Vitamin D and Covid-19

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Summary

Calcitriol, the active form of vitamin D, is a significant immune signalling molecule in both early innate immune response, and targeted immune response to intracellular viral infections.

Scientific evidence shows that vitamin D deficiency is associated with vulnerability to viral respiratory tract infections, tuberculosis and other chronic diseases. Recent evidence shows that vitamin D deficiency is associated with severe Covid-19 disease.

Vitamin D is obtained through eating animal products (meat and dairy), and through exposure to sunlight. Vitamin D deficiency is associated with people living in temperate latitudes, poor diet, dark skin, obesity, diabetes, and the elderly. These have all been shown to be major risk factors for severe Covid-19 disease.

Lockdown has had a detrimental effect on nutrition in general, and lack of exposure to sunlight has further decreased population vitamin D levels, increasing risk for severe Covid-19 disease.

Supplementation in vitamin D deficiency must be frequent in order to have a beneficial effect. Fish waste products, especially liver, are a plentiful, inexpensive source of vitamin D. Vitamin D food fortification was used extensively in 20th century Europe and its history is discussed.

It is proposed that fish waste should be sourced immediately and used to fortify staple foods such as maize meal and bread. The effect would be to reduce the fraction of severe Covid-19 infections. It should also reduce incidence of tuberculosis, possibly HIV, and other diseases.

Vitamin D physiology

Vitamin D exists in three forms: cholecalciferol (D3), calcifediol (25-OH D3, abbreviated to 25-D3) and calcitriol (1,25-diOH-D3, abbreviated to 1,25-D3).

Calcitriol is an immunologically active secosteroid. Its mechanism of action is similar to that of steroids: it crosses cell membranes, has its own dedicated cytosolic binding protein, is chaperoned into the cell nucleus, and changes cellular DNA transcription patterns accordingly. This distinguishes vitamin D from all other vitamins, which are enzyme co-factors.

D3 is acquired through eating food of animal origin, or through conversion of 7-dehydrocholesterol by sunlight (UVB). It is hydroxylated to 25-D3 in the liver. The kidneys hydroxylate 25-D3 to 1,25-D3. Circulating 1,25-D3 regulates gut absorption of calcium, and calcium metabolism in bone. There is a tight negative feedback loop to maintain appropriate levels of 25-D3 (inactive) and 1,25-D3 (active) forms.

This activity is known as endocrine: the action of a hormone circulating in the bloodstream acting on distant target organs. However 1,25-D3 has also been shown to have autocrine (self) and paracrine (local) activity in immune system function, dependent on circulating levels of 25-D3, and without negative feedback, establishing high local concentrations of 1,25-D3 in local areas of immune activity (Aranow).

Local levels of 1,25-D3 are generated through hydroxylation of circulating 25-D3l by macrophages (antigen-presenting cells). 1,25-D3 then has a number of local effects:

1. It activates chemotactic, phagocytic and cytotoxic activity of both the hydroxylating macrophages themselves (autocrine), and macrophages nearby (paracrine) (Yamamoto p2496).
2. It also suppresses proliferation of a targeted immune response by cytotoxic T-cells (Bhalla) and antibody-producing B-cells (Chen) through inhibiting interferon, interleukin-2 and tumour necrosis factor production.
3. It suppresses proliferation of natural killer (NK) cells, although it does not suppress NK cell activity (Weeres).

In basic terms, it promotes an early local innate immune response in the presence of infection, while holding off a targeted cellular immune response. It is a prolonged targeted cellular immune response that results in the overwhelmingly fatal pneumonitis and cytokine storm associated with Covid-19 death.

Vitamin D deficiency as a risk factor for disease

Vitamin D deficiency results in less available 25-D3 for hydroxylation. As a result, vitamin D deficiency is associated with susceptibility to a number of diseases:

Tuberculosis: The history of vitamin D deficiency and tuberculosis has been documented since 1849 (Williams). Vitamin D deficient individuals have a greater susceptibility to developing tuberculosis, and worse disease progression if infected with tuberculosis (Kearns).

