VITAMIN D
UpDates

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
Sales Manager
050 31 30 218 - fpoponcini@pacinieditore.it
Alessandra Crosato
Sales Manager
050 31 30 239 - acrosato@pacinieditore.it
Manuela Mori
Advertising and New Media Manager
050 31 30 217 - mmori@pacinieditore.it

Editing
Lucia Castelli
050 3130224 - lcastelli@pacinieditore.it

Graphics and pagination
Massimo Arcidiacono
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/topmenu/HOME.aspx. Digital edition - November 2022.

EDITORIAL

Maurizio Rossini

Department of Medicine,
Rheumatology Section, University of Verona

VITAMIN D
UpDates
2022;5(3):76-77

Dear Readers,
In this issue, we return to the theme of a possible relation between vitamin D and the risk of infection or serious clinical symptoms from infection with SARS-CoV-2.
We propose this topic because many scientific publications continue to treat it (more than 80 over the last four months, as you can see from the selection of references following the two articles). The results of these treatments have sometimes been contradictory and do not by any means allow us to draw conclusions, much less certainties, one way or another. At the same time, some have taken the liberty of making assertions about the correlation in a way that to my mind is inappropriate and imprudent.
We are also focusing on this theme because COVID-19 continues to take a significant number of lives. Indeed, as we approach winter, there are still many unknowns regarding the public health and social impact of clinical manifestations of infection with SARS-CoV-2 variants. We therefore felt the need to provide an update and a rigorous and objective overview of the current state of scientific knowledge on this theme. As is the practice of this journal, this task has been entrusted to experts who have worked and published in the field.
The first article presents summaries of the rationale and evidence for as well as doubts about the possible role of vitamin D in conditioning the risk of infection with SARS-CoV-2 and the severity of COVID-19. The author rightly begins by summarizing current evidence on the physiological role of vitamin D in connection with innate immunity, in particular with regard to antimicrobial action, and with acquired immunity, in the context of modulating action which is primarily anti-inflammatory and promotes immune tolerance. He then looks at the evidence on the association between vitamin D levels and the specific risk of infection with SARS-CoV-2. In addition, he examines indirect evidence, such as the high prevalence of hypocalcemia in patients hospitalized for COVID-19. These cases are characterized by the possible expression of the dysregulation of calcium and phosphorus homeostasis caused by vitamin D deficiency or by reduced exposure to UVB rays, which especially affects vitamin D status, as is well known.
We should note that the author's own published findings have not brought to light any direct relationship between indices of exposure to sunlight (including confinement to homes during the lockdown), 25(OH)D serum levels and infection with SARS-CoV-2. At the same time, he does admit the possible existence of other variables which have not been taken into consideration. The author correctly highlights the strong dependence on co-variables of the association described in numerous studies between vitamin D and infection risk, such as old age, comorbidity, obesity, gender, ethnicity and supplementation (and we should note in passing that the last-named factor is often neglected). For this reason, vitamin D deficiency may not be the cause but the result, or simply a risk marker. The same interpretive doubts also characterize the numerous observations which currently report an inverse correlation between vitamin D levels and severity of COVID-19.
Nonetheless, our current state of knowledge does not allow us to exclude a possible co-responsibility of vitamin D deficiency in conditioning the seriousness of some clinical manifestations of the illness and its outcomes (hospitalization, recourse to mechanical ventilation, transfer to

Correspondence
Maurizio Rossini
maurizio.rossini@univr.it

How to cite this article: Rossini M. Editorial. Vitamin D - UpDates 2022;5(3):76-77.

intensive care, and mortality). Some possible physio pathological mechanisms through which vitamin D deficiency might contribute to the pathogenesis of COVID-19 are believed to be known: vitamin D has the ability to mitigate the cytokine storm and acts as an endocrine modulator of the renin-angiotensin-aldosterone system, both of which are involved in the pathogenesis of acute respiratory distress syndrome. A response to current uncertainties might come from randomized controlled trials (RCTs) on vitamin D supplementation, as long as these are rationally designed and take into account that vitamin D could essentially act as a nutrient here and could therefore be effective only in patients with deficient levels. The meta-analysis of the few studies of this type which are currently available seem to indicate effectiveness on some outcomes, even if to a limited extent.

It is nonetheless undeniable that our present knowledge of the theme is characterized by broad variability and frequent discrepancy of the results. This circumstance indeed calls for a critical revision of the literature, which you will find in the second article of this issue. The authors summarize some of the most critical weaknesses of currently available publications, highlighting the use of unsatisfactory research tools or poorly designed trials. As the author of the first article recognizes, an important shortcoming is the bias of the temporal relation between vitamin D dosage and COVID-19 diagnosis, which varies in the different studies from one year before the diagnosis to simultaneous evaluation. This also appears relevant in light of the well-known phenomenon of reverse causality, that is, the fact that through inflammation the illness itself is associated with a reduction of 25(OH)D serum levels.

You will note that the statistical significance of correlations between 25(OH)D serum levels and the different outcomes depends on whether the dose was given before or during hospitalization. In addition, the reliability of currently available studies is not always sound, as several have been classified as low quality, given that they were subject to confounding factors or were lacking in detail or methodological adequacy. Then there is the problem of publication bias, which derives from the tendency to privilege the publication of studies with positive results. Other problems which sometimes characterize the literature on COVID-19 include the haste with which some preliminary data are confirmed, excessive simplification with generic conclusions which are not supported by statistically significant data, and the exceptional practice – given the urgency of the situation – of including observational studies in RCT meta-analyses. This has led to the publication of many low quality analyses with numerous confounding factors and therefore contradictory results. Such developments expose the scientific community to the risk of losing credibility.

All of these circumstances have contributed to the ongoing uncertainty as to the utility of vitamin D supplementation for the prevention and treatment of COVID-19. I personally fear that one day some people might conclude that in this field as well all we needed to do was rely on common sense to remedy a deficit, given the state of our knowledge about vitamin D and its degree of safety.

What do you think?