Sufficient Vitamin D Improves Covid-19 Outcomes
The Science Update
October 2020

Prepared by Connie Eash, MS
Website: CONNIEEASH.com
Email: cneash@gmail.com

==========

In my July report, I summarized studies that had shown significant decreases in critical outcomes and death when Covid-19 patients had 25(OH)D levels greater than 30 ng/ml.[1,2] Other studies found a correlation between low mean levels of vitamin D and a high number of cases and mortality per million population due to Covid-19 in 14 - 20 countries.[3,4]

New! Studies Since July 2020

These studies provide more evidence of the protective effect of sufficient vitamin D levels against the incidence of SARS-CoV-2 infection and its severity. Also included is the effective emergency use of Calcifediol [25(OH)D] to raise levels quickly:

- A study of 225 hospitalized Covid-19 patients found that levels of 25(OH)D over 30 ng/ml significantly reduced the severity of illness (p=0.02), hypoxia (p=0.004), unconsciousness (p=0.05), and CRP levels (p=0.01); sufficiency also correlated to an increase in blood lymphocyte percentage (p=0.05), which has been shown to protect against severe illness. In patients over 40 y.o., 9.7% with sufficient levels of D vs 20% of those with insufficient levels died. **Furthermore, 6.3% of those with levels greater than 40 ng/ml died. This was less than 1/3 the death rate of those with insufficient D levels and shows the possible benefit of higher blood levels of D.**[5]
- Mount Sinai studied 37 hospitalized Covid-19 patients, their 25(OH)D levels and severity of illness. A serum vitamin D level < 20 ng/mL was significantly associated with increased severity of illness as measured using a chest CT (p=0.001). These researchers urge that populations at risk for low serum 25(OH)D be tested and treated for deficiency.[6]
- Out of 76 hospitalized Covid-19 patients, 50 received standard of care plus Calcifediol 0.266 mg orally, on days 3 and 7, then weekly until discharge or ICU admission; the remaining 26 served as a control, receiving only standard of care. Despite a small sample size, results were significant (p<0.001). The **Calcifediol group showed a 93% reduction in the ICU admission rate**. Only one (2%) in the calcifediol group vs 13 (50%) in the control group required ICU admission. Two in the control group and none in the calcifediol group died. Calcifediol is the hormone derived from vitamin D3. It is better absorbed and faster acting, so more appropriate in emergency situations.[7]
- Vitamin D levels and SARS-CoV-2 test positivity rates were studied in 191,779 patients from all 50 U.S. states. There was 12.5% positivity for the virus in those with <20 ng/ml, 8.1% in those with 30-34 ng/ml, and 5.9% in those with >55 ng/ml. This regression was

statistically significant. **This again showed that higher 25(OH)D levels protected from contracting the virus**[8]

- Results of vitamin D testing performed between 2010 and 2019 were collected from a health database to assess the relationship between the prevalence of vitamin D deficiency and Covid-19 incidence in 200 localities in Israel. Researchers also matched 52,405 infected patients with 524,050 control individuals of the same sex, age, and region. **There was a highly significant correlation between the prevalence of vitamin D deficiency and Covid-19 incidence in localities (p<0.001)**. In the controls, there was a significant association between vitamin D deficiency and the risk of contracting Covid-19. In a further analysis of those who had acquired vitamin D formulations in the prior 4 months, **Covid-19 incidence was significantly lower in those who had purchased vitamin D drops, but not tablets.**[9]

Levels of 25(OH)D Must Be Over 30 ng/ml.

The Endocrine Society, based on a review of the scientific literature, recommends a blood level of at least 30 ng/ml.

- **Their recommended doses of D3:**
  - **600-1000 IU/day for children 1-18**
  - **1500-2000 IU/day in adults**
  - **3000 - 6000 IU/day if obese.**
  - **It is advisable to test. Initial doses should be higher, if D levels are lower than 30 ng/ml.**[10]

Another review of both the effect of D on the immune system and the effect of low D on influenza outcomes suggest that those at risk take a dose of 5000 IU/day to maintain a 25(OH)D concentration of 40-60 ng/ml.[11]

