‘Scientific Strabismus’ or two related pandemics: coronavirus disease and vitamin D deficiency

Murat Kara1, Timur Ekiz2a, Vincenzo Ricci3, Özgür Kara4, Ke-Vin Chang5 and Levent Özçakar1

1Department of Physical Medicine and Rehabilitation, Hacettepe University Medical School, Ankara, Turkey
2Department of Physical Medicine and Rehabilitation, Türkmenbaş Medical Center, Adana, Turkey
3Department of Biomedical and Neuromotor Science, Physical and Rehabilitation Medicine Unit, IRCCS Rizzoli Orthopaedic Institute, Bologna, Italy
4Geriatrics Unit, Yenimahalle Training and Research Hospital, Yıldırım Beyazıt University, Ankara, Turkey
5Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Bei-Hu Branch, Taipei, Taiwan

(Submitted 5 April 2020 – Final revision received 4 May 2020 – Accepted 7 May 2020 – First published online 12 May 2020)

Abstract
The WHO has announced the novel coronavirus disease (COVID-19) outbreak to be a global pandemic. The distribution of community outbreaks shows seasonal patterns along certain latitude, temperature and humidity, that is, similar to the behaviour of seasonal viral respiratory tract infections. COVID-19 displays significant spread in northern mid-latitude countries with an average temperature of 5–11°C and low humidity. Vitamin D deficiency has also been described as pandemic, especially in Europe. Regardless of age, ethnicity and latitude, recent data showed that 40% of Europeans are vitamin D deficient (25-hydroxyvitamin D (25(OH)D) levels <50 nmol/l), and 13% are severely deficient (25(OH)D < 30 nmol/l). A quadratic relationship was found between the prevalences of vitamin D deficiency in most commonly affected countries by COVID-19 and the latitudes. Vitamin D deficiency is more common in the subtropical and mid-latitude countries than the tropical and high-latitude countries. The most commonly affected countries with severe vitamin D deficiency are from the subtropical (Saudi Arabia 46%, Qatar 46%, Iran 33-4%, Chile 26-4%) and mid-latitude (France 27-3%, Portugal 21-2%, Austria 19-3%) regions. Severe vitamin D deficiency was found to be nearly 0% in some high-latitude countries (e.g. Norway, Finland, Sweden, Denmark and Netherlands). Accordingly, we would like to call attention to the possible association between severe vitamin D deficiency and mortality pertaining to COVID-19. Given its rare side effects and relatively wide safety, prophylactic vitamin D supplementation and/or food fortification might reasonably serve as a very convenient adjuvant therapy for these two worldwide public health problems alike.

Key words: Coronavirus: Death: Insufficiency: Europe: Acute respiratory syndrome

On 11 March 2020, the WHO announced the novel coronavirus disease (COVID-19) outbreak to be a global pandemic. The spread of COVID-19 is becoming unstoppable, and as of 15 May, more than 4 500 000 people have been infected and more than 300 000 people have died (Fig. 1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen of COVID-19. SARS-CoV-2, classified into two γ coronaviruses, is an enveloped, positive-sense and single-stranded RNA virus of about 30 kb. The life cycle of the virus with the host comprises mainly five steps as follows: attachment, penetration, biosynthesis, maturation and release. Once SARS-CoV-2 attaches to the host receptors, it penetrates the cells via endocytosis/membrane fusion. Herein, angiotensin-converting enzyme 2 is the entry and functional receptor of SARS-CoV-2. It has been shown that the spike for SARS-CoV-2, structural membrane proteins formed by the trans-membrane trimetric glycoprotein protruding from the viral surface, also binds to angiotensin-converting enzyme 2. After the viral contents are released inside the host cells, viral RNA enters the nucleus to replicate. As for the biosynthesis, viral mRNA is used to make viral proteins. The new viral particles are formed in the maturation step and then released.

Angiotensin-converting enzyme 2 plays an important role for the interaction between the classical and non-classical pathway of the renin angiotensin system. The former acts through the angiotensin II type 1 receptors, and its increased activity leads to fibrosis, inflammation and angiogenesis. The latter acts through the Mas receptors and has opposing effects to the angiotensin II type 1 receptors. Angiotensin-converting enzyme 2 is expressed by the epithelial cells of lungs, intestines, kidneys and blood vessels; therefore, the aforementioned

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

* Corresponding author: Timur Ekiz, email timurekiz@gmail.com
tissues/organs are vulnerable to SARS-CoV-2 infection. Additionally, activation of the renin angiotensin system is significantly associated with increased morbidity and mortality as in hypertension.

