



Short Communication

Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate



Simon Goddek

Mathematical and Statistical Methods (Biometris), Wageningen University, P.O. Box 16, 6700 AA Wageningen, The Netherlands

ARTICLE INFO

Article history:

Received 23 June 2020

Received in revised form 2 July 2020

Accepted 26 July 2020

Keywords:

Vitamin D

COVID-19

Coronavirus

Mortality rate

Immunology

ABSTRACT

The world is desperately seeking for a sustainable solution to combat the coronavirus strain SARS-CoV-2 (COVID-19). Recent research indicated that optimizing Vitamin D blood levels could offer a solution approach that promises a heavily reduced fatality rate as well as solving the public health problem of counteracting the general vitamin D deficiency. This paper dived into the immunoregulatory effects of supplementing Vitamin D₃ by elaborating a causal loop diagram. Together with D₃, vitamin K₂ and magnesium should be supplemented to prevent long-term health risks. Follow up clinical randomized trials are required to verify the current circumstantial evidence.

© 2020 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Introduction

The COVID-19 pandemic is a current pandemic of high international interest, caused by the coronavirus strain SARS-CoV-2. Up to date, there is no treatment to decrease the virus-caused infection and mortality rates (Cortegiani et al., 2020). More and more voices are being raised supporting the supplementation of Vitamin D₃ to counter the pandemic outbreak with the correlated mortality rates as well as economic and social consequences (Grant et al., 2020). In a recently published review article, Sharma et al. (2020) have critically discussed the association of vitamin D with viral infections. A recent clinical study from Iran (n = 611) stated that there were no COVID-19 deaths in a hospital if serum 25(OH)D concentrations were higher than 41 ng/mL and patients were younger than 80 (Maghbooli et al., 2020). Russian hospitals observed that the likelihood to have severe COVID-19 increases by the factor of 5 if vitamin D is deficient (Karonova et al., 2020). Similar observations have been made by Panagiotou et al. (2020). Tan et al. (2020) observed a significant reduction in oxygen support for older clients when providing them with a relatively low daily dose of 1000 IU D₃ OD, 150 mg magnesium OD, and 500 µg B12 OD upon admission. On the other hand, one retrospective cohort study that investigated the correlation between the mean D₃ serum levels of different European countries and the COVID-19 mortality rate was not considered significant (Ali, 2020). An explanation for this could be that testing conditions differ in each European country, making it

difficult to reach a conclusion in such a retrospective study. Also, the mean D₃ serum levels do not necessarily apply to people who are especially vulnerable to that virus (e.g. aged and bedridden people). This assumption is supported by De Smet et al. (2020) who documented a significantly lower median D₃ value in patients with COVID-19 compared to control subjects.

The obviously correlating vitamin D deficiency is linked to increasing the risk of many common and serious diseases (Holick, 2004). In a study conducted by Forrest and Stuhldreher (2011), vitamin D deficiency was defined as a serum 25(OH)D concentrations ≤20 ng/mL. 41.6% of the test subjects have been considered vitamin D deficient. Of the tested people of color (PoC) and Hispanics, the deficiency rate was even 69.2% and 82.1%, respectively. Similar observations with respect to patients' ethnicity have been made by Holick (2002) and Darling et al. (2020). The latter also states that serum 25(OH)D concentrations were lower in obese people that were tested COVID-positive, which is most likely due to increased relative body volume. Haq et al. (2016) even report that 82.5% of studied patients in the sun-intensive Middle East were vitamin D deficient. These observations with respect to common vitamin D deficiency, together with evidence of several experimental studies (Bendix-Struve et al., 2010; Casteels et al., 1998; Holick, 2005; Seibert et al., 2013), indicates that vitamin D is essential in the modulation of immune function (Aranow, 2011; Sassi et al., 2018).

