Vitamin D status as it relates to COVID-19 complications and death

Compiled by Dr. Alan Palmer

Prior to finding the summary below of studies on covid.us.org, I had accumulated and posted three dozen articles showing benefit of Vitamin D in prevention and outcomes with viral respiratory infections and COVID-19. Well, let's just say that they far exceeded my efforts as you will see below! But, before looking at the amazing assortment of studies they have compiled, I have found a few more very recent ones they hadn't included that you will see first.

I consider this a living document and will continue to add studies as they come out. So, check back from time to time for updates.

After reading this you may wonder why we need vaccines and expensive anti-viral drugs for viral respiratory infections (although medications may still have their place for the few that would still need it). Bringing everyone's Vitamin D level into optimal range would be a game changer! Don't believe me? Read on.

Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers.

Nature. Published November 19, 2020.

From the abstract:

The fatality rate was high in vitamin D deficient (21% vs 3.1%). Vitamin D level is markedly low in severe COVID-19 patients. Inflammatory response is high in vitamin D deficient COVID-19 patients. This all translates into increased mortality in vitamin D deficient COVID-19 patients. As per the flexible approach in the current COVID-19 pandemic authors recommend mass administration of vitamin D supplements to population at risk for COVID-19.

Conclusion

Vitamin D deficiency markedly increases the chance of having severe disease after infection with SARS Cov-2. The intensity of inflammatory response is also higher in vitamin D deficient COVID-19 patients. This all translates to increase morbidity and mortality in COVID-19 patients who are deficient in vitamin D. Keeping the current COVID-19 pandemic in view authors recommend administration of vitamin D supplements to population at risk for COVID-19.

https://www.nature.com/articles/s41598-020-77093-z

Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results.

Journal of the American Medical Association (JAMA). September 03, 2020.

Conclusions

The findings of this study suggest a role of vitamin D status, based on deficiency of levels and

treatment, in risk of COVID-19 infection. Randomized clinical trials of interventions to reduce vitamin D deficiency are needed to determine if those interventions could reduce COVID-19 incidence, including both broad population interventions and interventions among groups at increased risk of vitamin D deficiency and/or COVID-19.

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2770157

<u>Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled,</u> <u>study (SHADE study).</u>

British Medical Journal (BMJ). November 12th, 2020.

Conclusion:

A high dose, oral vitamin D supplementation to augment 25(OH)D >50 ng/ml helped to achieve SARS-CoV-2 RNA negativity in greater proportion of asymptomatic vitamin D-deficient individuals with SARS-CoV-2 infection along with a significant decrease in inflammatory marker. SARS-CoV-2 RNA negativity by cholecalciferol supplementation may help in reducing transmission rates of the highly contagious SARS-CoV-2 infection. A reassurance for public health workers regarding greater likelihood of SARS CoV-2 RNA negativity in individuals receiving therapeutic cholecalciferol supplementation will be encouraging.

https://pmj.bmj.com/content/early/2020/11/12/postgradmedj-2020-139065

Effect of Vitamin D3 Supplementation vs Placebo on Hospital Length of Stay in Patients with Severe COVID-19: A Multicenter, Double-blind, Randomized Controlled Trial.

Journal of Steroid Biochemistry and Molecular Biology. November 17th, 2020.

Conclusion:

In conclusion, we were able to report among frail elderly residents that bolus vitamin D3 supplementation taken during or just before COVID-19 was associated with less severe COVID-19 and better survival rate. No other treatment showed protective effect.

Vitamin D3 supplementation may represent an effective, accessible and well-tolerated treatment for COVID-19, the incidence of which increases dramatically and for which there are currently no treatments. Further prospective, preferentially interventional, studies are needed to confirm whether supplementing older adults with bolus vitamin D3 during or just before the infection could improve, or prevent, COVID-19.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7553119/

"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"

Journal of Steroid Biochemistry and Molecular Biology. August 2020.

Conclusion:

Our pilot study demonstrated that administration of a high dose of Calcifediol or 25-hydroxyvitamin D, a main metabolite of vitamin D endocrine system, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19. Calcifediol seems to be able to reduce severity of the disease, but larger trials with groups properly matched will be required to show a definitive answer.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456194/

Vitamin D status and outcomes for hospitalised older patients with COVID-19

British Medical Journal (BMJ). August 1st, 2020.