Correlations between 25(OH)D Deficiency and Disease

- **Cardiovascular Disease and High Blood Pressure** - The risks associated with low 25(OH)D levels include hypertension, coronary artery disease, ischemic heart disease, heart failure, stroke, and type 2 diabetes. A review of vitamin D and the cardiovascular outcomes explains activity of $1,25(OH)_2D$ on myocardiocytes and the vasculature, as well as systemic effects on insulin sensitivity, the renin-angiotensin system, the lipid profile, and inflammation. [12]
- **Influenza** - D3, 1200 IU/day, significantly decreased the diagnosis of Influenza A in a randomized, blind study of 334 schoolchildren. 10.8% of the D group and 18.6% controls were positive for the virus.[13]
- **Type 2 Diabetes** - A meta-analysis of 71 studies found an association of low 25(OH)D levels with type 2 diabetes.[14]
- **Prostate Cancer** - Out of 190 men undergoing a radical prostatectomy, 87 men demonstrated aggressive prostate cancer. Compared to the controls, the men with the aggressive cancer were 2.64 times more likely to have 25(OH)D levels less than 30 ng/ml ($p = 0.01$).[15]
- **Colorectal Cancer** - Pooled data from 17 cohorts, including 5706 colorectal patients and 7107 controls, showed that for each increase of 10 ng/ml 25(OH)D levels, the colorectal

cancer risk was 19% lower in women and 7% lower in men.[16]

- **Breast Cancer** - A cohort study followed 1666 women with breast cancer over 8 years. Compared to women with 25(OH)D deficiency (<20 ng/ml), those with sufficient levels (>30 ng/ml) had a 28% reduced risk of all-cause death. In premenopausal women, significance was even stronger, with breast cancer specific survival 63% less and invasive disease-free survival 42% less in the sufficient group.[17]
- **Pulmonary Disease** - A blind, randomized study of children found that those drinking D fortified milk had half the incidence of Acute Respiratory Infection as those drinking non-fortified milk.[18] A review of 3 randomized, European studies, including 469 subjects, showed that D supplementation substantially reduced the rate of moderate to severe COPD exacerbations in patients with baseline 25(OH)D levels less than 25 nmol/L (10 ng/L), but not in those with higher baseline levels.[19] A meta-analysis of 25 randomized controlled studies showed that Vitamin D supplements provided significant protection against acute respiratory tract infections. Correlation was strongest when D supplements were given daily or weekly and in those with initial 25(OH)D levels less than 25 ng/ml.[20]

Risk Factors for D Deficiency

According to CDC statistics, the average 25(OH)D levels are below 30 ng/ml for every race and age group. According to the CDC, sufficiency is only reached in the top 90th percentile of whites and the hispanic youth.[21] Americans as a whole are at risk for insufficient levels of vitamin D, but especially these groups:

- **The elderly**, who live in temperate climates and lack D in their diet, are deficient.[22] Aging can decrease the ability of the skin to produce D3 by two-fold.[23]
- **Skin Color** - The pigment melanin protects the skin from sun damage, but also slows the production of vitamin D3, even in children. In two vitamin D trials, skin types and 25(OH)D were measured in 296 healthy 8- to 18-year-old children. Low 25(OH)D was associated with an increase in both the Fitzpatrick sun-reactive skin typing and melanin index.[24]
- **Obesity** - D accumulates in fat cells, thus lowering blood levels. Studies show vitamin D deficiency in 80-90% of obese individuals. The obese need 2-3 times the normal dose to maintain a 25(OH)D level above 30 ng/ml.[25,26] Obese children are also susceptible to Vitamin D deficiency. In one study, 49% of the obese children vs 21% of normal weight children were deficient. This deficiency climbed to 87% in obese African-American children.[27]
- **Liver and kidney damage** can result in deficiencies of the active forms of D3, since it is converted to 25(OH)D in the liver and 1,25(OH)2D in the kidney.

Risk Factors for Severe Covid-19 Outcomes and Death.

- **Age** - An early study of 1000 Covid-19 patients found that age is a significant

risk for organ injuries, secondary infection, critical illness and death.[28]

- **Skin Color** - Covid incidence and death rates are higher among the black populations in Chicago, Louisiana, and Michigan. John Hopkins found that predominately black counties have more than 3-fold higher infection rate and 6-fold higher death rate than predominately white counties.[29] Of the 106 health workers in the UK, who died from Covid-19 as of April 22, 63% were from the black and ethnic communities. Furthermore, 94% of the doctors and 71% of the nurses who died from Covid-19 were black and ethnic.[30]
- **Obesity** - Those under 60 with a BMI over 35 were at least twice as likely to be admitted to the ICU for Covid-19 and 3 times as likely to die from virus.[31]

Aged Care Facilities

The elderly are at higher risk for both severe illness and death due to Covid-19 and for low 25(OH)D levels. Data compiled as of June 19, by the Foundation for Research on Equal Opportunity shows that 43% of COVID-19 deaths in the US have been in nursing homes or care facilities. New Hampshire, North Dakota, Rhode Island and Minnesota each experienced 78-80% of their COVID deaths in those facilities.[32]

Several conditions in the elderly are responsible for vitamin D deficiency:

- Skin content of 7-dehydrocholesterol is reduced in the elderly, contributing to a decrease in D3 synthesis.
- Gastrointestinal disease inhibits the absorption of D supplements.
- Liver and kidney disease reduce the metabolism of D3 into the active metabolites.