HIV: Macrophages are the most populous CD4+ cell in the urogenital tract (Abraham), so are a likely initial infection target from sexual transmission, causing further spread and infection by recruiting CD4+ T-cells (Koppensteiner). Activated macrophages are less susceptible to HIV-1 infection (Gobeil), and a sufficient 1,25-D3 response will recruit less CD4+ T-cells to the site. Therefore vitamin D deficiency may cause an individual to be more susceptible to HIV infection upon exposure.

Upper respiratory tract infections: Vitamin D deficiency is associated with increased incidence of upper respiratory tract infections (Ginde). Vitamin D3 supplementation during the winter reduced the incidence of influenza in schoolchildren (Urashima).

Acute respiratory distress syndrome: Vitamin D Deficiency has been shown to contribute directly to acute respiratory distress syndrome (Dancer).

Diabetes: Individuals with vitamin D deficiency are at higher risk of insulin resistance and metabolic syndrome (Chiu).

Autoimmune disorders: There is an association between vitamin D deficiency and the development of several autoimmune diseases, such as SLE, thyrotoxicosis, type 1 DM, MS, iridocyclitis, Crohn's disease, ul-cerative colitis, psoriasis vulgaris, seropositive RA, polymyalgia rheumatica (Murdaca). This is again likely due to the failure of an effective innate immune response resulting in a pathological targeted response.

Vitamin D and Covid-19

On 9 April 2020, a study from the Philippines showed that in a population of 212 Covid-19-infected patients, serum 25-D3 level was lowest in critical cases, but highest in mild cases which thereby increase the odds of having a mild clinical outcome rather than a critical outcome by approximately 19.61 times (Alipio).

On 26 April 2020, a study of 780 Covid-19 patients in Indonesia showed that when controlling for age, sex, and comorbidity, vitamin D deficiency was strongly associated with COVID-19 mortality (Raharusun).

On 6 May a UK study of 20 European countries found significant relationships between vitamin D levels and the number COVID-19 cases, and especially the mortality caused by this infection (Ilie).

On 11 May 2020, an Irish study of 12 European countries showed a positive correlation between vitamin D deficiency and Covid-19 mortality (Laird).

Prevalence of Vitamin D deficiency

Vitamin D deficiency is associated with lower socio-economic populations due to lack of dietary meat and dairy. It is also associated with low sunlight exposure due to temperate regions and winter. Covid-19 lockdown regulations may be exacerbating vitamin D deficiency due to both lack of adequate nutrition and sunlight.

Vitamin D deficiency is also prevalent in dark skinned populations due to the UVB light being absorbed by melanocytes before it can act on 7-dehydrocholesterol in the bloodstream (Rostand).

Vitamin D deficiency prevalent in South Africa and other African countries (Mogire).

The elderly are at risk for lower levels of vitamin D as a result of decreased cutaneous synthesis and dietary intake of vitamin D. Epidemiologic evidence indicates an association between low levels of vitamin D and diseases associated with aging such as cognitive decline, depression, osteoporosis, cardiovascular disease, hypertension, type 2 diabetes, and cancer. (Meehan).

There is a consistent association in the published literature between obesity and lower serum 25-D3 concentrations (Vanlint).

Vitamin D deficiency is prevalent in HIV+ individuals, and is also associated with anti-retroviral therapy (Coelho).

Assessment

The overlap between known risk factors for severe Covid-19 disease and conditions causing, or caused by, vitamin D deficiency is remarkable. Combined with a well established scientific basis for how vitamin D affects immune system function, and the assumed prevalence of vitamin D deficiency in South Africa, both baseline and due to the effects of lockdown, urgent action is required to reduce vitamin D deficiency in the population.

Vitamin D supplementation

There is a major caveat regarding vitamin D supplementation: it is a hormone precursor and it is fat soluble. Therefore it has the extremely rare potential to be toxic in large doses for prolonged periods.

Vitamin D toxicity is only observed in regular ingestion of therapeutic products or foods either naturally rich in, or extensively fortified with, vitamin D. Therefore moderate supplementation of existing staple foods (maize meal and bread) is the optimal supplementation method for South Africa. Inexpensive crude vitamin D extracts can be sourced from fish waste, including tuna liver and small oily fish such as mackerel, pilchards and sardines (Schmid).

