Vitamin D: nothing new under the sun
Dear Readers,

I don’t know about you, but I’m beginning to wonder whether in the uncritical application of statistical methodology at the base of evidence-based medicine we haven’t forgotten the presupposition that is supposed to guide it: the physiopathological and clinical rationale. Let me explain more clearly: in the Journal of the American Medical Association (JAMA) were recently published the recommendations of the United States Preventive Service Task Force (USPSTF) on the use of vitamin D and/or calcium supplements for primary prevention of fractures in adults living in senior communities [1]. The report concludes that on the basis of available studies there is insufficient evidence in terms of a risk-benefit evaluation for recommending calcium or vitamin D supplementation; indeed, the task force advises against supplements of vitamin D and calcium doses ≤ 400 IU or 1000 mg/day, respectively, in postmenopausal women because of the increased risk of kidney stones.

Pity that these recommendations are not applicable to persons with a history of osteoporotic fractures, with a high risk of falls, or with diagnoses of osteoporosis of vitamin D deficiency [1], given that these subjects were largely excluded from the examined studies! Seeing that common sense tells us, based on our knowledge of physiopathology, that vitamin D is only needed when it is lacking, such an assertion, to my mind, is much like proving that turning on a light in a well-lit room is useless (if not harmful)! Was it then necessary to employ a task force and to conduct a complex analysis to reach this conclusion?

I worry also about the media effect of the concluding message, which I imagine might be simplified and communicated or received uncritically for editorial reasons or for basic incompetence. And what about people who are at risk of deficiency? Let’s not worry about prevention and let’s wait to find evidence for the deficiency, with all the costs involved, or let’s take action only when the person becomes a patient with a symptomatology. We also have to consider that the task force in question – justifiably in my view – defines the evidence as insufficient in terms of a risk-benefit analysis to warrant screening of vitamin D deficiency in asymptomatic adults.

On the other hand, I believe that it is also justifiable to aim to reduce the exorbitant costs of vitamin D supplementation by lowering expectations and refining our judgement of when action needs to be taken; we need to simplify our procedures and use common sense to avoid having recourse to expensive solutions which are ultimately of little use. A new development in this sense is represented by the recent authorization of the Agenzia Italiana del Farmaco (AIFA) for the marketing of a new calcifediol formula in gel capsules. We certainly welcome new solutions, especially if they are low cost, which expand the range of therapeutic options for doctors in the interest of patients, at the same time keeping in mind that calcifediol is the form of vitamin D which is produced and metabolized physiologically.

What puzzles me is the package insert of this new calcifediol-based product. In particular I am concerned about:

- the inappropriate expression of the contents in IUs of vitamin D, when it is known that calcifediol is not at all comparable to cholecalciferol in terms of pharmacokinetics and perhaps of pharmacodynamics as well; indeed, the extent of the equivalence relationship between them is still a topic of discussion today [2]. This could create another element of confusion about vitamin D.
dosages, which could be dangerous in terms of safety;
• the instruction and the recommended dose for the "treatment of vitamin D deficiency in cases in which it is necessary to initially administer high doses." Are we to consider 0.266 mg of calcifediol once a month as a high dose if it is half of what has been deemed necessary in recent studies conducted by the school of Prof. Minisola [3,4] and given that the half-life of calcifediol is 2-3 weeks [5]?
• the instruction that "the treatment of vitamin D deficiency in cases ... in which an administration that extends over time is preferable, as in the following conditions: as a coadjuvant treatment of osteoporosis, in patients suffering from malabsorption syndrome, renal osteodystrophy, and in corticosteroid-bone induced diseases." On the basis of what evidence are calcifediol treatments extended over time preferable in these pathologies?
• the need – repeated several times – for a "regular control of serum concentrations of 25-OH-cholecalciferol." This caution may derive from the fact that the increase of serum levels of 25-OH-cholecalciferol following the use of calcifediol is not physiologically regulated, unlike what occurs with cholecalciferol. It is a pity that the use of this calcifediol formula, which is indeed more expensive, may be compromised by the high management costs in clinical practice;
• the statement that "in case of hepatic insufficiency, the absence of the production of bile salts will prevent absorption of the calcifediol," when in fact it is reported that intestinal absorption of calcifediol, unlike that of cholecalciferol, takes place mostly through the portal vein [6] and is not dependent on the presence of bile acids [7]. It is therefore justifiable, also given the possible deficit of 25OH-hydroxylase in conditions of serious hepatic insufficiency, to prefer the use of calcifediol in this case [2].
What do you think?
I hope you enjoy reading this issue.

