Vitamin D in Long COVID-19

Subjects: Infectious Diseases

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Coronavirus disease 2019 (COVID-19) has quickly become a global pandemic. Reports from different parts of the world indicate that a significant proportion of people who have recovered from COVID-19 are suffering from various health problems collectively referred to as “long COVID-19”. Common symptoms include fatigue, shortness of breath, cough, joint pain, chest pain, muscle aches, headaches, and so on. Vitamin D is an immunomodulatory hormone with proven efficacy against various upper respiratory tract infections. Vitamin D can inhibit hyperinflammatory reactions and accelerate the healing process in the affected areas, especially in lung tissue. Moreover, vitamin D deficiency has been associated with the severity and mortality of COVID-19 cases, with a high prevalence of hypovitaminosis D found in patients with COVID-19 and acute respiratory failure. However, no evidence has been found to support a role of vitamin D supplementation in reducing symptoms of long-COVID-19. On the other hand, having a higher vitamin D level before SARS-CoV-2 infection or raising it rapidly at the first symptoms of infection can significantly reduce the risk and severity of COVID-19.

Keywords: COVID-19 ; SARS-CoV-2 ; long COVID-19 ; vitamin D ; inflammation

1. Introduction

Because of the recent advances in the pathophysiological mechanisms that occur with the novel coronavirus disease 2019 (COVID-19), there is growing interest to profoundly investigate the role of vitamin D and its deficiency to increase the susceptibility and negative results of COVID-19. Vitamin D is a secosteroid produced by the skin mainly due to exposure to sunlight in the form of cholecalciferol, and diet provides about 20% of the daily requirement of this vitamin [1].

Vitamin D deficiency has been defined as a serum concentration of 25-hydroxyvitamin D (25OHD) < 20 ng/mL (50 nmol/L) [2]. It is noteworthy to emphasize that it has been reported that its concentrations in women are lower than in men due to the proportion and distribution of fat tissue [3].

Goërtz et al. assessed 2113 patients with confirmed or suspected COVID-19 diagnosis and found that at least 87% of them continued with symptoms later than 60 days of the first symptom (of which 32% reported one or two symptoms and 55% reported three or more symptoms) [4]. The conditions (up to 60 days) following infection with COVID-19 are known as prolonged, long-lasting, post-acute, long-term, or chronic effects; among them, the most common symptoms are fatigue, dyspnea, and insomnia [5]. Vitamin D deficiency has also been related to all these symptoms [6]. Carpagnano et al. found a high prevalence of vitamin D deficiency in COVID-19 patients with acute respiratory failure [7]. It is important to emphasize that vitamin D deficiency is related to many other diseases and conditions that will increase the risk of developing a long-term COVID-19 [2][4][6][8]. In this respect, Savanelli et al. reported that vitamin D deficiency is the greatest predictor of the prevalence of dyslipidemia and hypertension in patients with coronary heart disease, suggesting the presence of both factors in cardiovascular risk in this group of patients [8]. Furthermore, according to a recent review, this virus may provoke a new onset of type 2 diabetes mellitus with undetermined clinical and metabolic components, providing a possible role for COVID-19 in developing type 2 diabetes mellitus [9].

For these reasons, vitamin D has been identified as one of the critical components for treating COVID-19 infection [6][10][11]. However, there is more to explain of how vitamin D works in prolonged COVID-19 patients.

2. Long COVID-19 and Vitamin D

The pandemic’s beginning with COVID-19 was characterized by a great concern to contain the contagion of the disease. Almost two years after the health emergency was declared, the focus is the health of those who have survived the disease [12]. As of 18 February 2022, over 409 million confirmed cases and over 5.8 million deaths had been reported globally [13].

These data highlight the large number of people who had COVID-19 and have recovered; in some of them, the consequences will persist in the long term. It is estimated that one-third of patients have persisting symptoms for six months after contracting the infection [14]. Thus, there is an increased need to provide healthcare for long-term symptoms.

