

# VITAMIN D

UpDates

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## Managing Editor:

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## Publisher

Pacini Editore Srl  
Via Gherardesca 1 • 56121 Pisa  
Tel. 050 313011 • Fax 050 3130300  
Info@pacinieditore.it  
www.pacinieditore.it

## B.U. Pacini Editore Medicina

Andrea Tognelli  
Medical Project - Marketing Director  
Tel. 050 3130255  
atognelli@pacinieditore.it

## Copy Editor

Lucia Castelli  
Tel. 050 3130224  
lcastelli@pacinieditore.it

## Graphics and Layout

Massimo Arcidiacono  
Tel. 050 3130231  
marcidiacono@pacinieditore.it

## Print

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# EDITORIAL

## Maurizio Rossini

Department of Medicine, Branch of Rheumatology, University of Verona

Dear Readers,

As you know, vitamin D is a subject of great interest; we are daily bombarded with news on the topic in different fields of specialization, some swaying us in one direction and some in another... You may have noticed the growing scientific interest on this subject, as attested by the increasing number of publications on PubMed since 2000, which even today stands at a high level, even if the number has begun to plateau (Fig. 1).

It comes as no surprise that in addition to its noted impact on human skeleton and phosphocalcic metabolism, vitamin D can also have extraskeletal effects. There are at least five good reasons in support of this: vitamin D receptors are present in numerous cells – I would say they are nearly ubiquitous; vitamin D controls the transcription of numerous genes; it has endocrine effects, and not only calcitropic ones; the activation and catabolism of vitamin D take place in several organs and tissues; and it has intracrine and paracrine effects in numerous cells of various natures.

Most available studies on the effects of vitamin D are preclinical or observational (Fig. 2). The latter often describe associations between a lack of vitamin D and the incidence, activity or outcomes of many illnesses, but they have an intrinsic limit of not being able to document a sure causal relationship. On the other hand, randomized, double-blind, placebo controlled clinical trials relative to supplementation – the only ones able to scientifically verify the effects of vitamin D – are few in number, sometimes for ethical reasons, and often suffer from bias (Fig. 3).

The most frequent bias is the treatment of subjects without deficiency, forgetting that as a nutrient vitamin D can only have effects when it is lacking. Recently we have seen, for example, a publication of a study [1] in which subjects, who were for the most part not deficient, were given supplements: the conclusion of the ineffectiveness, in terms of preventing fractures and falls, of vitamin D supplements for adults living in senior communities created confusion among both doctors and patients. Instead, the researchers should have first verified – by

means of an epidemiologic study – the prevalence of vitamin D deficiency to understand whether the administration of a supplement would be at best useless, if not harmful, in that kind of community and in that population group. When studies are carried out which make little sense – like the one we have just described – which are of poor quality, which are conducted with extremely variable doses and administration modes of vitamin D, and which adopt different or unknown protocols in completely different clinical conditions – in these cases, meta-analyses may produce misleading results and conclusions.

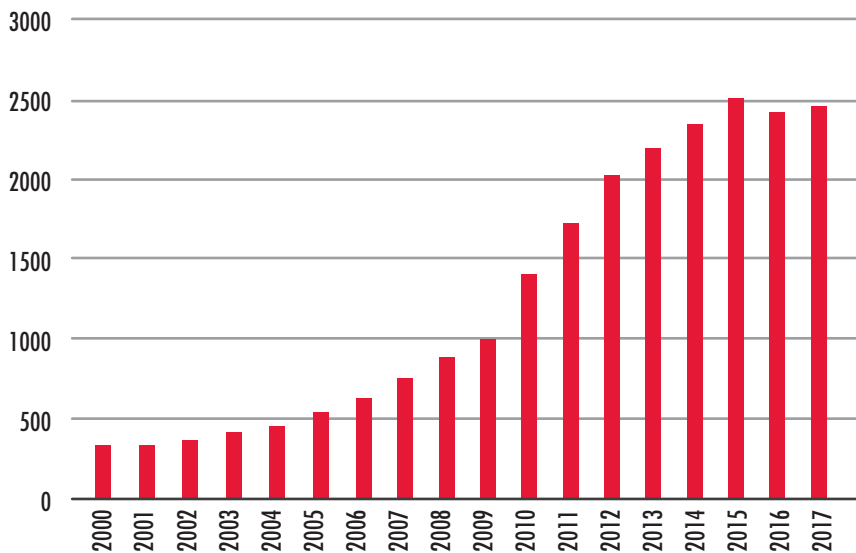
For example, the recent meta-analysis conducted by Zhao et al., published in JAMA [2], mixed together studies using D2 or D3, with doses that ranged from 400 IU/day of vitamin D to 500000 IU/year ± variable doses of calcium, in subjects with completely different or unknown vitamin D profiles and calcium intake, and with extremely variable – or worse, unknown – fracture risk conditions. It should not surprise us that the results are not statistically significant. Likewise, the attempt in this meta-analysis to rationalize the analysis by having recourse to the evaluation of a subgroup with baseline serum levels of 25(OH)D < 20 ng/mL is tainted by the fact that this fundamental datum is only available in very few studies; it was therefore mostly estimated on the basis of the dosage in a small subgroup of subjects, who were not necessarily representative of the entire population under examination.