The history of vitamin D food fortification in Europe is extensive and has been continuous since the 1930s (Wacker).

There is extensive literature on methods of food fortification (Pilz), and recent Covid-19-specific supplementation advice in the BMJ Nutrition Journal (Lanham-New).

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Cited works

Abraham, Soman N, and Yuxuan Miao. "The Nature of Immune Responses to Urinary Tract Infections." *Nature Reviews. Immunology*, U.S. National Library of Medicine, Oct. 2015, www.ncbi.nlm.nih.gov/pmc/articles/PMC4926313.

Alipio, Mark. "Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19)." *SSRN*, 9 Apr. 2020, papers.ssrn.com/sol3/papers.cfm?abstract_id=3571484.

Aranow, Cynthia. "Vitamin D and the Immune System." *Journal of Investigative Medicine : the Official Publication of the American Federation for Clinical Research*, U.S. National Library of Medicine, Aug. 2011, www.ncbi.nlm.nih.gov/pmc/articles/PMC3166406.

Bhalla, A K, et al. "1,25-Dihydroxyvitamin D3 Inhibits Antigen-Induced T Cell Activation." *Journal of Immunology (Baltimore, Md. : 1950)*, U.S. National Library of Medicine, Oct. 1984, www.ncbi.nlm.nih.gov/pubmed/6206136.

Chen, Sheng, et al. "Modulatory Effects of 1,25-Dihydroxyvitamin D3 on Human B Cell Differentiation." *Journal of Immunology (Baltimore, Md. : 1950)*, U.S. National Library of Medicine, 1 Aug. 2007, www.ncbi.nlm.nih.gov/pubmed/17641030.

Chiu, Ken C, et al. “Hypovitaminosis D Is Associated with Insulin Resistance and Beta Cell Dysfunction.” *The American Journal of Clinical Nutrition*, U.S. National Library of Medicine, May 2004, www.ncbi.nlm.nih.gov/pubmed/15113720.

Coelho, Lara, et al. “Vitamin D3 Supplementation in HIV Infection: Effectiveness and Associations with Antiretroviral Therapy.” *Nutrition Journal*, BioMed Central, 18 Aug. 2015, www.ncbi.nlm.nih.gov/pmc/articles/PMC4538921.

Dancer, Rachel C A, et al. “Vitamin D Deficiency Contributes Directly to the Acute Respiratory Distress Syndrome (ARDS).” *Thorax*, BMJ Publishing Group Ltd, 1 July 2015, thorax.bmj.com/content/70/7/617.

Ginde, Adit A, et al. “Association between Serum 25-Hydroxyvitamin D Level and Upper Respiratory Tract Infection in the Third National Health and Nutrition Examination Survey.” *Archives of Internal Medicine*, U.S. National Library of Medicine, 23 Feb. 2009, www.ncbi.nlm.nih.gov/pmc/articles/PMC3447082.

Gobeil, Lise-Andrée, et al. “Differential HIV-1 Endocytosis and Susceptibility to Virus Infection in Human Macrophages Correlate with Cell Activation Status.” *Journal of Virology*, American Society for Microbiology, Oct. 2012, www.ncbi.nlm.nih.gov/pubmed/22787228.

Ilie, Petre Cristian, et al. “The Role of Vitamin D in the Prevention of Coronavirus Disease 2019 Infection and Mortality.” *Aging Clinical and Experimental Research*, Springer International Publishing, 6 May 2020, link.springer.com/article/10.1007/s40520-020-01570-8.

Kearns, Malcolm D, and Vin Tangpricha. “The Role of Vitamin D in Tuberculosis.” *Journal of Clinical & Translational Endocrinology*, Elsevier, 23 Aug. 2014, www.ncbi.nlm.nih.gov/pmc/articles/PMC5684962.

Koppensteiner, H., et al. “Macrophages and Their Relevance in Human Immunodeficiency Virus Type I Infection.” *Retrovirology*, BioMed Central, 4 Oct. 2012, retrovirology.biomedcentral.com/articles/10.1186/1742-4690-9-82.