The risk factors for long COVID-19 differ somewhat from those for COVID-19 [15]. One study reported that having hypertension, obesity, a psychiatric condition, or an immunosuppressive condition was associated with increased risk of long COVID-19 [16]. On the other hand, long COVID-19 is more likely in women and the age group most affected is somewhat lower. One reason for middle age being a more important risk factor for long COVID-19 is that the risk of mortality increases rapidly with increasing age. A review of COVID-19 mortality rates for 66,646 inpatients in the U.S. admitted from April to June 2020 found increasing mortality rates with increasing age: 40–49 years, 5.8%; 50–59 years, 10.6%; 60–69 years, 18.0%; 70–79 years, 26.5%; and 80+ years, 34.4% [17]. For both COVID-19 mortality and long COVID-19, admission to an intensive care unit is a very important risk factor. Thus, the difference in age profile between mortality and long COVID-19 is that older COVID-19 patients are more likely to die. The reason for more women having long COVID-19 is also likely due to men having a higher mortality rate from COVID-19.

A study involving 4182 COVID-19 cases from Sweden, the UK, and the USA investigated the risk factors for long COVID-19 [18] A total of 558 participants reported symptoms lasting longer than 4 weeks, 189 > 8 weeks, and 95 > 12 weeks. Factors significantly associated with long COVID-19 were age (52 (43–59) years), asthma, heart disease, visit to a hospital, and number of symptoms.

A review of risk factors for long COVID-19 stated that several biomarkers were elevated including D-dimer, interleukin-6 (IL-6), C-reactive protein, procalcitonin, and neutrophils count [19]. A study conducted in western Mexico involving 22 vitamin D supplemented COVID-19 outpatients (mean 25OHD = 22.4 ng/mL) and 20 non-supplemented patients (mean 25OHD = 23.4 ng/mL) found that, although ferritin concentrations were significantly lower in supplemented patients, d-dimer concentrations were not significantly different [20]. A study in India also reported no significant effect on d-dimer concentrations with vitamin D supplementation of 69 COVID-19 patients [21]. Additionally, a high-dose vitamin D supplementation study conducted in Turkey involving 95 hospitalized COVID-19 patients found that increasing mean 25OHD concentration from 23 to 35 ng/mL had no significant effect on ferritin, d-dimer concentrations, but was associated with reduced fibrinogen concentrations [22].

Epstein–Barr virus (EBV) reactivation appears to be a risk factor for severe COVID-19 and also appears to be associated with long COVID-19. A study in the UK involving 128 COVID-19 patients, 17 had EBV reactivation and more severe COVID-19 and adverse outcomes [23]. A study in Turkey found long COVID-19 in 56 of 185 COVID-19 patients and that 20 of 30 long COVID-19 patients were positive for EBV reactivation vs. 2 of 20 controls [24]. Vitamin D supplementation of 20,000 IU/week over 96 weeks was found to significantly reduce humoral immune responses to the latent EBV antigen EBNA1 in relapsing-remitting multiple sclerosis [25].

One of the reasons why vitamin D supplementation may be ineffective in treating long COVID-19 is that the SARS-CoV-2 virus can downregulate vitamin D receptors. This has been observed for cytomegalovirus infection [26][27], hepatitis B virus [28], and hepatitis C virus [29]. EBV has been found to block activation of gene expression through is EBNA-3-ptotein [30]. If downregulation is not complete, it might be that very high vitamin D doses would be able to have some effect, but not in the cells with VDRs downregulated.

Although many of the multi-organ manifestations of COVID-19 are known, the possible long-term implications remain unknown [31][32]. Given the recentness of the COVID-19 pandemic, it is not possible to estimate, by itself, the long-term effects. However, there are similar coronavirus events that have happened previously, such as SARS-CoV-1 and Middle East respiratory syndrome coronavirus [33]. Although the current COVID-19 has lower mortality rates than those mentioned above [34], the reports describe similarities, allowing to know the possible long-term implications and thus take actions to minimize complications [33]. Some of the long-term manifestations of these other pandemics were: matched exercise capacity and carbon monoxide diffusing capacity, cardiovascular complications, hematological manifestations, thrombotic complications, central nervous system manifestations, and renal and gastrointestinal complications [33].

Wang et al. stated that COVID-19 could leave long-lasting consequences in at least three critical areas: pulmonary, neuronal, and neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease, and multiple sclerosis [35].

A recent study based on survivors of COVID-19 found that 78 patients out of 100 who had recovered had abnormal cardiovascular findings on magnetic resonance imaging; also, 36 of them suffered dyspnea and unusual fatigue [36]. It should be noted that these consequences were not only observed in those patients who had a severe illness but also in those with mild and moderate presentations [37][38]. Many questions remain unanswered, but the variation in viral load and

differential immune response can explain why some have long COVID-19 and others do not [39]. Ahearn-Ford et al. presented data that proposed that inflammatory cytokine pathways altered during infection could continue during convalescence [40].

