

The authors should definitely take into consideration the following paper: Biesalski HK. Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship? Nfs Journal. 2020 Aug;20:10–21. doi: 10.1016/j.nfs.2020.06.001. Epub 2020 Jun 7. PMID: PMC7276229. This paper describes in detail the rationale the authors are following. Various comorbidities (known or unrecognized yet, i.e., hypertension, diabetes, CVD, metabolic syndrome) are associated or aggravated with low vitamin D plasma levels, which would lead to an increased susceptibility of serious-critical illness from SARS-CoV-2 and potentially death. That is why the following recent article warrants also the authors' attention: Lakkireddy, M., Gadiga, S.G., Malathi, R.D. et al. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. Sci Rep 11, 10641 (2021). <https://doi.org/10.1038/s41598-021-90189>

-REPLY: Thank you very much, we added these references and discussed the results in the revised version of the manuscript.

last paragraph: "Papadimitriou et al performed an important investigation on the association of Vitamin D deficiency and COVID-19 [1], but COVID-19 patients' clinical characteristics were not evaluated. Vitamin D levels can be influenced by many factors such as sun exposure, genetic, supplementation, and comorbidities [18–20]." R: to be more accurate, Papadimitriou et al. performed an important ecological investigation...., but obviously.... clinical characteristics... COULD NOT BE evaluated. The effect of old age however expressed as Life Expectancy, was analyzed in this study, showing a stunning benefit in the elderly, should their Vitamin D concentrations reach 40-60 ng/ml.

-REPLY: Thank you, we agree. We corrected our sentence.

It is important in this R's opinion to highlight: 1. that the world pandemic of Vitamin D deficiency has been mainly driven by "The Big Vitamin D mistake" referring, as explained in detail in the 1st reference of this Letter, to the IOM's erroneous statistical calculations, a mistake never admitted in public so far, despite the very serious publications that have proven it. This mistake, along with the worldwide campaigns of the dermatological societies have led to an unprecedented vitamin D deficiency pandemic. Much ink has been dropped on the apparently controversial recommendations of the former IOM and the Endocrine Society Expert Committee recommendations, with the simultaneous claim of an unsubstantiated fear of vitamin D toxicity. The latter being limited to the well known but especially rare vitamin D hypersensitivity disorder, and real "toxicity" (i.e. mainly asymptomatic subtle elevation of Ca concentrations in serum and in urine, however potentially dangerous for renal function in the long term) becoming a possible threat if vitamin D levels exceeded 250 ng/ml. 2. that the disagreement between IOM and the Endocrine Society has a solution well described in the manuscript of Papadimitriou et al. in the WJV: the upper tolerable vitamin D daily doses that IOM accepts are practically IDENTICAL with those that the Endocrine Society judges as safe doses that DO NOT require medical supervision. 3. Since medical supervision is not required with the above doses, in somebody not already on supplementation for any reason, and unknown vitamin D concentrations, rapid safe replenishment could be achieved with the upper tolerable daily doses for up to 2 months as described in the Endocrine Society guidelines. 4. The benefit of vitamin D in cancer incidence has been proven by the VITAL study (please see details in reference #1) 5. It is noteworthy that Public Health authorities have not issued any guidelines so far regarding vitamin D supplementation at least during the #stay at home and lockdown periods aiming at least to protect musculoskeletal health, for which there exists GLOBAL CONSENSUS. If this were done at least, some important extraskeletal benefit in the protection from COVID-19 could have been obtained. 6. Protection of Public Health can not rely only on passive immunization. For the vaccines to exhibit

their full benefit, a well-functioning immune system is an obvious prerequisite. And vitamin D, is not a vitamin, but an "essential" hormone that can be produced in our body provided that we ARE sufficiently exposed to UVB. Since this prerequisite can no longer be met in the modern world, safe replenishment and practically continuous supplementation are the only reasonable approaches to achieve active immunization but also protection from important comorbidities as those that the authors very well describe in their Letter.

-REPLY: Dear reviewer, we agree with your statement and in the light of your comment and the reference manuscript (The Big Vitamin D mistake), we reformulated the manuscript, highlighting the importance to regulate vitamin D levels.

Finally the following concluding statement at the end of this manuscript: "It is not clear if lack of Vitamin D or comorbidities associated with low vitamin D increases the risk factor for COVID-19." is not supported by the letter itself. On the contrary, in the R's opinion, Evidence Based Medicine has already proven that lack of vitamin D together with known or unrecognized yet comorbidities - probably aggravated by vitamin D deficiency - increase the danger for serious-critical illness and death from COVID-19 disease.

-Reply: We reformulated the sentence to "In summary, Vitamin D hypovitaminosis is associated with comorbidities that are known to affect COVID-19 severity and outcome. Further investigations should focus on patients with low vitamin D levels with and without comorbidities, and supplementation trials to investigate the effects of Vitamin D on the immune response to COVID-19 and COVID-19 vaccines."

The title of this Letter "The incidence of vitamin D deficiency and comorbidities in moderate and severe Coronavirus disease–2019 patients" could better serve its

purpose rephrased as "The role of vitamin D deficiency and comorbidities in COVID-19 disease"

-REPLY: Thank you for the suggestion, we modified the title according to your suggestion.