Conclusion:

Our study has demonstrated that patients over the age of 65 years presenting with symptoms consistent with COVID-19 are more likely to be vitamin D deficient. There appears to be a clinically relevant association between this and elevated markers of cytokine release syndrome and increased risk of respiratory failure requiring ventilatory support. Although there was no apparent mortality difference between the two groups, this may reflect the overall poor prognosis associated with the higher prevalence of frailty and comorbidities in our older cohort of patients. Vitamin D status may be a prognosticator for COVID-19, and supplementation might improve outcomes. Further studies in all age groups are awaited to validate this. Older adults with vitamin D deficiency and COVID-19 may demonstrate worse morbidity outcomes. Vitamin D status may be a useful prognosticator.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456620/

Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study.

July 20th, 2020.

From the discussion:

The main finding of this study was the low plasma 25(OH)D level association with COVID- 19 hospitalization risks, for patients tested positively for COVID-19, after adjusting for age, gender, SES and chronic, mental and physical disorders. Hence, low 25(OH)D level was identified as independently associated with the likelihood of COVID-19 infection. This finding is in agreement with the results of other studies (5,7,9-15,19,30-42). Further, reduced risk of acute respiratory tract infection following vitamin D supplementation has been reported (43,44).

https://pubmed.ncbi.nlm.nih.gov/32700398/

COVID.US.org section: from https://covid.us.org/vitamin-d/

Can Vitamin D help against Covid-19?_Numerous studies included

Substantial evidence from scientific studies shows that vitamin D reduces risk of infection, of a severe case, and of death from Covid-19.

Vitamin D articles

- * Vitamin D versus Covid-19: part one
- * Vitamin D versus Covid-19: part two
- * Vitamin D versus Covid-19: part three
- * Fighting Covid-19: Vitamin D, Magnesium, Vitamin B12
- * <u>Vitamin D and Covid-19 Clinical Trials</u> from ClinicalTrials.gov ongoing trials.

Vitamin D videos

- * Vitamin D NOW for COVID-19 by Allan Mishra, MD and DareToBeVital.com
- * Video: Does Vitamin D Protect Against COVID-19? by Dr. JoAnn E. Manson, MD, DrPH
- * Dr. Mobeen Syed on immune system benefits of vitamin D
- * Dr. Syed again on Vitamin D overview and description of an RCT
- * Dr. Roger Seheult of MedCram on vitamin D

Vitamin D commentary

For more vitamin D commentary, see this article.

Summary

Having normal healthy blood levels of vitamin D reduces Covid-19 risks, including risk of infection [7, 8, 9, 11, 12, 14, 16, 23, 27], of having a severe case [1, 3, 4, 5, 15, 17, 20, 22, 24, 25, 26], of needing hospitalization, ICU care, and/or mechanical ventilation [2, 10, 14, 15, 21, 22, 24, 26], as well as the risk of dying from Covid-19 [4, 6, 7, 9, 12, 13, 17, 18, 19, 22, 24, 25, 28].

Experts recommend Vitamin D supplementation as a measure against Covid-19 [81, 83, 84], at a dosage of 10,000 IU per day for a few weeks or a month, reducing to 5,000 IU/day thereafter [81, 84]. Doses of 10,000 IU/day are necessary to raise vitamin D levels in 97.5% of the population to optimal levels; lower doses may not be effective in everyone [82]. Doses as high as 40,000 IU/day are unlikely to result in vitamin D toxicity [82].

Additional benefits of vitamin D. Studies have shown that a high intake of vitamin D reduces risk of respiratory tract infections [101], stroke [102], multiple sclerosis [103], rheumatoid arthritis [104], type 2 diabetes [105], breast cancer [106], prostate cancer [107], colon cancer [108], and all-cause mortality [109].

Vitamin D can be taken daily or once-a-week. A one-time bolus of 300,000 IU of vitamin D is safe [87, 90] and may be useful when vitamin D cannot be taken daily, or when someone becomes ill and needs to raise their vitamin D levels as quickly as possible. Calcifediol can be used in-hospital to treat patients with Covid-19 and low vitamin D [21].