A recent review stated that the effects on the central nervous system after an acute phase of COVID-19 could be perpetuated over time as a neuro-COVID-19. They reported 12 neurological deficits in long COVID-19, such as mental fog, tremors, confusion, and stiff limbs [41]. For their part, Logue et al. investigated the symptoms that persisted after COVID-19 infection in a longitudinal prospective cohort study with 234 patients. The results show that the most persistent manifestations were fatigue (13.6%) and loss of the sense of smell or taste (13.6%) [14].

The importance of vitamin D in long COVID-19 has recently been published [42]. This pro-hormone, fat-soluble is obtained to a greater extent through sun exposure, but there is also a lower contribution from diet [43]. Diet is an essential determinant of 25OHD concentrations. In particular, Crowe reported that 25OHD concentrations were higher in meat and fish eaters than in vegetarians and vegans, who exclude specific food sources of vitamin D from their diet [1]. More recently, a positive association has been reported between 25OHD concentrations and adherence to the Mediterranean diet, a nutritional pattern effective in preventing and treating obesity-related diseases due to the synergistic action of many nutrients with anti-inflammatory and antioxidant properties [44]. The best-known function of this vitamin is related to the normal mineralization of the bones since it contributes to the absorption of calcium in the intestine and the maintenance of adequate levels of calcium and phosphate in serum, having a fundamental role in the prevention of rickets in children and osteomalacia and osteoporosis in adults [45].

The possibility of vitamin D acting as an immunomodulator has generated great interest recently [46]. However, it has many other functions, including the modulation of cell growth, neuromuscular function, immune function, and a reduction in inflammation [45]. It is important to note that 25OHD concentrations can be decreased in the presence of acute inflammation.

Likewise, more studies are needed to understand better the health impact of the prolonged period of COVID-19 in these patients. Before the pandemic, it was already known that low 25OHD concentrations were associated with fatigue and muscle weakness in the general population. Townsend et al. investigated the relationship between 25OHD concentrations and fatigue and reduced exercise tolerance in 149 patients 79 days after COVID-19 [42]. They evaluated the participants using the Chalder Fatigue score, six-minute walk test, and the modified Borg scale. By applying multivariable linear and logistic regression models, they concluded that there was a correlation between vitamin D and persistent vitamin D fatigue and reduced exercise tolerance in this population of COVID-19 patients. It is important to note that this work only evaluated two of the ample diversity of long COVID-19 symptoms [42]. However, fatigue is the most common symptom of long COVID-19 and is seen in other viral infections [47].

Pizzini et al. studied, in a prospective, multicenter study on long-term sequelae after suffering COVID-19 in 109 patients, the associations of 25OHD concentrations with the presentation of COVID-19 [48]. It was observed that a high proportion of patients presented alteration of vitamin D metabolism eight weeks after diagnosis. Patients with severe COVID-19, most likely due to prolonged hospitalization, showed a disturbing parathyroid-vitamin-D axis within their recovery phase. However, low 25OHD concentrations were not related to the burden of persistent symptoms, concluding that although vitamin D deficiency is common among COVID-19 patients, it was not associated with long-term disease outcomes [48]. Due to the novelty of the disease and the different reported results, it is essential to continue with more studies to evaluate the possible effect of vitamin D in the long post-COVID-19 period.

Overall, the COVID-19 pathology is still characterized by cytokine storm, resulting in endothelial inflammation, microvascular thrombosis, and multiple organ failure [49]. Hyperinflammation is a critical component of severe COVID-19, which is associated with poor outcomes underneath the cytokine storm umbrella term [50]. Thus, an important way to minimize or avoid long COVID-19 is to raise 25OHD concentrations before SARS-CoV-2 infection or COVID-19.

Another way to reduce the risk of long COVID-19 is to aggressively treat SARS-CoV-2 infection and COVID-19 as soon as possible after symptoms are manifest. In one study, raising serum 25OHD concentrations to a mean value near 35 ng/mL in a few days to two weeks for hospitalized COVID-19 patients significantly reduced mortality rates but did not seem to affect symptoms [22]. On the other hand, treating hospitalized COVID-19 patients with high-dose calcifediol has been found to significantly reduce admission to the Intensive Care Unit and death rates [51].