The threshold of Vitamin D deficiency is a continuous subject of discussion. Whereas the European Food Safety Authority recommends a minimum serum level of 25(OH)D of 25 nmol/L (i.e. 10 ng/mL) (EFSA, 2016), many scholars consider this value way too conservative. A study that was conducted in Kenya on healthy black

E-mail address: simon.goddek@wur.nl (S. Goddek).

males showed that 25(OH)D levels <30 ng/mL were associated with a significant rise in physiological markers such as parathyroid hormone (PTH) (Kagotho et al., 2018). Thus, desirable 25(OH)D levels are rather to be found between 30–48 ng/mL (Bischoff-Ferrari, 2008; Raftery and O’Sullivan, 2015; Vieth, 2011), i.e. 3–5 times higher than recommended by the European authorities. Looking into optimal 25(OH)D serum levels from an epidemiological and evolutionary perspective could be another approach to getting a rough indication on these levels (Carlberg, 2019; Luxwolda et al., 2012). It has been shown that traditional African hunter-gatherers had an average serum level of 48 ng/mL.

This publication set out to show the metabolic pathways behind the immunomodulating effect of vitamin D by following a systems thinking approach. The output will also give advice on which other dietary supplements one should consider.

Methodology

One of the basic principles that is used to combine valuable scientific findings and knowledge from often interdisciplinary domains is called systems analysis. Causal loop diagrams (CLDs) functioned as a tool to illustrate the principle of causality of 25(OH)D serum levels on the human metabolism and form the basis for

systems analysis (Mabin et al., 2006). Such causal loop diagrams are powerful instruments for problem identification and problem resolving purposes by breaking down a comprehensive system into fragments in order to enhance its comprehensibility (Haraldsson, 2004).

Visualizing concepts makes it much easier to understand complex correlations and casualties (i.e. cause and effect mechanisms). The problem (in this case immune systems that have difficulties coping with COVID-19) stands in the center of the systems analysis. Data on the impact of vitamin D₃ on the immune system have been collected and elaborated in the results and discussion section. Based on these findings, the CLDs have been created and digitized using the Vensim software (Ventana Systems, 2015).

Results and Discussion

Figure 1 illustrates a causal loop diagram coping with the effects of vitamin D₃ and K₂ supplementation. The diagram will be elaborated and discussed throughout this section.

In a simplified scheme, the majority of the previtamin D₃ is both acquired in the human skin from the conversion of 7-dehydrocholesterol through cutaneous solar ultraviolet radiation (Kheiri