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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. 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 nongenomic 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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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 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

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

![Metabolic steps of vitamin D activation and biological effects.](image-url)
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>
<thead>
<tr>
<th>Level of 25(OH)D</th>
<th>Consensus range</th>
<th>Negative outcomes of deficiency status (if chronic)</th>
</tr>
</thead>
</table>
| > 10-12 ng/ml   | General consensus | • Reduced intestinal absorption of calcium  
• Secondary hyperparathyroidism 
• Reduced or below normal levels of calcium and phosphoenemia 
• 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 and possible 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 |

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]

<table>
<thead>
<tr>
<th>Case study</th>
<th>Dosage used</th>
<th>Basal 25(OH)D levels of patients:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5,110 subjects (50-84 years old)</td>
<td>200,000 IU in 1st month then 100,000 IU/month</td>
<td>% pz &lt; 10 ng/ml</td>
<td>2%</td>
<td>% pz 10-20 ng/ml</td>
<td>22%</td>
</tr>
</tbody>
</table>

Zhao et al., 2017 [11]

<table>
<thead>
<tr>
<th>Mean basal baseline 25(OH)D levels in vitamin D studies</th>
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<tbody>
<tr>
<td>27,631 (58-82 average age)</td>
<td>800 IU or less in more than 50% of the studies</td>
<td>% &lt; 10 ng/ml</td>
<td>0%</td>
</tr>
</tbody>
</table>

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.

References
INTRODUCTION
The principal role of vitamin D is to regulate calcium and phosphate metabolism and to preserve bone tissue mineralization. Nonetheless, its extra-skeletal functions are also appreciated, including those regarding its immunomodulatory, antiproliferative and anti-infective effects. Vitamin D is of further interest in dermatology, as it is synthesized in the skin following exposure to UV rays, and its deficiency has been repeatedly demonstrated in certain diseases, such as psoriasis, atopic dermatitis and vitiligo. In addition, some derivatives of vitamin D synthesis, such as calcipotriol and tacalcitol, are commonly used as medications for the topical treatment of psoriasis and other immune-mediated skin diseases, given their anti-inflammatory properties. This article will deal with the role of vitamin D in psoriasis.

SKIN AS A VITAMIN D SYNTHESIZING ORGAN
Vitamin D and parathormone regulate the homeostasis of calcium and phosphate, acting in the intestine, bone tissue and kidneys. Following exposure to sunlight, 7-dehydrocholesterol (7-DHC or provitamin D) is converted into previtamin D3 in the skin; in turn, previtamin D3 undergoes isomerization into vitamin D3 (cholecalciferol) within several hours [1]. The cutaneous synthesis of vitamin D3 is influenced by various factors, such as skin phenotype, age, the use of sunscreens, season, latitude, the time of exposure to the sun, and the surface area exposed to it [Table I] [2]. Vitamin D3 synthesized in the skin and consumed with food is metabolized in the liver by the 25-hydroxylase enzyme into 25(OH)D3, or calcifediol, which represents the main circulating metabolite of vitamin D; it is the best gauge of general vitamin D status. Levels of 25(OH)D3 between 30 and 100 ng/mL indicate an adequate general vitamin D status, while levels below 20 ng/mL signal vitamin D deficiency, which can be associated with muscular weakness, bone pain and an increased risk of bone fracture. Levels between 20 and 30 ng/mL indicate insufficiency [3]. In turn, 25(OH)D3 is converted in the kidneys, thanks to the 25(OH)D-1α-hydroxylase enzyme, into its metabolically active form, 1,25(OH)2D3. Renal production of 1,25(OH)2D3 is mainly regulated by parathormone. Once activated into 1,25(OH)2D3, vitamin D carries out its biological activity by activating its high-affinity nuclear receptor. Vitamin D receptors are ubiquitous in the body, present also in keratinocytes: this explains why vitamin D can carry out anti-proliferative functions. At our latitude, 80% of vitamin D requirements is supplied by exposure to sunlight, while only 20% derives from food consumption. Vitamin D is not present in most foods: the major food source is animal fat, and especially fatty fish, such as salmon and herring [4].

IMMUNE FUNCTIONS OF VITAMIN D
Vitamin D plays an important role in the regulation of the innate and acquired immune systems. Vitamin D can act on the cells of the immune system, including lymphocytes, macrophages, dendritic cells and keratinocytes, in an endocrine, autocrine and paracrine manner. Regarding its effects on the innate immune system, vitamin D stimulates macrophages and epithelial cells to produce antimicrobial peptides such as defensins and cathelicidins

| TABLE I. Factors that influence cutaneous synthesis of vitamin D. |
|------------------------|------------------------|
| **Phenotype**          |                        |
| **Age**                |                        |
| **Surface area of skin exposed to sunlight** |                        |
| **Sunscreen use**      |                        |
| **Seasons**            |                        |
| **Latitude**           |                        |
| **Time of exposure to sunlight** |                        |