It should be noted that most of the research results are based on COVID-19 variants that are no longer dominant such as the Delta variant. The Omicron variant is associated with 30–45% lower attendance for emergency care and 50–70% lower hospital admission rate in the UK than the Delta variant was [52]. A preliminary report from South Africa also

indicates that Omicron COVID-19 is much less severe than Delta COVID-19 [53]. Oxygen therapy use was 75% lower, mechanical ventilation use was nearly 90% lower, admission to intensive care units was about 40% lower, length of stay was 70% lower, and death rates were 90% lower. Although the mean age of Omicron COVID-19 patients (36 years vs. 59 years for Delta COVID-19 patients) explains some of the differences, it implies that those who survived Omicron COVID-19 are much less likely to experience serious long COVID-19. However, it is too soon to determine whether this will be the case.

References

1. Crowe, F.L.; Steur, M.; Allen, N.E.; Appleby, P.N.; Travis, R.C.; Key, T.J. Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: Results from the EPIC–Oxford study. Public Health Nutr. 2011, 14, 340–346.
2. Barrea, L.; Frias-Toral, E.; Pugliese, G.; Garcia-Velasquez, E.; Carignano, M.D.L.A.; Savastano, S.; Colao, A.; Muscogiuri, G. Vitamin D in obesity and obesity-related diseases: An overview. Minerva Endocrinol. 2021, 46, 177–192.
3. Muscogiuri, G.; Barrea, L.; Di Somma, C.; Laudisio, D.; Salzano, C.; Pugliese, G.; De Alteriis, G.; Colao, A.; Savastano, S. Sex Differences of Vitamin D Status across BMI Classes: An Observational Prospective Cohort Study. Nutrients 2019, 11, 3034.
4. Goërtz, Y.M.J.; Van Herck, M.; Delbressine, J.M.; Vaes, A.W.; Meys, R.; Machado, F.V.C.; Houben-Wilke, S.; Burtin, C.; Posthuma, R.; Franssen, F.M.E.; et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: The post-COVID-19 syndrome? ERJ Open Res. 2020, 6, 00542–02020.
5. Callard, F.; Perego, E. How and why patients made Long COVID. Soc. Sci. Med. 2020, 268, 113426.
6. Pereira, M.; Dantas Damascena, A.D.; Galvão Azevedo, L.M.G.; de Almeida Oliveira, T.D.A.; da Mota Santana, J.D.M. Vitamin D deficiency aggravates COVID-19: Systematic review and meta-analysis. Crit. Rev. Food Sci. Nutr. 2020, 62, 1308–1316.
7. Carpagnano, G.E.; Di Lecce, V.; Quaranta, V.N.; Zito, A.; Buonamico, E.; Capozza, E.; Palumbo, A.; Di Gioia, G.; Valerio, V.N.; Resta, O. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. J. Endocrinol. Investig. 2020, 44, 765–771.
8. Savanelli, M.C.; Scarano, E.; Muscogiuri, G.; Barrea, L.; Vuolo, L.; Rubino, M.; Savastano, S.; Colao, A.; Di Somma, C. Cardiovascular risk in adult hypopituitaric patients with growth hormone deficiency: Is there a role for vitamin D? Endocrine 2015, 52, 111–119.
9. Mahrooz, A.; Muscogiuri, G.; Buzzetti, R.; Maddaloni, E. The complex combination of COVID-19 and diabetes: Pleiotropic changes in glucose metabolism. Endocrine 2021, 72, 317–325.
10. Damascena, A.D.; Azevedo, L.M.G.; Oliveira, T.A.; Santana, J.D.M.; Pereira, M. Addendum to vitamin D deficiency aggravates COVID-19: Systematic review and meta-analysis. Crit. Rev. Food Sci. Nutr. 2021, 1–6.
11. Giustina, A. Hypovitaminosis D and the endocrine phenotype of COVID-19. Endocrine 2021, 72, 1–11.
12. Klok, F.A.; Boon, G.J.; Barco, S.; Endres, M.; Geelhoed, J.M.; Knauss, S.; Rezek, S.A.; Spruit, M.A.; Vehreschild, J.; Siegerink, B. The Post-COVID-19 Functional Status scale: A tool to measure functional status over time after COVID-19. Eur. Respir. J. 2020, 56, 2001494.
13. World Health Organization. Weekly Epidemiological Update on COVID-19. Available online: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-COVID-19---15-february-2022 (accessed on 1 March 2022).
14. Logue, J.K.; Franko, N.M.; McCulloch, D.J.; McDonald, D.; Magedson, A.; Wolf, C.R.; Chu, H.Y. Sequelae in Adults at 6 Months After COVID-19 Infection. JAMA Netw. Open 2021, 4, e210830.
15. Crook, H.; Raza, S.; Nowell, J.; Young, M.; Edison, P. Long COVID—mechanisms, risk factors, and management. BMJ 2021, 374, n1648.
16. Tenforde, M.W.; Kim, S.S.; Lindsell, C.J.; Rose, E.B.; Shapiro, N.I.; Files, D.C.; Gibbs, K.W.; Erickson, H.L.; Steingrub, J.S.; Smithline, H.A.; et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network—United States, March–June 2020. MMWR. Morb. Mortal. Wkly. Rep. 2020, 69, 993–998.
17. E Goodman, K.; Magder, L.S.; Baghdadi, J.D.; Pineles, L.; Levine, A.R.; Perencevich, E.N.; Harris, A.D. Impact of Sex and Metabolic Comorbidities on Coronavirus Disease 2019 (COVID-19) Mortality Risk Across Age Groups: 66 646 Inpatients Across 613 U.S. Hospitals. Clin. Infect. Dis. 2020, 73, e4113–e4123.