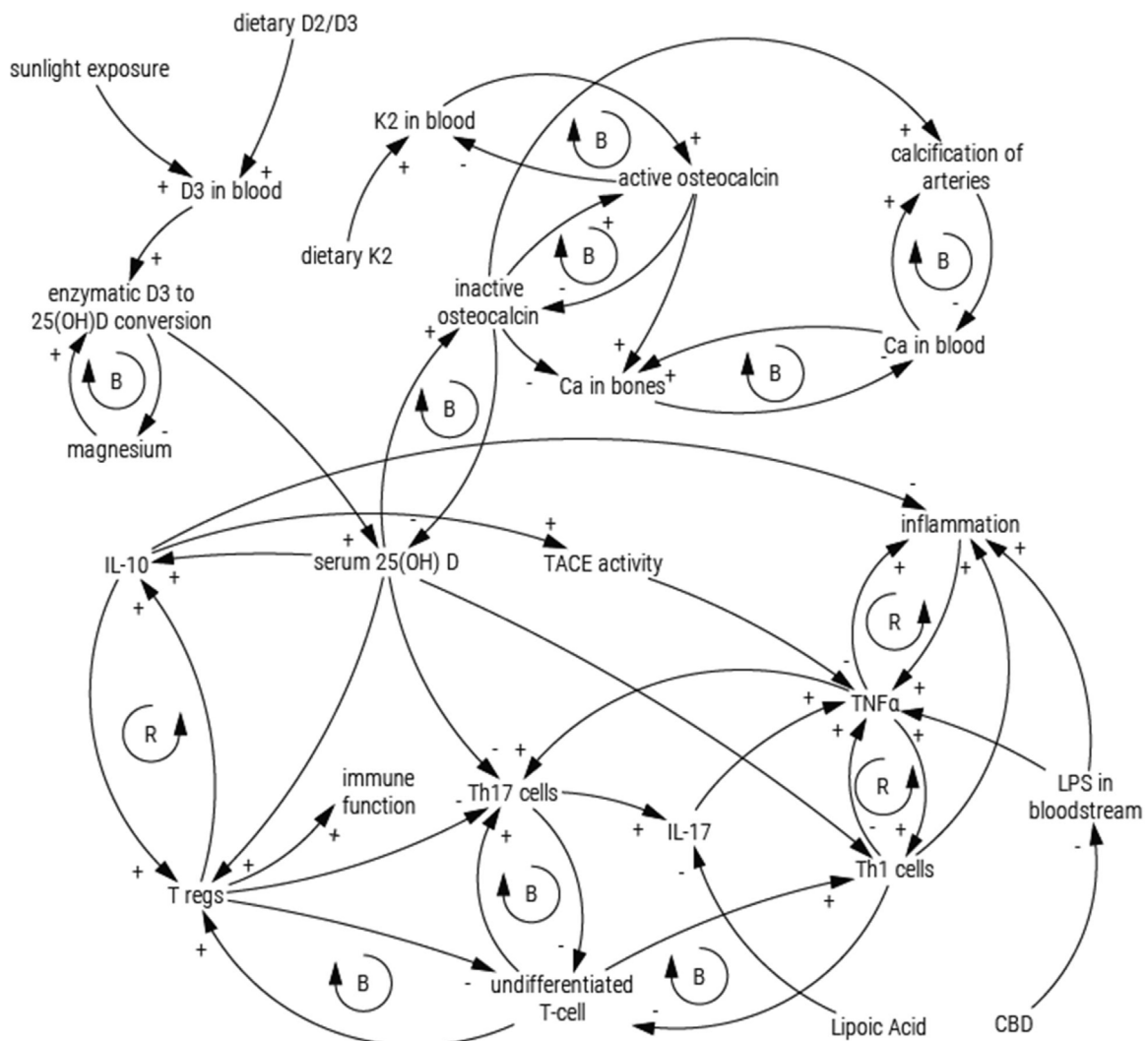


Figure 1. Causal loop diagram of the impact of vitamin D3 on the immune system.

Table 1
Tabular indicator for raising the 25(OH)D blood serum levels from 20 ng/mL to 40 ng/mL and maintaining them after consultation with the physician (von Helden, 2011).

| Body weight | 10 days fill up | Daily D3 supplementation (IU) | Daily K2 (MK7) supplementation (μ g) |
|-------------|-----------------|-------------------------------|---|
| 50 | 14.000 | 2.200 | 100 |
| 60 | 16.800 | 2.600 | 120 |
| 70 | 19.600 | 3.000 | 140 |
| 80 | 22.400 | 3.500 | 160 |
| 90 | 25.200 | 3.950 | 180 |
| 100 | 28.000 | 4.380 | 200 |
| 110 | 30.800 | 4.820 | 220 |

et al., 2018), and to a lesser extent through dietary supplementation (D₂ and D₃). The metabolic pathway continues in the liver where D₂ and D₃ are hydroxylated to 25(OH)D. 25(OH)D is eventually transformed into 1,25(OH)₂Vitamin D₃ (the physiologically active form of vitamin D) in the kidneys (Keane et al., 2018). The high degree of vitamin D deficiency may not be due solely to the modern office-lifestyle (i.e. home - car - office - car - home; repeat) but also depend on factors such as higher latitude, degree of skin pigmentation, seasons (i.e. winter) and dietary intake (i.e. fatty fish, liver, fermented foods, etc.) (Mithal et al., 2009).

Oral supplementation of D₃ is the easiest means to prevent deficiencies. A frequent argument against supplementation of vitamin D₃ is that an increased intake could lead to a vitamin D toxicity, also called hypervitaminosis D (Orme et al., 2016). This again can cause hypercalcemia, which is the buildup of calcium in the blood leading to vascular calcification, osteoporosis, and kidney stones. However, it has been reported that the reason for hypercalcemia rather lays in a vitamin K₂ deficiency (Flore et al., 2013; Vermeer and Theuwissen, 2011), as K₂ activates the bone gamma-carboxyglutamic acid-containing protein (osteocalcin) through carboxylation. Activated osteocalcin deposits calcium in the bones, whereas non-activated osteocalcin inhibits calcium absorption by the bones. As the osteocalcin synthesis rate is increased by higher 25(OH)D serum levels, K₂ is required as a natural antagonist (Yasui et al., 2006; Dofferhoff et al., 2020).