Sunlight on skin can produce significant amounts of vitamin D, butt he amount of skin exposed must be more than the face and hands [89]. Face, hands, and arms exposed to sunlight is a minimum for reaching vitamin D normal levels [88, 89].

Other Vitamins

articles:

- * Riboflavin (Vitamin B2) as an Inhibitor of Covid-19
- * MATH+ Protocol for prophylaxis and mild cases (Vitamins D, C, B1)

videos:

* Dr. Mobeen Syed: Vitamin K Deficiency Leads to Poor COVID-19 Outcome

Vitamin D versus Covid-19, Studies

1. Alipio, Mark. "Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19)." SSRN 3571484 (9 April 2020). <u>Study Link</u> | <u>PDF Link</u>

2. Lau, Frank H., et al. "Vitamin D insufficiency is prevalent in severe COVID-19." medRxiv (28 April 2020). <u>Study Link</u> | <u>PDF Link</u>

3. Daneshkhah, Ali, et al. "The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients." medRxiv (2020).

Study Link | PDF Link

4. Davies, Gareth, Attila R. Garami, and Joanna C. Byers. "Evidence Supports a Causal Model for Vitamin D in COVID-19 Outcomes." medRxiv (2020). <u>Study Link | PDF Link</u>

5. De Smet, Dieter, et al. "Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics." medRxiv (2020).

Study Link | PDF Link

6. Raharusun, Prabowo, et al. "Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study." (2020). <u>PDF file</u> | <u>PDF Link</u>

7. Ilie, Petre Cristian, Simina Stefanescu, and Lee Smith. "The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality." Aging Clinical and Experimental Research (2020): 1. <u>Study Link | PDF Link</u>

8. D'Avolio, Antonio, et al. "25-hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2." Nutrients 12.5 (2020): 1359. Study Link | PDF Link

9. Laird, E., et al. "Vitamin D and Inflammation: Potential Implications for Severity of Covid-19." Ir Med J; Vol 113; No. 5; P81: 2020.

PDF file | PDF Link

10. Faul, J.L., et al. "Vitamin D Deficiency and ARDS after SARS-CoV-2 Infection." Ir Med J; Vol 113; No. 5; P84: 2020. <u>PDF file</u> | <u>PDF Link</u>

11. Meltzer, David O., et al. "Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence." medRxiv (2020).

Study Link | PDF Link

12. Li, Yajia, et al. "Sunlight and vitamin D in the prevention of coronavirus disease (COVID-19) infection and mortality in the United States." (2020).

PDF file | PDF Link

13. Pugach, Isaac Z. and Pugach, Sofya "Strong Correlation Between Prevalence of Severe Vitamin D Deficiency and Population Mortality Rate from COVID-19 in Europe." medRxiv (2020). <u>Study Link | PDF Link</u>

14. Merzon, Eugene, et al. "Low plasma 25(OH) vitamin D3 level is associated with increased risk of COVID-19 infection: an Israeli population-based study." medRxiv (2020). — Low vitamin D increased risk (adjusted OR) of infection with Covid-19 by 45% and of hospitalization for Covid by 95%. <u>Study Link</u> | <u>PDF Link</u> 15. Panagiotou, Grigorios et al., "Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity: results of a local audit of practice." medRxiv (2020). Conclusion: "we found that patients requiring ITU admission [*in the ICU*] were more frequently vitamin D deficient than those managed on medical wards [*on the floor*], despite being significantly younger." <u>PDF file Link</u> | <u>PDF Link</u>

16. Chang, Timothy S., et al. "Prior diagnoses and medications as risk factors for COVID-19 in a Los Angeles Health System." medRxiv (2020).

Study Link | PDF Link

~ Risk factors included vitamin D deficiency, which increased risk of COVID-19 diagnosis by 80% (OR 1.8 [1.4-2.2], p=5.7 x 10-6).

17. Maghbooli, Zhila, et al. "Vitamin D Sufficiency Reduced Risk for Morbidity and Mortality in COVID-19 Patients." Available at SSRN 3616008 (2020).

Study Link | PDF Link

~ Vitamin D sufficiency reduced clinical severity and inpatient mortality.