18. Sudre, C.H.; Murray, B.; Varsavsky, T.; Graham, M.S.; Penfold, R.S.; Bowyer, R.C.; Pujol, J.C.; Klaser, K.; Antonelli, M.; Canas, L.S.; et al. Attributes and predictors of long COVID. Nat. Med. 2021, 27, 626–631.

19. Yong, S.J. Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. Infect. Di s. 2021, 53, 737–754.

20. Sánchez-Zuno, G.; González-Estevez, G.; Matuz-Flores, M.; Macedo-Ojeda, G.; Hernández-Bello, J.; Mora-Mora, J.; P érez-Guerrero, E.; García-Chagollán, M.; Vega-Magaña, N.; Turrubiates-Hernández, F.; et al. Vitamin D Levels in COVI D-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation. J. Clin. Med. 2021, 10, 2 378.

21. Sabico, S.; Enani, M.A.; Sheshah, E.; Aljohani, N.J.; Aldisi, D.A.; Alotaibi, N.H.; Alshingetti, N.; Alomar, S.Y.; Alnaami, A. M.; Amer, O.E.; et al. Effects of a 2-Week 5000 IU versus 1000 IU Vitamin D3 Supplementation on Recovery of Sympto ms in Patients with Mild to Moderate COVID-19: A Randomized Clinical Trial. Nutrients 2021, 13, 2170.

22. Gönen, M.S.; Alaylıoğlu, M.; Durcan, E.; Özdemir, Y.; Şahin, S.; Konukoğlu, D.; Nohut, O.K.; Ürkmez, S.; Küçükece, B.; Balkan, I.I.; et al. Rapid and Effective Vitamin D Supplementation May Present Better Clinical Outcomes in COVID-19 (SARS-CoV-2) Patients by Altering Serum INOS1, IL1B, IFNg, Cathelicidin-LL37, and ICAM1. Nutrients 2021, 13, 404 7.

23. Xie, Y.; Cao, S.; Dong, H.; Lv, H.; Teng, X.; Zhang, J.; Wang, T.; Zhang, X.; Qin, Y.; Chai, Y.; et al. Clinical characteristic s and outcomes of critically ill patients with acute COVID-19 with Epstein-Barr virus reactivation. BMC Infect. Dis. 2021, 21, 1–8.

24. Gold, J.; Okyay, R.; Licht, W.; Hurley, D. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. Pathogens 2021, 10, 763.

25. Røsjø, E.; Lossius, A.; Abdelmagid, N.; Lindstrøm, J.C.; Kampman, M.T.; Jørgensen, L.; Sundström, P.; Olsson, T.; Stef fensen, L.H.; Torkildsen, Ø.; et al. Effect of high-dose vitamin D3 supplementation on antibody responses against Epste in–Barr virus in relapsing-remitting multiple sclerosis. Mult. Scler. J. 2016, 23, 395–402.