Using D supplements in nursing homes has been shown to prevent deficiency.[33]

New Zealand offers government sponsored Vitamin D supplements, 50,000 IU/month, to all residents of aged care facilities, thus raising serum 25(OH)D to sufficient levels. Of the 75% of residents who took the supplement, 98.5% had sufficient serum 25(OH)D levels, compared to only 35% of those not on a supplement.[34]

Multisystem Inflammatory Syndrome in Children (MIS-C)

- As of June 25, the NY Department of Health reports 225 cases and 3 deaths in New York of children experiencing symptoms similar to Kawasaki Disease (KD) and toxic shock-like syndrome, possibly due to COVID-19. Although the children do not test positive for the virus, most do test positive for SARS-CoV-2 antibodies, indicating a previous infection. As of June 21, at least 300 cases have been reported in the US.[35]
- According to the CDC: "KD… is an acute febrile illness of unknown etiology that primarily affects children younger than 5 years of age…Clinical signs include fever, rash, swelling of the hands and feet, irritation and redness of the whites of the eyes, swollen lymph glands in the neck, and irritation and inflammation of the mouth, lips, and throat. KD is a leading cause of acquired heart disease in the United States…In 2009, the estimated number of hospitalizations with KD was 5447 for children under 5 years of age."[36]

First diagnosed in the 1970s, it is associated with unidentified viral infections.

- A 2016 comparison of 79 children with KD and healthy sex-/age-matched controls showed that **98.7% of KD patients had vitamin D levels below 30 ng/ml.** Significantly more KD patients had severely low levels of vitamin D when compared to controls. A subgroup that developed coronary artery abnormalities had even lower levels when compared to others with KD (4.92 vs 9.41 ng/ml).[37]

Testing 25(OH)D Levels

In order to prevent severe illness and death due to Covid-19, future pandemics, and other diseases, it is critical to monitor patients' 25(OH)D levels and, using advice such as sun exposure and supplementation, increase levels to a minimum of 30 ng/ml. At present, only high risk groups have insurance coverage for such testing. In light of new information about the risk and prevalence of D deficiency, testing of all patients should be routine and covered by insurance.

Concern for Toxicity

Warnings of Vitamin D toxicity consider the toxic levels to be anywhere from 100 to 300 ng/ml.[38] A 2018 report considered the risk of vitamin D toxicity when 25(OH)D levels are over 150 ng/ml, which may be caused by long-term doses in excess of 10,000 IU/day. In addition, certain rare conditions may cause Vitamin D hypersensitivity and toxicity, even with normal 25(OH)D levels. These include Williams-Beuren syndrome, Chronic Kidney Disease, and granulomatous diseases. Normally, the first sign of toxicity would be an excess of calcium in the blood or urine and very low parathyroid activity.[39]

Vitamin K2 and magnesium are known to work in conjunction with vitamin D.

- **Vitamin K2** strengthens bone and reduces hypercalcemia by activating matrix GLA protein, thus promoting the entry of calcium into bone.[40]
- **Magnesium** is a cofactor for the activation of vitamin D in both the liver and kidneys, as well as with many vitamin D functions, such as bone health, cardiovascular disease, and metabolic syndrome. Magnesium intake is recommended for vitamin D optimization.[41]

Note: This is not meant to replace recommendations for sanitation and personal protection, nor the advice of your physician.

Vitamin D's protective effect against Covid-19 has inspired interest in many researchers. Due to the proliferation of this research, preprints are included. Waiting for the peer review and publishing of current research of a non-patented nutrient could take months or longer and would not be prudent in this case. Please use the references to learn the details and judge the quality of these studies for yourself.