* See this Expression of Concern by the editors of PLoS One

18. Panarese and Shahini, "Letter: Covid-19 and Vitamin D" Alimentary Pharmacology and Therapeutics, April 12, 2020. Link to Letter | PDF Link

~ Covid-19 mortality increases with increasing latitude (by nation), and vitamin D blood levels decrease with increasing latitude. The authors propose that low levels of vitamin D increase Covid-19 mortality.

19. Carpagnano, Giovanna Elisiana, et al. "Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19." Journal of Endocrinological Investigation (2020): 1-7. <u>Study Link</u> | <u>PDF Link</u> ~ "A survival analysis highlighted that, after 10 days of hospitalization, severe vitamin D deficiency patients had a 50% mortality probability, while those with vitamin D = 10 ng/mL had a 5% mortality risk (p = 0.019)."

20. Mardani, R., et al. "Association of vitamin D with the modulation of the disease severity in COVID-19." Virus Research (2020): 198148. <u>Study Link</u> | <u>PDF Link</u>

21. Castillo, Marta Entrenas, et al. "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." The Journal of Steroid Biochemistry and Molecular Biology (2020): 105751. <u>Study Link | PDF Link</u>

22. Radujkovic, et al. "Vitamin D Deficiency and Outcome of COVID-19 Patients." Nutrients 2020, 12(9), 2757; Study Link | PDF Link

— "The present study demonstrates an association between VitD deficiency and severity of COVID-19. VitD-deficient patients had a higher hospitalization rate and required more (intensive) oxygen therapy and IMV. In our patients, when adjusted for age, gender, and comorbidities, VitD deficiency was associated with a 6-fold higher hazard of severe course of disease and a ~15-fold higher risk of death."

23. Israel, Ariel, et al. "The link between vitamin D deficiency and Covid-19 in a large population." MedRxiv 9/7/2020. <u>Study Link</u> | <u>PDF Link</u>

24. Jae Hyoung Im, et al. "Nutritional status of patients with coronavirus disease 2019 (COVID-19)." International Journal of Infectious Diseases. August 7, 2020. <u>PDF Link</u> | <u>PDF Link</u>

25. Gennari L, et al "Vitamin D deficiency is independently associated with COVID-19 severity and mortality" ASBMR 2020; Abstract 1023. <u>Study Link</u> | <u>PDF Link</u>

26. Baktash, Vadir, et al. "Vitamin D status and outcomes for hospitalised older patients with COVID-19." Postgraduate Medical Journal (2020). <u>Study Link</u> | <u>PDF Link</u>

- "The main findings of our study suggest that older patients with lower serum concentrations of 25(OH)D, when

compared with aged-matched vitamin D-replete patients, may demonstrate worse outcomes from COVID-19. Markers of cytokine release syndrome were raised in these patients and they were more likely to become hypoxic and require ventilatory support in HDU." [HDU is high dependency unit]

27. Kaufman HW, et al. "SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels." (2020) PLoS ONE 15(9): e0239252. <u>Study Link</u> | <u>PDF Link</u>

- Optimum vitamin D blood level for reducing Covid-19 infection was found to be in the 50's (ng/ml). This is the first study to show that 25(OH)D at levels above 30 have additional benefits.

28. Brenner, Hermann, Bernd Holleczek, and Ben Schöttker. "Vitamin D Insufficiency and Deficiency and Mortality from Respiratory Diseases in a Cohort of Older Adults: Potential for Limiting the Death Toll during and beyond the COVID-19 Pandemic?." Nutrients 12.8 (2020): 2488. <u>PDF Link</u>

"Compared to those with sufficient vitamin D status, participants with vitamin D insufficiency and deficiency had strongly increased respiratory mortality, with adjusted hazard ratios (95% confidence intervals) of 2.1 (1.3-3.2) and 3.0 (1.8-5.2) overall, 4.3 (1.3-14.4) and 8.5 (2.4-30.1) among women, and 1.9 (1.1-3.2) and 2.3 (1.1-4.4) among men. Overall, 41% (95% confidence interval: 20-58%) of respiratory disease mortality was statistically attributable to vitamin D insufficiency or deficiency. Vitamin D insufficiency and deficiency are common and account for a large proportion of respiratory disease mortality in older adults, supporting the hypothesis that vitamin D3 supplementation could be helpful to limit the burden of the COVID-19 pandemic, particularly among women."