It has also been observed that D₃ supplementation led to an increase in anti-inflammatory and immunoregulating interleukin 10 (IL-10) cytokines and reduced frequency in Th17 cells (Allen et al., 2012), which in turn leads to a decrease in IL-17 and the proinflammatory cytokine TNF α production, decreasing inflammatory effects in the host (Ferreira et al., 2020; Latella and Viscido, 2020). Also, Zheng et al. (2014) reported that TNF α promotes pathogenic Th17 cell differentiation. On the other hand, IL-10 reduces the activity of the TNF- α -converting enzyme (TACE) (Brennan et al., 2008). Brennan et al. (2008) also observed that lipopolysaccharides (LPS) in the bloodstream enhanced TNF α values.

Whereas Th1 and Th17 cells are proinflammatory, regulatory T-cells (Tregs) have anti-inflammatory effects. Prietl et al. (2013, 2010) proclaim that vitamin D₃ supplementation showed an increase in regulatory Tregs and a more tolerogenic immunological status in general. As illustrated in Figure 1, a chronic D₃ deficit would shift the T-cell ratio towards the inflammatory pathway. Given the fact that an abundance of Th17 cells are highly associated with autoimmune diseases (Waite and Skokos, 2011; Yasuda et al., 2019), it is therefore unsurprising that many fatal cases showed comorbidities.

There are many follow-up studies required to substantiate and consolidate the hypothesis that there is a strong correlation between low 25(OH)D serum concentrations and mortality rates. But what we know is that people with “sufficient” vitamin D blood serum levels tend to have considerably less severe symptoms caused by COVID-19 (Pugach & Pugach, 2020).

Dietary considerations

Given that vitamin D₃ is an immunoregulating hormone and can be considered safe when supplementing it together with K₂, Table 1 provides a rough guideline on how to raise vitamin D levels to desired values. Supplementation of magnesium (200–250 mg/day) should also be considered, as all enzymes that metabolize vitamin D seem to require magnesium (Uwitonze and Razzaque, 2018).

Other dietary supplementations to consider are: (1) lipoic acid has been shown to inhibit pro-inflammatory IL-6 and IL-17 production (Salinthon et al., 2010); (2) omega-3 fatty acids that are anti-inflammatory and reduce kinase excretion. Consume as a supplement or in form of cod liver oil or fatty fish (such as salmon) once or twice per week (Vasquez, 2016); (3) Cannabidiol (CBD) that promotes anti-inflammatory IL-10 secretion (Joffre et al., 2020) while preventing LPS-induced microglial inflammation (dos-Santos-Pereira et al., 2020); and (4) Green Tea, since epigallocatechin-3-gallate is the most biologically active catechin in green tea. It reduces Th17 cells and increases regulatory T-cells (Byun et al., 2014).

Conclusions

Recent COVID-19-related data evaluation showed indications that a high 25(OH)D blood serum level might have an impact on the mortality rate of coronavirus patients. Even though ethical issues might arise (Muthuswamy, 2013), the paper's hypothesis requires clinical randomized trials to verify the circumstantial evidence. This publication illustrated the metabolic mechanisms behind that observed phenomenon. It is highly suggested to also consider K₂ and magnesium intake to avoid unintended long-term side-effects such as arteriosclerosis and osteoporosis.

Conflict of interests

The author declares that they have no competing interests in this section.

Ethics approval and consent to participate

Not applicable.

Consent of publication

Not applicable.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Funding

Not applicable.

Author's contributions

One author only. I wrote everything.