References

[1] Alipio M. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019. Preprint posted: 9 Apr 2020 Last revised: 7 May 2020. https://papers.ssrn.com/sol3/Papers.cfm?abstract_id=3571484

[2] Raharusun P, Sadiah P, Cahni B, Erdie A, Cipta B. Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study (April 26, 2020). Available at SSRN: https://ssrn.com/abstract=3585561 or http://dx.doi.org/10.2139/ssrn.3585561

[3] Ilie, PC, Stefanescu S. & Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res* (2020). https://doi.org/10.1007/s40520-020-01570-8

[4] Laird E, Rhodes J, Kenny RA. Vitamin D and Inflammation: Potential Implications for Severity of Covid-19. *Ir Med J*; Vol 113; No. 5; P81. http://imj.ie/vitamin-d-and-inflammation-potential-implications-for-severity-of-covid-19/

[5] Maghbooli Z, Sahraian MA,Ebrahimi M, Pazoki M, Kafan S, Tabriz HM, Hadadi A, Montazeri M, Nasiri M, Shirvani A, Holick MF. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. Sept 25, 2020 PLoS ONE 15(9): e0239799. https://doi.org/10.1371/journal.pone.0239799

[6] Pepkowitz SH, Hobel CJ, Mirocha JM, Sobhani K, Huynh CA, Jawanda H, Hasan W. Vitamin D Deciency is Associated with Increased COVID-19 Severity: Prospective Screening of At-Risk Groups is Medically Indicated. https://doi.org/10.21203/rs.3.rs-83262/v1

[7] Castillo ME, Costa LME, Barrios JMV, Díaz JFA, Miranda JL, Bouillon R, Gomez JMQ. 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, Vol 203, October 2020, 105751. https://doi.org/10.1016/j.jsbmb.2020.105751

[8] Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF (2020) SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. Sept 17, 2020. PLoS ONE 15(9): e0239252. https://doi.org/10.1371/journal.pone.0239252

[9] Ariel Israel A, Cicurel A, Feldhamer I, Dror Y, Giveon SM, Gillis D, Strich D, Lavie G. The link between vitamin D deficiency and Covid-19 in a large population. Sept 7, 2020. doi: https://doi.org/10.1101/2020.09.04.2018826

[10] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011 Jul; 96(7):1911-30.

[11] Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients* 2020 Apr 2;12(4). pii: E988. doi: 10.3390/nu12040988

[12] Saponaro F, Marcocci C, Zucchi R. Vitamin D status and cardiovascular outcome. *J Endocrinol Invest* 42, 1285–1290 (2019). https://doi.org/10.1007/s40618-019-01057-y

[13] Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *The American Journal of Clinical Nutrition*, May 2010, 91(5): 1255–1260, https://doi.org/10.3945/ajcn.2009.29094

[14] Rafiq S, Jeppese PB. Is Hypovitaminosis D Related to Incidence of Type 2 Diabetes and High Fasting Glucose Level in Healthy Subjects: A Systematic Review and Meta-Analysis of Observational Studies. *Nutrients*. 2018 Jan; 10(1): 59. doi: 10.3390/nu10010059

[15] Nyame YA, Murphy AB, Bowen DK, et al. Associations Between Serum Vitamin D and Adverse Pathology in Men Undergoing Radical Prostatectomy. *J Clin Oncol*. 2016;34(12):1345−1349. doi:10.1200/JCO.2015.65.1463

[16] McCullough ML, Zoltick ES, Weinstein SJ, Fedirko V, Wang M, Cook NR, Eliassen AH, et al. Circulating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts, *JNCI: Journal of the National Cancer Institute,* Volume 111, Issue 2, February 2019, Pages 158–169. https://doi.org/10.1093/jnci/djy087

[17] Yao S, Kwan ML, Ergas IJ, Roh JM, Cheng TYD, Hong CC, McCann SE, Tang L, Davis W, Liu S, Quesenberry CP Jr, Lee MM, Ambrosone CB, Kushi LH, Association of Serum Level of Vitamin D at Diagnosis With Breast Cancer Survival: A Case-Cohort Analysis in the Pathways Study, March 2017, *JAMA Oncol.* 2017;3(3):351-357. doi:10.1001/jamaoncol.2016.4188

[18] Camargo CA, Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, Sumberzul N,and Rich-Edwards JW. Randomized Trial of Vitamin D Supplementation and Risk of Acute Respiratory Infection in Mongolia. *Pediatrics* September 2012, 130 (3) e561-e567; DOI: https://doi.org/10.1542/peds.2011-3029

[19] Jolliffe DA, Greenberg L, Hooper RL, Mathyssen C, Rafiq R, de Jongh RT, Camargo CA, Griffiths CJ, Janssens W, Martineau AR. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. *Thorax* April 2019; 74(4).

[20] Martineau Adrian R, Jolliffe David A, Hooper Richard L, Greenberg Lauren, Aloia John F, Bergman Peter et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data *BMJ* 2017; 356 :i6583

[21] National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population 1999-2002. https://www.cdc.gov/nutritionreport/99-02/pdf/nr_ch2b.pdf

[22] Wyskida M, Wieczorowska-Tobis K, Chudek J. Prevalence and factors promoting the occurrence of vitamin D deficiency in the elderly. *Postepy Higieny i Medycyny Doswiadczalnej* (Online). 2017 Mar;71(0):198-204. DOI: 10.5604/01.3001.0010.3804.