29. Pepkowitz, Samuel H., et al. "Vitamin D Deficiency is Associated with Increased COVID-19 Severity: Prospective Screening of At-Risk Groups is Medically Indicated." (2020). <u>PDF File</u>

- Persons hospitalized for Covid-19 were more than twice as likely to need ICU care if they had with vitamin D deficiency.

30. Mandal, Amit KJ, et al. "Vitamin D status may indeed be a prognosticator for morbidity and mortality in patients with COVID-19." Journal of Medical Virology. <u>PDF Link</u>

- Findings: "patients with low concentrations of 25OH-D (<or=30nmol/l) demonstrated clinically relevant, elevated markers of cytokine release syndrome and were more likely to become hypoxic and require ventilatory support."

31. Karahan and Katkat. "Impact of Serum 25(OH) Vitamin D Level on Mortality in Patients with COVID-19 in Turkey." The journal of nutrition, health & aging (2020). <u>PDF File</u>

32. Faniyi, et al. "Vitamin D status and seroconversion for COVID-19 in UK healthcare workers who isolated for COVID-19 like symptoms during the 2020 pandemic." medRxiv 6 Oct. 2020. <u>PDF Link</u>

— "Vitamin D deficiency is a risk factor for COVID-19 seroconversion for NHS healthcare workers especially in BAME male staff."

33. Yılmaz, Kamil, and Velat Şen. "Is Vitamin D Deficiency a Risk Factor for Covid 19 in Children?." Pediatric Pulmonology. <u>Study Link</u>

— "The symptom of fever was significantly higher in COVID- 19 patients who had deficient and insufficient vitamin D levels than in patients who had sufficient vitamin D level."

- "Patients with COVID-19 had significantly lower vitamin D levels 13.14 ng/ml than did the controls 34.81 ng/ml."

34. Annweiler, C. et al. "Vitamin D and survival in COVID-19 patients: A quasi-experimental study." The Journal of Steroid Biochemistry and Molecular Biology, 13 October 2020. <u>Study Link</u>

 Bolus vitamin D3 supplementation during or just before COVID-19 was associated with less severe COVID-19 and better survival rate in frail elderly.

35. Han, Jenny E., et al. "High dose vitamin D administration in ventilated intensive care unit patients: a pilot double blind randomized controlled trial." Journal of clinical & translational endocrinology 4 (2016): 59-65. <u>Study Link</u>
— Hospital stay cut in half for patients needing ICU care and ventilation and receiving 100,000 IU Vitamin D3 daily for 5 days. Note that this was not a Covid-19 specific study, but a study of ICU patients on mechanical ventilation.

36. De Smet, Dieter, et al. "Serum 25 (OH) D Level on Hospital Admission Associated With COVID-19 Stage and Mortality." American journal of clinical pathology (2020). <u>Study Link</u>

- Covid-19 patients admitted to hospital were 3.87 times more likely to die from Covid-19, if they had vitamin D deficiency.

37. Rastogi, Ashu, et al. "Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study)." Postgraduate medical journal (2020). <u>Study Link</u>

 Covid-19 patients were given 60,000 IU vitamin D daily for 7 days; these patients were 3.0 times more likely to become negative for Covid-19 than patients not given vitamin D.

38. Afshar, Parviz, Mohammad Ghaffaripour, and Hamid Sajjadi. "Suggested role of Vitamin D supplementation in COVID-19 severity." Journal of Contemporary Medical Sciences 6.4 (2020). <u>Study Link</u>

- 300,000 IU vitamin D3 once, then 100 IU per kilogram of body weight per day; greatly reduced deaths and length of hospital stay for Covid-19.

39. Luo, Xia, et al. "Vitamin D Deficiency Is Inversely Associated with COVID-19 Incidence and Disease Severity in Chinese People." The Journal of Nutrition (2020). <u>Study Link</u>

- vitamin D deficiency (<30 nmol/L) (OR: 2.72) was significantly associated with COVID-19 severity.

40. Pereira, Marcos, et al. "Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis." Critical reviews in food science and nutrition (2020): 1-9. <u>Study Link</u>

— severe cases of COVID-19 present 64% more vitamin D deficiency compared with mild cases. A vitamin D concentration insufficiency increased hospitalization and mortality from COVID-19. We observed a positive association between vitamin D deficiency and the severity of the disease.