References

- Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health* 2020; doi:http://dx.doi.org/10.1016/j.jiph.2020.06.021 In press.
- Allen AC, Kelly S, Basdeo SA, Kinsella K, Mulready KJ, Mills KHG, et al. A pilot study of the immunological effects of high-dose vitamin D in healthy volunteers. *Mult Scler* 2012;18:1797–800, doi:http://dx.doi.org/10.1177/1352458512442992.
- Aranow C. Vitamin D and the immune system. *J Investig Med* 2011;59:881–6, doi:http://dx.doi.org/10.2310/JIM.0b013e31821b8755.
- Bendix-Struve M, Bartels LE, Agnholt J, Dige A, Jørgensen SP, Dahlerup JF. Vitamin D3 treatment of Crohn's disease patients increases stimulated T cell IL-6 production and proliferation. *Aliment Pharmacol Ther* 2010;32:1364–72, doi:http://dx.doi.org/10.1111/j.1365-2036.2010.04463.x.
- Bischoff-Ferrari HA. Optimal Serum 25-Hydroxyvitamin D Levels for Multiple Health Outcomes. In: Reichrath J, editor. Sunlight, vitamin D and skin cancer, advances in experimental medicine and biology. New York, NY: Springer; 2008. p. 55–71, doi:http://dx.doi.org/10.1007/978-0-387-77574-6_5.
- Brennan FM, Green P, Amjadi P, Robertshaw HJ, Alvarez-Iglesias M, Takata M. Interleukin-10 regulates TNF- α -converting enzyme (TACE/ADAM-17) involving a TIMP-3 dependent and independent mechanism. *Eur J Immunol* 2008;38:1106–17, doi:http://dx.doi.org/10.1002/eji.200737821.
- Byun J-K, Yoon B-Y, Jhun J-Y, Oh H-J, Kim E, Min J-K, et al. Epigallocatechin-3-gallate ameliorates both obesity and autoinflammatory arthritis aggravated by obesity by altering the balance among CD4+ T-cell subsets. *Immunol Lett* 2014;157:51–9, doi:http://dx.doi.org/10.1016/j.imlet.2013.11.006.
- Carlberg C. Vitamin D: a micronutrient regulating genes. *Curr Pharm Des* 2019;25:1740–6, doi:http://dx.doi.org/10.2174/1381612825666190705193227.
- Casteels K, Waer M, Bouillon R, Depovere J, Valckx D, Laureys J, et al. 1,25-Dihydroxyvitamin D3 restores sensitivity to cyclophosphamide-induced apoptosis in non-obese diabetic (NOD) mice and protects against diabetes. *Clin Exp Immunol* 1998;112:181–7, doi:http://dx.doi.org/10.1046/j.1365-2249.1998.00568.x.
- Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care* 2020;57:279–83, doi:http://dx.doi.org/10.1016/j.jccr.2020.03.005.
- Darling AL, Ahmadi KR, Ward KA, Harvey NC, Alves AC, Dunn-Waters DK, et al. Vitamin D status, body mass index, ethnicity and COVID-19: initial analysis of the first-reported UK Biobank COVID-19 positive cases (n 580) compared with negative controls (n 723). *medRxiv* 2020; doi:http://dx.doi.org/10.1101/2020.04.29.20084277 2020.04.29.20084277 In preparation.
- De Smet D, De Smet K, Herroelen P, Gryspeerd S, Martens GA. Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. *medRxiv* 2020; doi:http://dx.doi.org/10.1101/2020.05.01.20079376 2020.05.01.20079376 In preparation.
- Dofferhoff ASM, Piscaer I, Schurgers LJ, Walk J, van den Ouweland JMW, Hackeng TM, et al. Reduced vitamin K status as a potentially modifiable prognostic risk factor in COVID-19. [237_TD\$DIFF]Preprints; 2020 In preparation.
- dos-Santos-Pereira M, Guimarães FS, Del-Bel E, Raisman-Vozari R, Michel PP. Cannabidiol prevents LPS-induced microglial inflammation by inhibiting ROS/NF- κ B-dependent signaling and glucose consumption. *Glia* 2020;68:561–73, doi:http://dx.doi.org/10.1002/glia.23738.
- EFSA. Vitamin D: EFSA sets dietary reference values [WWW Document]. *Eur Food Saf Auth* 2016; URL: https://www.efsa.europa.eu/en/press/news/161028 (Accessed 6.18.20).
