VITAMIN D
UpDates

Copyright by
Pacini Editore srl

Managing Director
Patrizia Pacini

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

Pacini Editore Medicine Division
Fabio Poponcini • Business Unit Manager
Tel: 050 31 30 218 • fpoponcini@pacinieditore.it

Alessandra Crosato • Account Manager
Tel: 050 31 30 239 • acrosato@pacinieditore.it

Francesca Gori • Business Development & Scientific Editorial Manager
fgori@pacinieditore.it

Manuela Mori • Digital Publishing & Advertising
Tel: 050 31 30 217 • mmori@pacinieditore.it

Editing
Lucia Castelli
Tel. 050 3130224 • lcastelli@pacinieditore.it

Graphics and pagination
Massimo Arcidiacono
Tel. 050 3130231 • marcidiacono@pacinieditore.it

Print
Industrie Grafiche Pacini • Pisa

ISSN: 2611-2876 (online)

Registration at the Court of Pisa no. 2/18 dated 23/2/2018
The editor remains available to those who are entitled with whom communication has not been possible as well as for any omissions. Photocopies for the reader's personal use (for their pro- reading, study or consultation) may be made within the limit of 15% of each volume/file of the periodical, excluding advertising pages, upon BP to SIAE of the fee provided for by Law no. 633 of 1941 and following the specific authorisation release of the by CLEARedi: https://www.clearedi.org/top-menu/HOME.aspx. Digital edition - March 2023.

EDITORIAL

Maurizio Rossini
Department of Medicine,
Rheumatology Section, University of Verona

VITAMIN D
UpDates
2023;6(1):2-3

AIFA UPDATE OF NOTES 79 AND 96 IN RELATION TO VITAMIN D: CONFIRMATIONS AND DOUBTS

In this issue we would like to again sum up vitamin D's role in phosphorus and calcium metabolism and in bone health.

We are doing this by publishing a summary on the correct use of vitamin D supplementation according to the recent recommendations published by the Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS) [1].

Specifically, you will find here an update on the definition of vitamin D deficiency, on the identification of individuals at risk, on whether or not serum 25(OH)D screening is advisable, and on the conditions that indicate when supplementation would be suitable and the procedures for its application that are preferable in terms of dosage and timing, all based on the most recent understanding.

You will also find guidance on how to supplement with vitamin D in cases of kidney or liver insufficiency or when there are concomitant drug treatments that interfere with vitamin D metabolism in the liver.

Finally, you will find indications on when toxic effects such as hypercalcaemia and hypercalciuria should be of concern. All of this is substantiated by appropriate bibliographic references, which you may wish to supplement with the most recent articles, which can also be found in the rich bibliographic selection included in this issue. Although the recent updates of the Italian Medicines Agency (AIFA) Notes 79 [2] and 96 [3] did acknowledge the SIOMMMS recommendations, unfortunately the agency's acknowledgement was only partial.

NOTE 79

☺ In the new version of Note 79's "general considerations", the recommendation to make use of calcium and vitamin D supplements, where diet and exposure to sunlight are inadequate, were rightly reiterated because a vitamin D deficiency, in particular, can largely nullify the effects of drugs used for the treatment of osteoporosis.

☹ Compared with the Note's previous version, which recommended the use of cholecalciferol in particular and ruled out the use of hydroxy metabolites on the basis of the previous guidelines published in 2011 [3], calcifediol was added as an alternative to cholecalciferol, citing as alleged support, among other things, the same guidelines[3] which instead indicated the use of calcifediol, in addition to cholecalciferol, only under conditions of severe liver failure. Rightly so, in the "particular warnings" of Note 96's new version, it was acknowledged that the main evidence of vitamin D's efficacy against fractures was achieved through the use of cholecalciferol, which appears to be the reference molecule for this indication. On the other hand, the clinical documentation for hydroxy analogues was very limited whilst the risk of hypercalcaemia is not at all negligible.

☹ In the new version of Note 79's "Special Warnings" about patients with severe renal insufficiency, supplementation with vitamin D_3 was again recommended, as it was in the

Correspondence
Maurizio Rossini
maurizio.rossini@univr.it

How to cite this article: Rossini M. Editorial. Vitamin D - UpDates 2023;6(1):2-3.

previous version. However, the possible use of 1-alpha-hydroxylated vitamin D metabolites for patients with this condition, which was supported by the old[3] and new guidelines[1], was surprisingly replaced with the use of 25-alpha-hydroxylated metabolites, yet with no bibliographic support.

NOTE 96

☺ The confirmation that screening extended to the general population would be inappropriate, is reasonable, considering that the determination of 25(OH)D levels should only be performed in the presence of risk factors for deficiency and when useful for patients' clinical management.

☺ Also appreciated was the new acknowledgement that supplemen-tation among people with severe vitamin D deficiency is appropriate, even when asymptomatic.