41. Katz, Joseph, Sijia Yue, and Wei Xue. "Increased risk for Covid-19 in patients with Vitamin D deficiency." Nutrition (2020): 111106. <u>Study Link</u>

- "patients with vitamin D deficiency were 5 times more likely to be infected with Covid-19 than patients with no deficiency after adjusting for age groups"

42. Arvinte, Cristian, Maharaj Singh, and Paul E. Marik. "Serum Levels of Vitamin C and Vitamin D in a Cohort of Critically III COVID-19 Patients of a North American Community Hospital Intensive Care Unit in May 2020: A Pilot Study." Medicine in drug discovery 8 (2020): 100064. <u>Study Link</u>

- "Serum levels of vitamin C and vitamin D were low in most of our critically ill COVID-19 ICU patients."

43. Yılmaz, Kamil, and Velat Şen. "Is vitamin D deficiency a risk factor for COVID-19 in children?." Pediatric Pulmonology 55.12 (2020): 3595-3601. <u>Study Link</u> | <u>Explanation of Study</u>

— Children in this study with higher vitamin D blood levels (20 ng/ml or higher) were 4.6 times more likely to have no symptoms while infected with Covid-19, and 72% less likely to have a moderate/severe case of Covid-19 than children with vitamin D deficiency.

44. Tan, Chuen Wen, et al. "A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients." medRxiv (2020). <u>Study Link</u>

— "a vitamin D / magnesium / vitamin B12 combination in older COVID-19 patients was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen support, intensive care support, or both."

45. Jain, Anshul, et al. "Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers." Scientific reports 10.1 (2020): 1-8. <u>Study Link</u>

— "The fatality rate was high in vitamin D deficient (21% vs 3.1%). Vitamin D level is markedly low in severe COVID-19 patients." In this study, patients with low vitamin D had a mortality rate of 21%; those with higher vitamin D had a mortality rate of only 3.1%. Those with higher vitamin D were more likely to have a mild case, and less likely to die; those with low vitamin D were more likely to have a severe case, and more likely to die.

46. Ling, Stephanie F., et al. "High-Dose Cholecalciferol Booster Therapy is Associated with a Reduced Risk of Mortality in Patients with COVID-19: A Cross-Sectional Multi-Centre Observational Study." Nutrients 12.12 (2020): 3799. <u>Study Link</u> — "In this observational study, treatment with cholecalciferol booster therapy, regardless of baseline serum 25(OH)D levels, appears to be associated with a reduced risk of mortality in acute in-patients admitted with COVID-19." In one group, the reduction in risk of death was 87%; in the other group, the reduction was 62%.

The evidence is overwhelming. Persons with Covid-19 should be given high-doses of Vitamin D3 (called "Cholecalciferol") to reduce risk of death. Many other studies (above) showed similar results.

47. Vassiliou, Alice G., et al. "Low 25-Hydroxyvitamin D Levels on Admission to the Intensive Care Unit May Predispose COVID-19 Pneumonia Patients to a Higher 28-Day Mortality Risk: A Pilot Study on a Greek ICU Cohort." Nutrients 12.12 (2020): 3773. <u>Study Link</u>

— "All patients who died within 28 days belonged to the low vitamin D group.... Critically ill COVID-19 patients who died in the ICU within 28 days appeared to have lower ICU admission 25(OH)D levels compared to survivors."

48. Anjum, S., et al. "Examine the association between severe Vitamin D deficiency and mortality in patients with Covid-19." Pakistan Journal of Medical and Health Sciences (2020): 1184-1186. <u>Study Link</u>

- "Patients with severe vitamin D deficiency had high rate of mortality (26.67%) as compared to patients with no vitamin D deficiency (7.5%)"

Additional Relevant Studies

61. Hastie, Claire E., et al. "Vitamin D concentrations and COVID-19 infection in UK Biobank." Diabetes & Metabolic Syndrome: Clinical Research & Reviews (2020). <u>Study Link</u>

— This study used Vitamin D data from 2006 to 2010 and looked at whether those patients were more or less likely to become infected with Covid-19 "for the period 16th March 2020 to 14th April 2020." At that early a date in the pandemic, when few persons were transmitting the disease, the risk of infection is much more likely to be related to being at high risk via profession or close association to an infected person by circumstance. It was not widespread enough for a factor like vitamin D blood levels to show up in the data. Also, the vitamin D levels were from 10 years or more before the date of infection. Finally, vitamin D has a much larger effect on disease severity than on infection.