On the other hand, vitamin D deficiency has also been described as pandemic and a global public health problem, especially in Europe (Table 1). Regardless of age, ethnicity and latitude, recent data showed that 40% of Europeans are vitamin D deficient (25-hydroxyvitamin D (25(OH)D) levels < 50 nmol/l), and 13% are severely deficient (25(OH)D < 30 nmol/l). According to regression analyses, a quadratic relationship was found between the prevalences of vitamin D deficiency in most commonly affected countries by COVID-19 and the latitudes (Fig. 2). Interestingly, vitamin D deficiency is more common in the subtropical and mid-latitude countries than the tropical and high-latitude countries. Contrary to the expectation, the most commonly affected countries with severe vitamin D deficiency are from the subtropical (Saudi Arabia 46%, Qatar 46%, Iran 33-4%, Chile 26-4%) and mid-latitude (France 27-3%, Portugal 21-2%, Austria 19-3%) regions. On the other hand, severe vitamin D deficiency was found to be nearly 0% in some high-latitude countries (e.g. Norway, Finland, Sweden, Denmark and Netherlands). The low prevalences of severe vitamin D deficiencies in high-latitude countries (except for the UK; 23-7%) can possibly be attributed to the high awareness of vitamin D deficiency, high amount of vitamin D supplementation, food fortification and health policies as well. Indeed, as the main source of vitamin D is exposure of the skin to sun (UV-B), it has long been supposed that living in a sunny country guarantees sufficient vitamin D levels. However, there is increasing evidence that vitamin D deficiency may have been underestimated/ignored in low latitude, even in tropical countries.

The risks for vitamin D deficiency encompass obesity, elderly, lack of proper sun (UV-B) exposure, dark skin, smoking, living with air pollution and the presence of co-morbid diseases such as infection, cancer, CVD, chronic respiratory disease, osteoporosis, sarcopenia and diabetes mellitus. Further, it is known that severe vitamin D deficiency dramatically increases the risk of mortality, infections and many other diseases. As such, it should indisputably be prevented whenever detected/possible.

Vitamin D hormone has important functions – including immunomodulant, anti-inflammatory and anti-infective roles. It acts via monocyte and cell-mediated immunity stimulation, suppression of lymphocyte proliferation, antibody production and cytokine synthesis. Human lung cells are able to intracellularly convert the inactive 25(OH)D to its active form 1,25(OH)D which reduces proinflammatory cytokines and increases peptides (e.g. the innate antimicrobial peptide cathelicidin). Cathelicidin has direct antiviral activity against enveloped respiratory viruses such as hepatitis B, influenza, respiratory syncytial virus and possibly the COVID-19 as well. Other than the above-mentioned functions, vitamin D has also anti-fibrotic effects. The renin-inhibiting activity and down-regulation of the renin angiotensin system activity seem to be the beneficial effects of vitamin D. Moreover, vitamin D has been shown to suppress angiotensinogen and regulate its expression.

---

**Fig. 2**. The world map illustrates the total deaths and percentage of severe vitamin D deficiency in countries most commonly affected by COVID-19. Severe vitamin D deficiency (%): (i), >30 (South Arabia, Qatar, Iran, China); (ii), 20–30 (France, Chile, UK, Portugal); (iii), 10–20 (Austria, Pakistan, Italy, Poland, Brazil, Israel, Croatia, Romania, Turkey, Germany); (iv), 5–10 (India, Russia, Switzerland, Canada, Belgium, USA, South Korea, Ireland, Spain); (v), <5 (Greece, Singapore, Mexico, Japan, Ecuador, Australia, Sweden, Malaysia, Norway, Finland, Denmark, Netherlands). Total deaths: (a), >25 000 (USA, UK, Italy, France, Spain); (b), 5000–10 000 (Brazil, Belgium, Germany, Iran, The Netherlands, Canada); (c), 1000–5000 (China, Mexico, Turkey, Sweden, India, Ecuador, Russia, Peru, Switzerland, Ireland, Portugal, Romania); (d), 500–1000 (Poland, Pakistan, Japan, Austria, Denmark); (e), <500 (Chile, Finland, Saudi Arabia, Israel, South Korea, Norway, Greece, Malaysia, Australia, Croatia, Singapore, Qatar).
The distribution of community outbreaks shows seasonal patterns along certain latitude, temperature, and humidity, that is, similar to the behaviour of seasonal viral respiratory tract infections. It has been reported that COVID-19 displays significant spread in mid-latitude (35–50° N) regions and/or in those with an average temperature of 5–11°C and low humidity (Fig. 1).\(^\text{1,50}\) Coronavirus are very stable at 4°C (viable for up to 3 d) and can survive at −20°C (for up to 2 years).\(^\text{11}\) Depending on some parameters (e.g. temperature, humidity and sunlight), they can live on different surfaces for a few days. They are thermolabile; decreased sunlight, low temperatures and less humidity seem to be favourable for COVID-19.\(^\text{11}\)