26. Rieder, F.J.; Gröschel, C.; Kastner, M.-T.; Kosulin, K.; Laengle, J.; Zadnikar, R.; Marculescu, R.; Schneider, M.; Lion, T.; Bergmann, M.; et al. Human cytomegalovirus infection downregulates vitamin-D receptor in mammalian cells. J. Steroi d Biochem. Mol. Biol. 2016, 165, 356–362.

27. Robak, O.; Kastner, M.-T.; Stecher, C.; Schneider, M.; Andreas, M.; Greinix, H.; Kallay, E.; Honsig, C.; Steininger, C. Cy tomegalovirus Infection Downregulates Vitamin D Receptor in Patients Undergoing Hematopoietic Stem Cell Transplan tation. Transplantation 2020, 105, 1595–1602.

28. Gotlieb, N.; Tachlytski, I.; Lapidot, Y.; Sultan, M.; Safran, M.; Ben-Ari, Z. Hepatitis B virus downregulates vitamin D rece ptor levels in hepatoma cell lines, thereby preventing vitamin D-dependent inhibition of viral transcription and productio n. Mol. Med. 2018, 24, 53.

29. Abdel-Mohsen, M.A.; El-Braky, A.A.-A.; Ghazal, A.A.E.-R.; Shamseya, M.M. Autophagy, apoptosis, vitamin D, and vita min D receptor in hepatocellular carcinoma associated with hepatitis C virus. Medicine 2018, 97, e0172.

30. Yenamandra, S.P.; Hellman, U.; Kempkes, B.; Darekar, S.D.; Petermann, S.; Sculley, T.; Klein, G.; Kashuba, E. Epstein -Barr virus encoded EBNA-3 binds to vitamin D receptor and blocks activation of its target genes. Cell Mol. Life Sci. 20 10, 67, 4249–4256.

31. Gupta, A.; Madhavan, M.V.; Sehgal, K.; Nair, N.; Mahajan, S.; Sehrawat, T.S.; Bikdeli, B.; Ahluwalia, N.; Ausiello, J.C.; Wan, E.Y.; et al. Extrapulmonary manifestations of COVID-19. Nat. Med. 2020, 26, 1017–1032.

32. Wadman, M.; Couzin-Frankel, J.; Kaiser, J.; Matacic, C. A rampage through the body. Science 2020, 368, 356–360.

33. Higgins, V.; Sohaei, D.; Diamandis, E.P.; Prassas, I. COVID-19: From an acute to chronic disease? Potential long-term health consequences. Crit. Rev. Clin. Lab. Sci. 2020, 58, 297–310.

34. Wu, A.; Peng, Y.; Huang, B.; Ding, X.; Wang, X.; Niu, P.; Meng, J.; Zhu, Z.; Zhang, Z.; Wang, J.; et al. Genome Compos ition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microbe 2020, 27, 325–32 8.

35. Wang, F.; Kream, R.M.; Stefano, G.B. Long-Term Respiratory and Neurological Sequelae of COVID-19. Med. Sci. Moni t. 2020, 26, e928996.

36. Puntmann, V.O.; Carerj, M.L.; Wieters, I.; Fahim, M.; Arendt, C.; Hoffmann, J.; Shchendrygina, A.; Escher, F.; Vasa-Nic otera, M.; Zeiher, A.M.; et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovere d From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020, 5, 1265.

37. Zemb, P.; Bergman, P.; Camargo, C.A., Jr.; Cavalier, E.; Cormier, C.; Courbebaisse, M.; Hollis, B.; Joulia, F.; Minisola, S.; Pilz, S.; et al. Vitamin D deficiency and the COVID-19 pandemic. J. Glob. Antimicrob. Resist. 2020, 22, 133–134.