Laird, E, et al. “Vitamin D and Inflammation – Potential Implications for Severity of Covid-19.” *Irish Medical Journal*, 11 May 2020, imj.ie/vitamin-d-and-inflammation-potential-implications-for-severity-of-covid-19.

Lanham-New, Susan A, et al. “Vitamin D and SARS-CoV-2 Virus/COVID-19 Disease.” *BMJ Nutrition, Prevention & Health*, BMJ Specialist Journals, 13 May 2020, nutrition.bmj.com/content/early/2020/05/15/bmjnph-2020-000089.

Meehan, Meghan, and Sue Penckofer. “The Role of Vitamin D in the Aging Adult.” *Journal of Aging and Gerontology*, U.S. National Library of Medicine, Dec. 2014, www.ncbi.nlm.nih.gov/pmc/articles/PMC4399494.

Mogire, Reagan M, et al. “Prevalence of Vitamin D Deficiency in Africa: A Systematic Review and Meta-Analysis.” *The Lancet. Global Health*, U.S. National Library of Medicine, 27 Nov. 2019, pubmed.ncbi.nlm.nih.gov/31786117.

Murdaca, Giuseppe, et al. “Emerging Role of Vitamin D in Autoimmune Diseases: An Update on Evidence and Therapeutic Implications.” *Autoimmunity Reviews*, U.S. National Library of Medicine, Sept. 2019, www.ncbi.nlm.nih.gov/pubmed/31323357.

Pilz, Stefan, et al. “Rationale and Plan for Vitamin D Food Fortification: A Review and Guidance Paper.” *Frontiers in Endocrinology*, Frontiers Media S.A., 17 July 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC6056629.

Raharusun, Prabowo, et al. “Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study.” *SSRN Electronic Journal*, 26 Apr. 2020, doi:10.2139/ssrn.3585561.

Rostand, Stephen G. “Ultraviolet Light May Contribute to Geographic and Racial Blood Pressure Differences.” *Hypertension*, 1 Aug. 1997, www.ahajournals.org/doi/full/10.1161/01.hyp.30.2.150.

Schmid, Alexandra, and Barbara Walther. “Natural Vitamin D Content in Animal Products.” *Advances in Nutrition (Bethesda, Md.)*, American Society for Nutrition, 1 July 2013, www.ncbi.nlm.nih.gov/pmc/articles/PMC3941824.

Urashima, Mitsuyoshi, et al. “Randomized Trial of Vitamin D Supplementation to Prevent Seasonal Influenza A in Schoolchildren.” *The American Journal of Clinical Nutrition*, U.S. National Library of Medicine, May 2010, www.ncbi.nlm.nih.gov/pubmed/20219962.

Vanlint, Simon. “Vitamin D and Obesity.” *Nutrients*, MDPI, 20 Mar. 2013, www.ncbi.nlm.nih.gov/pmc/articles/PMC3705328.

Wacker, Matthias, and Michael F Holick. “Sunlight and Vitamin D: A Global Perspective for Health.” *Dermato-Endocrinology*, Landes Bioscience, 1 Jan. 2013, www.ncbi.nlm.nih.gov/pmc/articles/PMC3897598.

Weeres, Matthew A, et al. “The Effects of 1,25-Dihydroxyvitamin D3 on in Vitro Human NK Cell Development from Hematopoietic Stem Cells.” *Journal of Immunology (Baltimore, Md. : 1950)*, U.S. National Library of Medicine, 1 Oct. 2014, www.ncbi.nlm.nih.gov/pmc/articles/PMC4363084.

Williams, C. J. B. “Cod-Liver Oil in Phthisis.” *London Journal of Medicine*, U.S. National Library of Medicine, Jan. 1849, www.ncbi.nlm.nih.gov/pmc/articles/PMC2543222.

Yamamoto, Nobuto. “Vitamin D and the Immune System.” *Encyclopedia of Immunology (Second Edition)*, Elsevier, 28 Nov. 2004, www.sciencedirect.com/science/article/pii/B0122267656006460.