Although natural UV (UV-C) from the sunlight may not be strong enough to kill COVID-19, its antimicrobial efficacy has long been shown to inactivate, thus preventing the transmission of airborne-mediated infections such as influenza and tuberculosis.\(^\text{51}\) Further, UV-B from the sun can induce endogenous vitamin D in the skin – being the main source of vitamin D other than the dietary intake or supplementation. These factors might possibly be explanatory as regards the low prevalence of COVID-19 in subtropical and southern countries.

Patients infected with COVID-19 have higher mortality rates if they are older, that is, 8.0% (70–79 years) and 14.8% (>80 years). The similar rates for co-morbid conditions are 10.5% (CVD), 7.3% (diabetes mellitus), 6.3% (chronic...
respiratory disease), 6.0% (hypertension) and 5.6% (cancer)\(^5\). Older adults with any of these co-morbid diseases are at high risk for COVID-19 infection—especially in the presence of severe vitamin D deficiency\(^53\). To this end, since there is positive/strong evidence concerning the effects of vitamin D against viral respiratory infections, it would not be unsound to say that vitamin D supplementation may decrease viral induction and inflammatory genes, and incidence/severity of respiratory tract infections\(^48\). In this sense, a meta-analysis of twenty-five randomised controlled trials showed that vitamin D supplementation has a preventive effect against acute respiratory tract infections and that the benefit is higher in those subjects receiving daily or weekly vitamin D without additional bolus doses, and in those having severe vitamin D deficiency at baseline\(^54\).

Although vitamin D was primarily recognised for bone metabolism, increasing evidence indicates its proper function for nearly every tissue in the body including brain, heart, lung, muscle, immune system and skin\(^55\). Therefore, the treatment of vitamin D deficiency would be vital for several diseases including cardiovascular and neurological disorders, cancers, autoimmune diseases and infections as well\(^55\). Likewise, a recent review recommended that in people at risk of influenza/COVID-19 infection, 250 μg/d of vitamin D\(_3\) for a few weeks (or a month) that is, to rapidly increase the 25(OH)D concentrations and then 125 μg/d in the follow-up can be considered\(^47\). The target should be to raise its value above 40–60 ng/ml. Additionally, the authors also suggested higher vitamin D\(_3\) doses for infected patients with COVID-19. For sure, attention should be paid not to take high calcium supplementation for potential risk of hypercalcemia while taking high doses of vitamin D\(_3\). Needless to say, as vitamin D is synthesised mainly in the skin, sun (UV-B) exposure (15–20 min daily) inducing the light pink colour of minimal erythema would be the natural way of production and activation of vitamin D by keratinocytes\(^55\).

Accordingly, presenting this paper, we would like to call attention to the possible association between severe vitamin D deficiency and mortality pertaining to COVID-19. Given its rare side effects and relatively wide safety, prophylactic vitamin D supplementation and/or food fortification might reasonably serve as a very convenient and incomparable/invaluable adjuvant therapy for these two worldwide public health problems alike.

Acknowledgements

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

M. K. performed study concept and design, acquisition of the data, writing and drafting the manuscript, and final approval and is the guarantor of the manuscript. T. E. performed study concept and design, acquisition of the data, writing and drafting the manuscript and final approval. V. R. performed study concept and design, writing and drafting the manuscript and final approval. O. K. performed study concept and design, writing and drafting the manuscript and final approval. L. O. performed study concept and design, writing and drafting the manuscript, and final approval and is the supervisor.

The authors report no conflicts of interest.