Furthermore, available studies almost always lack verification of the 25(OH)D serum level at the end of the study in the untreated placebo group; as has been observed in some studies [3], the control group does not turn out to be mostly deficient, probably as a result of the widespread and common tendency today of self-managed vitamin D supplementation.

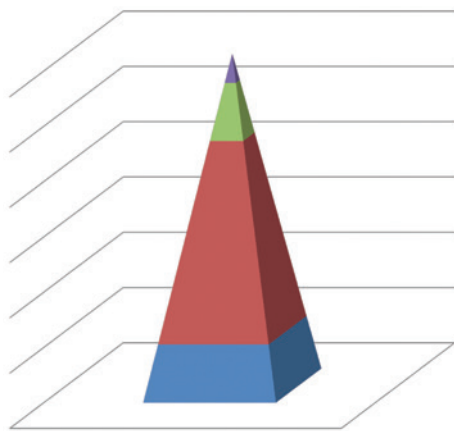
## Correspondence

MAURIZIO ROSSINI

maurizio.rossini@univr.it

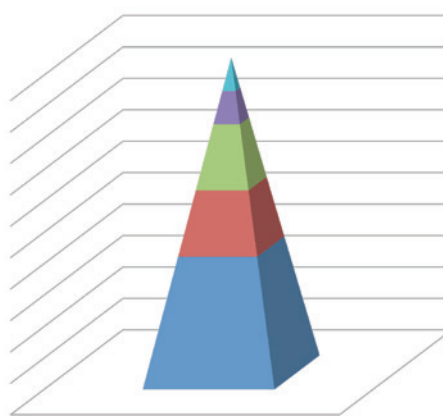


**FIGURE 1.** Number of publications on PubMed with vitamin D mentioned in the title.



- Interventional studies (suppl., RCTs)
- Longitudinal observational studies
- Cross-sectional observational studies
- Preclinical evidence

**FIGURE 2.** Characteristics of available vitamin D studies.



- Inadequate evaluations
- Inadequate outcomes
- Inadequate doses
- Controls with vitamin D sufficiency
- Patients with vitamin D sufficiency

**FIGURE 3.** Biases in vitamin D RCTs.

Such considerations are not possible if – whether for a lack of competence or simply of time – it is not feasible to access the enormous literature that is becoming progressively available, even if we limit ourselves to reading abstracts.

This new journal emerges from the need – which is, I believe, widely felt – to have access to a publication which provides updates and guidance on this topic. It therefore aims to collect by field of specialization articles published on PubMed over the last several months (over 200 in the month of January alone!), in the hope is that this will enable readers to stay in touch with important developments and to make sense of the nearly daily barrage of news in this field. The journal will also present comments, in-depth analyses and reviews on the part of some of the major experts in the various main specializations to help readers keep abreast of the certainties and uncertainties regarding vitamin D.

I hope you enjoy reading the journal.

### References

- <sup>1</sup> Khaw KT, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. *Lancet Diabetes Endocrinol* 2017;5:438-47.
- <sup>2</sup> Zhao JG, Zeng XT, Wang J, et al. Association between calcium or vitamin d supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA* 2017;318:2466-82.
- <sup>3</sup> McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA* 2013;309:155-62.