimating its extra-skeletal effects) and those who rather limit themselves to acknowledging an exclusive role, usually only for circumscribed metabolic problems regarding bone conditions (rickets and osteomalacia).

In reality, there can be no doubt that vitamin D carries out actions that are not limited to calcium absorption. Vitamin D is involved in the regulation of 3% of human genes, while many cells have an enzymatic apparatus able to locally convert vitamin D into the 25(OH)D metabolite and/or 25(OH)D into calcitriol, with paracrine and autocrine regulatory effects on proliferation, differentiation and cellular function [5]. Having said this, we should emphasize that at the moment we do not have certain data which give us an idea of the ideal necessary levels to be able to take advantage of these positive effects; nor do we possess any convincing interventional studies which can assure us as to the modes, doses and duration of treatment that might be considered optimal. For this reason, and in total accord with what has been recently stated in an interesting position paper of the European Society for Clinical and Economic aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [6], it is currently absolutely unfeasible to recommend either supplementation or the use of pharmacological doses or products based on vitamin D for the prevention of chronic extra-skeletal pathologies.

The uncertainty which concerns various operational and scientific aspects of vitamin D is felt in Italy as well, as is confirmed by the recent conference among experts held in Verona ("D-bate: Myth or reality: the real-life opinions of Italian experts"). This meeting involved 50 specialists from different fields (internists, rheumatologists, endocrinologists, geriatricians, pediatricians, dermatologists, gynecologists and nephrologists), who considered a number of themes concerning vitamin D: a publication with the main viewpoints that emerged from discussion of the various proposed topics is currently in preparation.

In any case, from a first glance at the perspectives of the individual participants, there emerges a quite heterogeneous picture regarding nearly all the treated themes. In fact some specific questions turned out to be quite divisive. For example, while 40% of the participants believes that serum levels are sufficient for warranting supplementation, for 60% supplementation should only be used in specific cases. A difference of

TABLE I.
Threshold of circulating 25(OH)D levels proposed as ideal. Consensus range and negative outcomes of chronic deficiency status.

Level of 25(OH)D	Consensus range	Negative outcomes of deficiency status (if chronic)
> 10-12 ng/ml	General consensus	• Reduced intestinal absorption of calcium • Secondary hyperparathyroidism • Reduced or below normal levels of calcemia and phosphoremia • Failed mineralization of osteoid tissue General consensus osteomalacia and BMD reduction (in adults); rickets (during childhood) • Radiological evidence of skeletal abnormalities for rickets/osteomalacia • Extra-skeletal abnormalities with myopathy of proximal limb muscles andpossible cardiomyopathy
> 20 ng/ml	Broad consensus	• Below normal levels of intestinal calcium absorption • Secondary hyperparathyroidism • Increase of bone turnover • Increase of bone loss • Accelerated osteoporosis
> 30 ng/ml	Low consensus	The Endocrine Society agrees on the limit of 20 ng/mL for the general population but recommends levels of > 30 ng/mL for at risk or fragile subjects

opinion is also evident on the question of the ideal vitamin D level to be attained: for 38% the threshold is 20 ng/ml, while 62% believes it should be greater than 30 ng/ml. The majority of participants (60%) believes that current data are already convincing with regard to the extra-skeletal effects of vitamin D; on the other hand, 78% demands controlled clinical studies (RCTs), not only observational studies, before underwriting the therapy.

It is evident that what is required is to initiate some process that is able to shed clarity on the topic: if the world of experts is divided on these themes, we can only imagine the confusion among "lay persons." This becomes a particularly contentious problem, given that hypovitaminosis D is by no means a circumscribed issue: vitamin D deficiency is indeed such a widespread condition that it concerns the whole world [7], even if the seriousness and prevalence of deficiency varies considerably from country to country because of different customs and habits.

In Italy, vitamin D deficiency is particularly frequent, especially in the elderly and during the winter months: indeed nearly 80% of Italian women above 70 years of age have 25(OH)D blood levels < 12 ng/mL at the end of winter [8], such that the outcome of possible blood concentrations seems clear. If we then consider institutionalized patients or those with comorbidities, this statistic becomes even more dramatic [9]. It is therefore essential to clarify these questions such that doubts as to the crucial importance of correcting this deficiency are not created, from both personal and public health viewpoints. It is indeed true that still today there is no general consensus as to the optimal levels of vitamin D, not even for bone tissue (Table I). Nonetheless, we all agree that serious vitamin D deficiency (< 12-10 ng/mL) does not engender bone health and that levels > 30 ng/mL would be ideal, though we all

TABLE II.
Critical evaluation of two recent publications reporting negative results on musculoskeletal vitamin D effects. The first study (Khaw et al., 2017) [10] is a large controlled clinical trial (RCT), while the second, (Zhao et al., 2017) [11] is a meta-analysis of clinical trials in which vitamin D was used. Note that only a small percentage of treated participants effectively had vitamin D deficiency.

Khaw et al., 2017 [10]				
Case study	Dosage used	Basal 25(OH)D levels of patients:		
		% pz < 10 ng/ml	% pz 10-20 ng/ml	% pz > 20 ng/ml
5,110 subjects (50-84 years old)	200,000 IU in 1st month then 100,000 IU/month	2%	22%	76%
Zhao et al., 2017 [11]				
		Mean basal baseline 25(OH)D levels in vitamin D studies		
		% < 10 ng/ml	% 10-20 ng/ml	% > 20 ng/ml
27,631 (58-82 average age)	800 IU or less in more than 50% of the studies	0%	28%	57%
N.B.: no basal vitamin D levels were recorded in 15% of the cases.				

believe that it is preferable to bring these values at least to above 20 ng/mL. These assertions already represent a fundamental frame of reference for handling the wave of further uncertainty created by the findings of some studies and meta-analyses, often produced by groups in New Zealand, which aim to show that vitamin D supplementation does not actually have relevant effects and is therefore completely unnecessary. The interpretation of these studies requires – as is always the case – a critical analysis that does not limit itself to a glance at the final results or, what is worse, a mere reading of the title. When reading studies, and the meta-analyses based on them, we must consider certain aspects that are by no means secondary, such as the characteristics of the examined population, the doses used, the duration of the follow-up, the degree to which treatment is followed, and possible interferences caused by the presence of other sources of vitamin D (diet or exposure to sunlight). A clinical trial is not automatically credible just because it is controlled double blind: its validity greatly depends on these other points as well.

Administering high doses of vitamin D over a long period of time does not necessarily provide the certainty of having carried out an adequate study. If we select a population with vitamin D sufficiency, which therefore does not have further need for it (Table II), what are we to expect? If we err in choosing the patients, no statistical analysis will resolve this basic mistake!

To conclude: vitamin D is attracting great scientific and public interest. The potential benefits that the correction of hypovitaminosis D can bring are significant.

For years our country has been a leader in dealing with this problem; the results are beginning to become clearer on more than one front. The climate of increasing confusion and uncertainty over the last few years must not put a stop to valid and rational studies and contributions. Everyone, including specialists, doctors and patients, must demand that the most authoritative scientific societies bring clarity into the field by aiming to create greater levels of consensus and by requiring that clinical studies are constructed on credible foundations from the start.

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