References

1. World Health Organization (2020) Coronavirus disease (COVID-19) situation reports. Geneva: World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/ (accessed May 2020).
2. Yuki K, Fujigoi M & Koatsogiannaki S (2020) COVID-19 pathophysiology: a review. Clin Immunol 2020, 108427.
3. Vaduganathan M, Vardeny O, Michel T, et al. (2020) Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 382, 1653–1659.
4. Zou X, Chen K, Zou J, et al. (2020) Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med (epublication ahead of print version 12 March 2020).
5. Eymundsdottir H, Chang M, Geirsdottir OG, et al. (2019) Association between vitamin D deficiency and insulin resistance markers in euthyroid non-diabetic individuals. Diabetes Metab Syndr 13, 258–263.
6. Orces CH (2015) Vitamin D status among older adults residing in the littoral and Andes mountains in Ecuador. ScientificWorldJournal 2015, 545297.
7. Clark P, Vivanco-Muñoz N, Piña JT, et al. (2015) High prevalence of hypovitaminosis D in Mexicans aged 14 years and older and its correlation with parathyroid hormone. Arch Osteoporos 10, 225.
8. Solis-Urra P, Cristi-Montero C, Romero-Parrà J, et al. (2019) Passive commuting and higher sedentary time is associated with vitamin D deficiency in adult and older women: results from Chilean National Health Survey 2016–2017. Nutrients 11, 300.
9. Formiga F, Ferrer A, Megido MJ, et al. (2014) Low serum vitamin D is not associated with an increase in mortality in oldest old subjects: the Octabaix three-year follow-up study. Gerontology 60, 10–15.
10. Veronese N, Sergi G, De Rui M, et al. (2014) Serum 25-hydroxyvitamin D and incidence of diabetes in elderly people: the PRO.V.A. Study. J Clin Endocrinol Metab 99, 2351–2358.
11. Aspell N, Laird E, Healy M, et al. (2019) The prevalence and determinants of vitamin D status in community-dwelling older adults: results from the English Longitudinal Study of Ageing (ELSA). Nutrients 11, 1253.
12. Cougnard-Grégoire A, Merle BM, Korobelnik JF, et al. (2015) Vitamin D deficiency in community-dwelling elderly is not associated with age-related macular degeneration. J Nutr 145, 1865–1872.
13. Vetter VM, Spira D, Banszerus VL, et al. (2020) Epigenetic clock and leukocyte telomere length are associated with vitamin D status, but not with functional assessments and frailty in the Berlin Aging Study II. J Gerontol A Biol Sci Med Sci (epublication ahead of print version 23 April 2020).
14. Karanova T, Andreeva A, Nikitina I, et al. (2016) Prevalence of vitamin D deficiency in the North-West region of Russia: a cross-sectional study. J Steroid Biochem Mol Biol 164, 230–234.
15. Özçakır ZA, Goz M & Türkübeyler BH (2017) Prevalence of vitamin D deficiency in otherwise healthy individuals between the ages of 18 and 90 years in southeast Turkey. Wien Klin Wochenschr 129, 854–855.
16. Hoge A, Donneau AF, Sreed S, et al. (2015) Vitamin D deficiency is common among adults in Wallonia (Belgium, 51°30’ North): findings from the Nutrition, Environment and Cardio-Vascular Health study. Nutr Res 35, 716–725.
17. Ten Haaf DSM, Balvers MGJ, Timmers S, et al. (2019) Determinants of vitamin D status in physically active elderly in the Netherlands. Eur J Nutr 58, 3121–3128.
18. Öztürk ZA, Gol M & Türkbeyler E (2016) Serum concentrations of 25-hydroxyvitamin D and immunoglobulins in an older Swiss cohort: results of the Senior Labor Study. BMC Med 11, 176.
19. Duarte C, Carvalheiro H, Rodrigues AM, et al. (2020) Prevalence of vitamin D deficiency and its predictors in the Portuguese population: a nationwide population-based study. Arch Osteoporos 15, 36.
20. Buebener D, McGuigan F, Gerdhemi P, et al. (2014) Vitamin D insufficiency over 5 years is associated with increased fracture risk—an observational cohort study of elderly women. Osteoporos Int 25, 2767–2775.
21. Elmdahl I, Meyer AL, Wotta D, et al. (2017) Vitamin D intake and status in Austria and its effects on some health indicators. Austrian J Nutr Metab 4, 1050.
22. Khosla S, Eisman JA, Adachi JD, et al. (2015) Vitamin D deficiency in community-dwelling elderly is not associated with an increased risk of cognitive impairment. Arch Osteoporos 11, 23.