☺ AIFA's finding appropriate the raising of the minimum desirable threshold of serum 25(OH)D levels from 20 ng/mL (or 50 nmol/L) to 30 ng/mL (or 75 nmol/L) among patients with hyperparathyroidism (whether primary or secondary) and among those with osteoporosis or other established osteopathies was significant, recognising that correction of vitamin D deficiency remains, together with correction of deficient dietary calcium intake, one of the cornerstones of treatment for osteoporosis. Yet, vitamin D supplementation in healthy subjects without vitamin D deficiency understandably appears to be unnecessary, as shown by the far from surprising results of recent clinical studies.

☺ Also reasonable was the warning about using excessive doses of vitamin D, especially because of the potential negative effects on bone resorption as reported by our studies [5,6].

☺ Also, the new inclusion among recipients of vitamin D prescription covered by the National Health Service (NHS) without needing 25(OH)D screening, in addition to those who are institutionalised, those with severe motor deficits or who are bedridden living at home was also appreciated, given that exposure to sunlight, as rightly recognised, is the primary mechanism for meeting vitamin D requirements.

☹ Then there was still little acknowledgement of other conditions at risk of vitamin D deficiency such as those related to forced conditions of reduced sun exposure (for example, due to work or cultural reasons or conditions contraindicating exposure to UVB rays) or those related to an inability to produce adequate amounts of vitamin D despite exposure to sunlight, such as advanced age [7].

☹ Indications are unclear for patients already on mineralisation therapy combined with vitamin D supplementation, as recommended in Note 79. It is believed that continued vitamin D supplementation should be borne by the NHS regardless of any determination of 25(OH)D among these patients as well.

☹ With regard to vitamin D prescription guidelines, the doses of cholecalciferol given in Annex 1 to the Note have often been found to be insufficient under certain conditions: specifically, among the elderly, the obese, in cases of severe liver failure or chronic therapies interfering with vitamin D metabolism in the liver, or in conditions of poor absorption.[1]

☹ In that same annex, as an alternative treatment to cholecalciferol, calcifediol is indicated. In fact, however, this latter supplement should be indicated as the second choice, so that the Note's "Special Warnings" regarding the greater evidence of efficacy and safety of cholecalciferol are not contradicted, especially when administered daily. Even calcifediol's alleged faster normalisation of 25(OH)D levels was also refuted by our recent study, which showed that appropriate doses of cholecalciferol were able to offer equivalent rapidity [8].

☹ Finally, in view of the potential extra-skeletal benefits of vitamin D, based on what is currently known, though there is no firm scientific evidence that supplementation does indeed provide a cost-effective benefit, we feel that, at this time, such benefits cannot be ruled out with certainty either. See, for example, a critical analysis of the VITAL Study [9-11] with lights and shadows in this issue.

What do you think?

References

1 Bertoldo F, Cianferotti L, Di Monaco M, et al. Definition, assessment, and management of vitamin D inadequacy: suggestions, recommendations, and warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS). Nutrients 2022;14: 4148. https://doi.org/10.3390/nu14194148

2 Aggiornamento della Nota AIFA 79. Gazzetta Ufficiale n. 31 del 7-2-2023.

3 Aggiornamento della Nota AIFA 96. https://www.gazzettaufficiale.it/eli/id/2023/02/20/23A00990/SG

4 Adami S, Romagnoli E, Carnevale V, et al.; Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS). [Guidelines on prevention and treatment of vitamin D deficiency. Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS)]. Reumatismo 2011;63:129-147. https://doi.org/10.4081/reumatismo.2011.129

5 Rossini M, Adami S, Viapiana O, et al. Dose-dependent short-term effects of single high doses of oral vitamin D(3) on bone turnover markers. Calcif Tissue Int 2012;91:365-9. https://doi.org/10.1007/s00223-012-9637-y

6 Rossini M, Gatti D, Viapiana O, et al. Short-term effects on bone turnover markers of a single high dose of oral vitamin D_3. J Clin Endocrinol Metab 2012;97:E622-E666. https://doi.org/10.1210/jc.2011-2448

7 Holick MF, Matsuoka LY, Wortsman J. Age, vitamin D, and solar ultraviolet. Lancet 1989;334:1104-1105. https://doi.org/10.1016/s0140-6736(89)91124-0

8 Fassio A, Adami G, Rossini M, et al. Pharmacokinetics of oral cholecalciferol in healthy subjects with vitamin D deficiency: a randomized open-label study. Nutrients 2020;12:1553. https://doi.org/10.3390/nu12061553

9 LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental vitamin D and incident fractures in midlife and older adults. N Engl J Med 2022;387:299-309. https://doi.org/10.1056/NEJMoa2202106

10 Hahn J, Cook NR, Alexander EK, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. BMJ 2022;376:e066452. https://doi.org/10.1136/bmj-2021-066452

11 Chandler PD, Chen WY, Ajala ON, et al. Effect of vitamin D3 supplements on development of advanced cancer: a secondary analysis of the VITAL Randomized Clinical Trial. JAMA Network Open 2020;3:e2025850. https://doi.org/10.1001/jamanetworkopen.2020.25850