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Vitamin D and psoriasis

Psoriasis is a chronic inflammatory disease of the skin that affects ca. 3% of the population of Italy; it manifests itself through erythematous scaly plaques located on such areas of the body as the elbows, knees and scalp. In some patients, psoriasis is more diffused and can involve much of the cutaneous surface (Fig. 1). In 30% of cases, psoriasis can result in a clinical progression with many symptoms for the patient and cause serious bone alteration (Fig. 2). Frequently psoriatic skin is infiltrated by myeloid granulocytes [10]. mDCs and pDCs express TLR-7 and -9, which recognize the substances released by the damaged keratinocytes, such as ssDNA, dsDNA and the antimicrobial peptide cathelicidin/LL-37. The LL37 and DNA complexes are powerful activators of the pDCs that release IFN-α and TNF-α, activators of adaptive immune response. LL-37 plays a fundamental role in the pathogenesis of psoriasis, as it also represents an important autoantigen [11]. Most patients with psoriasis express T lymphocytes, including Th17, which are reactive toward LL-37 [11]. Activated mDCs migrate to the draining lymph nodes causing the differentiation of naïve T cells in Th1 and Th17 effector cells. Sensitized Th1 and Th17 CD4+ lymphocyte populations and activated effector CDB+ T cells penetrate and accumulate according to a chemotaxis gradient in the skin. The keratinocytes activated by the cytokines that are produced by the Th17 and Th1 lymphocytes (INF-γ, IL-22, IL-17, TNF-α) release chemokines such as CCL20, CCL2, CCL5 and IL-8, which in turn recruit leucocytes, thus expanding the inflammatory process. The accumulation of T lymphocytes in the skin results in the secretion of proinflammatory cytokines of growth factors that stimulate the proliferation of keratinocytes, causing the appearance of psoriatic lesions.

Vitamin D can have significant effects in the pathogenetic mechanism of psoriasis. The gene that controls the expression of the vitamin D receptor (VDR), located on the 12q13.11 chromosome, contains more than 200 single-nucleotide polymorphisms (SNPs). In particular, the four most-studied SNPs (FokI, BsmI, Apal, TaqI) have been associated with various immune-mediated diseases, including psoriasis, atopic dermatitis and asthma [12]. Vitamin D inhibits...
NF-κB by increasing IκBα levels; it reduces the capacity of NF-κB to bind with DNA; it suppresses the transcription of NF-κB; and it represses the expression of IL-1, IL-6, IL-8 and TNF-α, proinflammatory cytokines that play an important role in the pathogenesis of psoriasis. In addition, vitamin D stimulates the expression of CT1A-4 and Foxp3, which in the presence of IL-2 induce the formation of Tregulatory lymphocytes (Treg). VDR signaling also acts in the JNK/c-jun pathway, inhibiting cellular proliferation [13].

In vitro studies and trials on animal models indicate the existence of an immunomodulating effect of vitamin D, which is shown by the switch from Th1/Th17 to Th2/Treg. Vitamin D is an important positive regulator in the expression of cathelicidin on the part of keratinocytes. By contrast, vitamin D and its analogs reduce the expression of other antimicrobial peptides, such as psoriasin (S100A7) and koebnerisin (S100A15), on the part of keratinocytes activated by IL17A, IL-22 and TNF-α. Psoriasin and koebnerisin act as powerful chemotactic and alarmin agents, which spread psoriatic inflammation.

Vitamin D deficiency has been reported in patients with psoriasis in various observational studies. In particular, in a study conducted in Florence, Ricceri et al. found that 97% of patients with psoriasis showed vitamin D levels below 30 ng/ml [14]. In another study carried out in Verona on 145 patients affected by chronic plaque psoriasis, 112 by rheumatoid arthritis and 141 healthy controls, we observed that vitamin D deficiency (25(OH)D levels < 20 ng/ml) was significantly greater in patients affected by psoriasis than in those suffering from rheumatoid arthritis and in the controls [15]. This deficiency in the population with psoriasis was particularly frequent during winter as compared to summer (81% vs. 37%).

Another study conducted in Spain showed that vitamin D deficiency affected patients with psoriasis and metabolic syndrome more frequently than the control group, there was an inverse correlation between 25(OH)D3 serum levels and glycermia and lipids [16]. Various open clinical trials have been conducted to study the effectiveness of vitamin D3 supplementation in psoriasis and psoriatic arthritis. In the only randomized, placebo controlled trial, 9 of 20 patients (45%) treated with 1 gram of 1-hydroxyvitamin D3 showed a slight improvement with respect to 8 of 21 subjects (38%) given the placebo. This difference was not statistically significant [17]. It has been reported that biological treatment with anti TNF-α biological drugs reduces vitamin D serum levels, unlike other systematic treatments, including those using cyclosporine and acitretin, by means of a mechanism that is currently unknown [18].

CONCLUSIONS

Vitamin D is produced by keratinocytes following exposure to sunlight; it regulates multiple immunological functions, in addition to skeletal ones. Beyond the skeletal system, vitamin D has immunomodulating, anti-inflammatory, anti-inflammatory and anti-inflammatory stress effects; it further controls cellular proliferation. Vitamin D deficiency has been described in several immune-mediated diseases, including psoriasis, which is a common skin disease that can also involve the musculoskeletal system. The clinical significance of hypovitaminosis D in psoriasis as well as the role and mode of its administration are topics currently under study. It is not known whether maintaining adequate levels of vitamin D can prevent the onset of autoimmune diseases or have a favorable effect on the natural course of the diseases, including psoriasis, even if there are some biological presuppositions that warrant such a hypothesis.

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