23. Kàppel M, Stavropoulos S, Kokkoris P, et al. (2015) Smoking is a significant determinant of low serum vitamin D in young and middle-aged healthy males. Hormones (Athens) 14, 245–250.
24. Laktas-Gelevich N, Korsic M, Crnecvic-Orlic Z, et al. (2010) Vitamin D status, dependence on age, and seasonal variations in the concentration of vitamin D in Croatian postmenopausal women initially screened for osteoporosis. Clin Rheumatol 29, 861–867.
25. Wei J, Zhu A & Ji JS (2019) A comparison study of vitamin D deficiency among older adults in China and the United States. Sci Rep 9, 17913.
26. Roben K, Butler LM, Wang R, et al. (2013) Genetic and environmental predictors of serum 25-hydroxyvitamin D concentrations among middle-aged and elderly Chinese in Singapore. Br J Nutr 109, 493–502.
27. Nakamura K, Kitamura K, Takachi R, et al. (2015) Impact of demographic, environmental, and lifestyle factors on vitamin D sufficiency in 9094 Japanese adults. Bone 74, 10–17.
28. Shin JH, Lee HT, Lim YH, et al. (2015) Defining vitamin D deficiency and its relationship to hypertension in postmenopausal Korean women. J Women’s Health (Larchmt) 24, 1021–1029.
36. Gill TK, Hill CL, Shanahan EM, et al. (2014) Vitamin D levels in an Australian population. *BMC Public Health* **14**, 1001.
37. Chin KY, Ima-Nirwana S, Ibrahim S, et al. (2014) Vitamin D status in Malaysian men and its associated factors. *Nutrients* **6**, 5419–5433.
38. Khosravi-Boroujeni H, Sarrafzadegan N, Sadeghi M, et al. (2017) Prevalence and trends of vitamin D deficiency among Iranian adults: a longitudinal study from 2001–2013. *J Nutr Sci Vitaminol (Tokyo)* **63**, 284–290.
39. Alfawaz H, Tamim H, Alharbi S, et al. (2014) Vitamin D status among patients visiting a tertiary care center in Riyadh, Saudi Arabia: a retrospective review of 3475 cases. *BMC Public Health* **14**, 159.
40. Mehboobali N, Iqbal SP & Iqbal MP (2015) High prevalence of vitamin D deficiency and insufficiency in a low income peri-urban community in Karachi. *J Pak Med Assoc* **65**, 946–949.
41. Saliba W, Rennert HS, Kersenbaum A, et al. (2012) Serum 25(OH)D concentrations in sunny Israel. *Osteoporos Int* **23**, 687–694.
42. El-Menyar A, Rahil A, Dousa K, et al. (2012) Low vitamin D and cardiovascular risk factors in males and females from a sunny, rich country. *Open Cardiovasc Med J* **6**, 76–80.
43. Mechenro J, Venugopal G, Kumar B, et al. (2018) Vitamin D status in Kancheepuram District, Tamil Nadu, India. *BMC Public Health* **18**, 1345.
44. Lips P, Cashman KD, Lamberg-Allardt C, et al. (2019) Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol* **180**, P23–P54.
45. Mendes MM, Hart KH, Botelho PB, et al. (2018) Vitamin D status in the tropics: is sunlight exposure the main determinant? *Nutr Bull* **43**, 428–434.
46. Schleicher RL, Sternberg MR, Looker AC, et al. (2016) National estimates of serum total 25-hydroxyvitamin D and metabolite concentrations measured by liquid chromatography-tandem mass spectrometry in the US population during 2007–2010. *J Nutr* **146**, 1051–1061.
47. Grant WB, Lahore H, McDonnell SL, et al. (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* **12**, E988.
48. Beard JA, Bearden A & Striker R (2011) Vitamin D and the anti-viral state. *J Clin Virol* **50**, 194–200.
49. Feldman D, Pike JW, Bouillon R, et al. (editors) (2017) *Vitamin D: Volume 1: Biochemistry, Physiology And Diagnostics*. Cambridge: Academic Press.
50. Sajadi MM, Habibzadeh P, Vintzileos A, et al. (2020) Temperature, humidity and altitude analysis to predict potential spread and seasonality for COVID-19. https://ssrn.com/abstract=3550308 (accessed March 2020).
51. Welch D, Buonanno M, Grilj V, et al. (2018) Far-UVC light: a new tool to control the spread of airborne-mediated microbial diseases. *Sci Rep* **8**, 2752.
52. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (2020) The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi* **41**, 145–151.
53. Alipio M (2020) Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (COVID-19). https://ssrn.com/abstract=3571484 (accessed April 2020).
54. Martineau AR, Jolliffe DA, Hooper RL, et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* **356**, i6583.
55. Mostafa WZ & Hegazy RA (2015) Vitamin D and the skin: focus on a complex relationship: a review. *J Adv Res* **6**, 793–804.