Vitamin D versus Covid, Commentary

81. Grant, William B., et al. "Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths." Nutrients 12.4 (2020): 988. <u>Study Link</u>

— "To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d.... For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful."

82. Garland, Cedric F., et al. "Vitamin D supplement doses and serum 25-hydroxyvitamin D in the range associated with cancer prevention." Anticancer research 31.2 (2011): 607-611. <u>Study Link</u>

— "Results: Serum 25(OH)D rose as a function of self-reported vitamin D supplement ingestion in a curvilinear fashion, with no intakes of 10,000 IU/d or lower producing 25(OH)D values above the lower-bound of the zone of potential toxicity (200 ng/ml). Unsupplemented all-source input was estimated at 3,300 IU/d. The supplemental dose ensuring that 97.5% of this population achieved a serum 25(OH)D of at least 40 ng/ml was 9,600 IU/d. Conclusion: Universal intake of up to 40,000 IU vitamin D per day is unlikely to result in vitamin D toxicity."

83. Charoenngam and Holick, "Immunologic Effects of Vitamin D on Human Health and Disease." Nutrients 2020, 12(7), 2097; <u>Study Link</u>

- "It is therefore proposed that supplementation of vitamin D can reduce the risk and severity of COVID-19 infection."

84. Sharma, Suresh K., et al. "Vitamin D: A cheap yet effective bullet against coronavirus disease-19–Are we convinced yet?." National Journal of Physiology, Pharmacy and Pharmacology 10.7 (2020): 0-0. Study Link

"Therefore, from reviewed literature, it seems fairly appropriate to suggest taking Vit-D at 10,000 IU/day as an adequate dose to enhance circulatory concentration of Vit-D into the optimal range of 40–60 ng/mL; after 1 month the dose can be reduced to 5000 IU/day to maintain serum levels."

85. Kroll, Martin H., et al. "Temporal relationship between vitamin D status and parathyroid hormone in the United States." PloS one 10.3 (2015): e0118108. <u>Study Link</u>

Based on 3.8 million lab results of adults in the U.S.: "Vitamin D deficiency and insufficiency was common (33% <20 ng/mL; 60% <30 ng/mL).... The percentage of patients deficient in 25(OH)D3 seasonally varied from 21% to 48%...."

87. Kearns, Malcolm, Jessica Alvarez, and Vin Tangpricha. "Large, single-dose, oral vitamin D supplementation in adult populations: a systematic review." Endocrine Practice 20.4 (2014): 341-351.

— "This review recommends that vitamin D3 be used for supplementation over vitamin D2 and concludes that single vitamin D3 doses ≥300,000 IU are most effective at improving vitamin D status and suppressing PTH concentrations for up to 3 months."

88. Robert P. Heaney, The Vitamin D requirement in health and disease; Journal of Steroid Biochemistry & Molecular Biology. doi:10.1016/j.jsbmb.2005.06.020

89. Alagöl, Faruk, et al. "Sunlight exposure and vitamin D deficiency in Turkish women." Journal of endocrinological investigation 23.3 (2000): 173-177.

90. Liu, Guoqiang, Tianpei Hong, and Jin Yang. "A Single Large Dose of Vitamin D Could be Used as a Means of Coronavirus Disease 2019 Prevention and Treatment." Drug Design, Development and Therapy 14 (2020): 3429.

Vitamin D versus Other Diseases

101. Martineau, Adrian R., et al. "Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data." bmj 356 (2017).

Study Link

- Recommend daily or weekly dose, but not bolus dosing.

102. Marniemi et al., Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects; Nutrition, Metabolism & Cardiovascular Diseases. Volume 15, Issue 3, Pages 188-197, June 2005. <u>Study</u> Link

103. Munger et al., Vitamin D intake and incidence of multiple sclerosis; Neurology. January 13, 2004 vol. 62 no. 1, p. 60-65. <u>Study Link</u>

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