38. Yelin, D.; Wirtheim, E.; Vetter, P.; Kalil, A.C.; Bruchfeld, J.; Runold, M.; Guaraldi, G.; Mussini, C.; Gudiol, C.; Pujol, M.; et al. Long-term consequences of COVID-19: Research needs. Lancet Infect. Dis. 2020, 20, 1115–1117.
39. Baig, A.M. Deleterious Outcomes in Long-Hauler COVID-19: The Effects of SARS-CoV-2 on the CNS in Chronic COVID Syndrome. ACS Chem. Neurosci. 2020, 11, 4017–4020.
40. Ahearn-Ford, S.; Lunjani, N.; McSharry, B.; MacSharry, J.; Fanning, L.; Murphy, G.; Everard, C.; Barry, A.; McGreal, A.; al Lawati, S.M.; et al. Long-term disruption of cytokine signalling networks is evident in patients who required hospitalization for SARS-CoV-2 infection. Allergy 2021, 76, 2910–2913.
41. Marshall, M. The lasting misery of coronavirus long-haulers. Nature 2020, 585, 339–341.
42. Townsend, L.; Dyer, A.; McCluskey, P.; O'Brien, K.; Dowds, J.; Laird, E.; Bannan, C.; Bourke, N.; Cheallaigh, C.N.; Byrne, D.; et al. Investigating the Relationship between Vitamin D and Persistent Symptoms Following SARS-CoV-2 Infection. Nutrients 2021, 13, 2430.
43. Muscogiuri, G.; Barrea, L.; Scannapieco, M.; Di Somma, C.; Scacchi, M.; Aimaretti, G.; Savastano, S.; Colao, A.; Marzullo, P. The lullaby of the sun: The role of vitamin D in sleep disturbance. Sleep Med. 2018, 54, 262–265.
44. Barrea, L.; Muscogiuri, G.; Laudisio, D.; Pugliese, G.; De Alteriis, G.; Colao, A.; Savastano, S. Influence of the Mediterranean Diet on 25-Hydroxyvitamin D Levels in Adults. Nutrients 2020, 12, 1439.
45. Georgakopoulou, V.E.; Mantzouranis, K.; Damaskos, C.; Karakou, E.; Melemeni, D.; Mermigkis, D.; Petsinis, G.; Sklapani, P.; Trakas, N.; Tsiafaki, X. Correlation Between Serum Levels of 25-Hydroxyvitamin D and Severity of Community-Acquired Pneumonia in Hospitalized Patients Assessed by Pneumonia Severity Index: An Observational Descriptive Study. Cureus 2020, 12, e8947.
46. Wu, D.; Lewis, E.D.; Pae, M.; Meydani, S.N. Nutritional Modulation of Immune Function: Analysis of Evidence, Mechanisms, and Clinical Relevance. Front. Immunol. 2019, 9, 3160.
47. Raveendran, A.; Misra, A. Post COVID-19 Syndrome ("Long COVID") and Diabetes: Challenges in Diagnosis and Management. Diabetes Metab. Syndr. Clin. Res. Rev. 2021, 15, 102235.
48. Pizzini, A.; Aichner, M.; Sahanic, S.; Böhm, A.; Egger, A.; Hoermann, G.; Kurz, K.; Widmann, G.; Bellmann-Weiler, R.; Weiss, G.; et al. Impact of Vitamin D Deficiency on COVID-19—A Prospective Analysis from the CovILD Registry. Nutrients 2020, 12, 2775.
49. Andrade, B.S.; Siqueira, S.; Soares, W.D.A.; Rangel, F.D.S.; Santos, N.; Freitas, A.D.S.; da Silveira, P.R.; Tiwari, S.; Alzahrani, K.; Góes-Neto, A.; et al. Long-COVID and Post-COVID Health Complications: An Up-to-Date Review on Clinical Conditions and Their Possible Molecular Mechanisms. Viruses 2021, 13, 700.
50. Mehta, P.; Fajgenbaum, D.C. Is severe COVID-19 a cytokine storm syndrome: A hyperinflammatory debate. Curr. Opin. Rheumatol. 2021, 33, 419–430.
51. Entrenas Castillo, M.E.; Entrenas Costa, L.M.E.; Vaquero Barrios, J.M.V.; Alcalá Díaz, J.F.A.; López Miranda, J.L.; Bouillon, R.; Quesada Gomez, J.M.Q. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. J. Steroid Biochem. Mol. Biol. 2020, 203, 105751.
52. Mahase, E. COVID-19: Hospital admission 50–70% less likely with omicron than delta, but transmission a major concern. BMJ 2021, 375.
53. Maslo, C.; Friedland, R.; Toubkin, M.; Laubscher, A.; Akaloo, T.; Kama, B. Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared with Previous Waves. JAMA 2022, 327, 583.