- Ferreira AO, Polonini HC, Dijkers ECF. Postulated adjuvant therapeutic strategies for COVID-19. *J Personal Med* 2020;10:80, doi:http://dx.doi.org/10.3390/jpm10030080.
- Flore R, Ponzianni FR, Di Rienzo TA, Zocco MA, Flex A, Gerardino L, et al. Something more to say about calcium homeostasis: the role of vitamin K2 in vascular calcification and osteoporosis. *Eur Rev Med Pharmacol Sci* 2013;17:2433–40.
- Forrest KYZ, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res* 2011;31:48–54, doi:http://dx.doi.org/10.1016/j.nutres.2010.12.001.
- Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* 2020;12:988, doi:http://dx.doi.org/10.3390/nu12040988.
- Haq A, Svobodová J, Imran S, Stanford C, Razzaque MS. Vitamin D deficiency: a single centre analysis of patients from 136 countries. *J Steroid Biochem Mol Biol* 2016;164:209–13, doi:http://dx.doi.org/10.1016/j.jsbmb.2016.02.007.
- Haraldsson HV. Introduction to System Thinking and Causal Loop Diagrams, Reports in Ecology and Environmental Engineering. KFS AB, Lund.; 2004.
- Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. *South Med J* 2005;98:1024–8.
- Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004;79:362–71, doi:http://dx.doi.org/10.1093/ajcn/79.3.362.
- Holick MF. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. *Curr Opin Endocrinol Diabetes Obes* 2002;9:87–98.
- Joffre J, Yeh C-C, Wong E, Thete M, Xu F, Zlatanova I, et al. Activation of CB1R promotes lipopolysaccharide-induced IL-10 secretion by monocytic myeloid-derived suppressive cells and reduces acute inflammation and organ injury. *J Immunol Author Choice* 2020;204:3339–50, doi:http://dx.doi.org/10.4049/jimmunol.2000213.
- Kagotho E, Omuse G, Okinda N, Ojwang P. Vitamin D status in healthy black African adults at a tertiary hospital in Nairobi, Kenya: a cross sectional study. *BMC Endocr Disord* 2018;18, doi:http://dx.doi.org/10.1186/s12902-018-0296-5.
- Karopova TL, Andreeva AT, Vashukova MA. уровень 25(OH)D в Сыворотке крови у больных COVID-19. Оригинальное исследование 2020;12, doi:http://dx.doi.org/10.22625/2072-6732-2020-12-3-21-2.
- Keane JT, Elangovan H, Stokes RA, Gunton JE. Vitamin D and the liver—correlation or cause? *Nutrients* 2018;10, doi:http://dx.doi.org/10.3390/nu10040496.
- Kheiri B, Abdalla A, Osman M, Ahmed S, Hassan M, Bachuwa G. Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. *Clin Hypertens* 2018;24, doi:http://dx.doi.org/10.1186/s40885-018-0094-4.
- Latella G, Viscido A. Controversial contribution of Th17/IL-17 toward the immune response in intestinal fibrosis. *Dig Dis Sci* 2020;65:1299–306, doi:http://dx.doi.org/10.1007/s10620-020-06161-1.
- Luxwolda MF, Kuipers RS, Kema IP, Dijck-Brouwer DAJ, Muskiet FAJ. Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/l. *Br J Nutr* 2012;108:1557–61, doi:http://dx.doi.org/10.1017/S0007114511007161.
- Mabin VJ, Davies J, Cox JF. Using the theory of constraints thinking processes to complement system dynamics' causal loop diagrams in developing fundamental solutions. *Int Trans Oper Res* 2006;13:33–57, doi:http://dx.doi.org/10.1111/j.1475-3995.2006.00532.x.
- Maghbooli Z, Ebrahimi M, Shirvani A, Nasiri M, Pazoki M, Kafan S, et al. Vitamin D Sufficiency Reduced Risk for Morbidity and Mortality in COVID-19 Patients (SSRN Scholarly Paper No. ID 3616008). Rochester, NY: Social Science Research Network; 2020, doi:http://dx.doi.org/10.2139/ssrn.3616008.