[23] J MacLaughlin and M F Holick, Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest* (1985). https://www.jci.org/articles/view/112134

[24] Khalid, A., Moore, C., Hall, C. et al. Utility of sun-reactive skin typing and melanin index for discerning vitamin D deficiency. *Pediatr Res* 82, 444–451 (2017). https://doi.org/10.1038/pr.2017.114

[25] Pereira-Santos M, Costa PRF, Assis AMO, Santos CAST, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. *Obesity Reviews* April 2015, 16(4): 341-349. https://www.ncbi.nlm.nih.gov/pubmed/25688659/

[26] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011 Jul; 96(7):1911-30.

[27] Turer CB, Lin H, Flores G. Prevalence of vitamin D deficiency among overweight and obese US children. *Pediatrics*. 2013 Jan; 131(1):e152-61. doi: 10.1542/peds.2012-1711. https://www.ncbi.nlm.nih.gov/pubmed/23266927

[28] Zhao M, Wang M, Zhang J, Gu J, Zhang P, Xu Y, Ye J, Wang Z, Ye D, Pan W, Shen B, He H, Liu M, Liu M, Luo Z, Li D, Liu J, Wan J. Comparison of clinical characteristics and outcomes of patients with coronavirus disease 2019 at different ages. *Aging*, 03 Jun 2020, 12.
DOI: 10.18632/aging.103298

[29] Yancy CW. COVID-19 and African Americans; *JAMA.* 2020;323(19):1891-1892. doi:10.1001/jama.2020.6548

[30] Kirby T. Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities. *Lancet Respir Med.* 2020 May 10, doi: 10.1016/S2213-2600(20)30228-9

[31] Fallik D. COVID-19 is hitting some patients with obesity particularly hard: Emerging data show BMI plays a role in who needs intensive care and who survives. *ScienceNews* April 22, 2020. https://www.sciencenews.org/article/coronavirus-covid19-obesity-risk-factor

[32]Girvan G, Roy A. The Foundation for Research on Equal Opportunity, June 19, 2020. https://freopp.org/the-covid-19-nursing-home-crisis-by-the-numbers-3a47433c3f70

[33] Wyskida M, Wieczorowska-Tobis K, Chudek J. Prevalence and factors promoting the occurrence of vitamin D deficiency in the elderly. *Postepy Higieny i Medycyny Doswiadczalnej* (Online). 2017 Mar;71(0):198-204. DOI: 10.5604/01.3001.0010.3804.

[34] MacDonell SO, Miller JC, Harper MJ, Wa DL. Vitamin D status and its predictors in New Zealand aged-care residents eligible for a government-funded universal vitamin D supplementation programme. *Public Health Nutrition*, Dec 2016, 19(18):3349-3360. DOI: https://doi.org/10.1017/S1368980016001683

[35] Hilotin J, COVID-19 children: 'Kawasaki-like' disease, what we know so far. Heads up from WHO, CDC as doctors stumped by illness in children with links to SARS-CoV-2. *Gulf News*, June 21, 2020.

[36] CDC Kawasaki Disease, https://www.cdc.gov/kawasaki/about.html

[37] Stagi S, Rigante D, Lepri G, Matucci Cerinic M, Falcini F. Severe vitamin D deficiency in patients with Kawasaki disease: a potential role in the risk to develop heart vascular abnormalities? *Clin Rheumatol*. 2016 Jul; 35(7):1865-72. doi: 10.1007/s10067-015-2970-6.

[38] Jones G. Pharmacokinetics of Vitamin D Toxicity. *J Clin Nutr* 2008 Aug;88(2):582S-586S. doi: 10.1093/ajcn/88.2.582S.

[39] Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, Płudowski P, Jones G. Vitamin D Toxicity–A Clinical Perspective. *Front. Endocrinol.*, 20 September 2018 | https://doi.org/10.3389/fendo.2018.00550

[40] Maresz K, Proper Calcium Use: Vitamin K2 as a Promoter of Bone and Cardiovascular Health. *Integr Med (Encinitas*). 2015 Feb; 14(1): 34–39.

[41] Uwitonze AM, Razzaque MS. Role of Magnesium in Vitamin D Activation and Function. *J Am Osteopath Assoc.* 2018;118(3):181-189. doi:10.7556/jaoa.2018.037