- Mithal A, Wahl DA, Bonjour J-P, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA* 2009;20:1807–20, doi:http://dx.doi.org/10.1007/s00198-009-0954-6.
- Muthuswamy V. Ethical issues in clinical research. *Perspect Clin Res* 2013;4:9–13, doi:http://dx.doi.org/10.4103/2229-3485.106369.
- Orme RP, Middleditch C, Waite L, Fricker RA. Chapter Eleven - The Role of Vitamin D3 in the Development and Neuroprotection of Midbrain Dopamine Neurons. In: Litwack G, editor. Vitamins & hormones, vitamin D hormone. Academic Press; 2016. p. 273–97, doi:http://dx.doi.org/10.1016/bs.vh.2015.10.007.
- Panagiotou G, Tee SA, Ihsan Y, Athar W, Marchitelli G, Kelly D, Boot CS, Stock N, Macfarlane J, Martineau AR, Burns G, Quinton R. Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. *Clin Endocrinol* 2020; doi:http://dx.doi.org/10.1111/cen.14276.
- Priest B, Pilz S, Wolf M, Tomaschitz A, Obermayer-Pietsch B, Graninger W, et al. Vitamin D supplementation and regulatory T cells in apparently healthy subjects: vitamin D treatment for autoimmune diseases?. *Isr Med Assoc J IMAJ* 2010;12:136–9.
- Priest B, Treiber K, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients* 2013;5:2502–21, doi:http://dx.doi.org/10.3390/nu5072502.
- Pugach IZ, Pugach S. Strong correlation between prevalence of severe vitamin D deficiency and population mortality rate from COVID-19 in Europe. *medRxiv* 2020; doi:http://dx.doi.org/10.1101/2020.06.24.20138644 2020.06.24.20138644 In preparation.
- Rafferty T, O'Sullivan M. Optimal vitamin D levels in Crohn's disease: a review. *Proc Nutr. Soc.* 2015;74:56–66, doi:http://dx.doi.org/10.1017/S0029665114001591.
- Salinthon S, Yadav V, Schillace RV, Bourdette DN, Carr DW. Lipoic acid attenuates inflammation via cAMP and protein kinase a signaling. *PLoS One* 2010;5, doi:http://dx.doi.org/10.1371/journal.pone.0013058.
- Sassi F, Tamone C, D'Amelio P. Vitamin D: nutrient, hormone, and immunomodulator. *Nutrients* 2018;10:1656, doi:http://dx.doi.org/10.3390/nu10111656.
- Seibert E, Heine GH, Ulrich S, Seiler S, Köhler H, Girdndt M. Influence of cholecalciferol supplementation in hemodialysis patients on monocyte subsets: a randomized, double-blind, placebo-controlled clinical trial. *Nephron Clin Pract* 2013;123:209–19, doi:http://dx.doi.org/10.1159/000354717.
- Tan CW, Ho LP, Kalimuddin S, Cherg BPZ, Teh YE, Thien SY, 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; doi:http://dx.doi.org/10.1101/2020.06.01.20112334 2020.06.01.20112334 In preparation.
- Uwitonze AM, Razzaque MS. Role of magnesium in vitamin D activation and function. *J Am Osteopath Assoc* 2018;118:181–9, doi:http://dx.doi.org/10.7556/jaoa.2018.037.
- Vasquez A. Inflammation mastery. 4th ed. International College of Human Nutrition and Functional Medicine; 2016.

- Ventana Systems. Documentation | Vensim URL <https://vensim.com/docs/> (Accessed 5.13.20). 2015.
- Vermeer C, Theuvsen E. Vitamin K, osteoporosis and degenerative diseases of ageing. *Menopause Int* 2011;17:19–23, doi:<http://dx.doi.org/10.1258/mi.2011.011006>.
- Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml). *Best Pract Res Clin Endocrinol Metab Vitamin D Classical and Novel Actions* 2011;25:681–91, doi:<http://dx.doi.org/10.1016/j.beem.2011.06.009>.
- von Helden R. *Gesund in sieben Tagen - Erfolge mit der Vitamin-D-Therapie*. 30th ed. Dresden: Hygeia-Verlag; 2011.
- Waite JC, Skokos D. Th17 response and inflammatory autoimmune diseases [WWW Document]. *Int J Inflamm* 2011;., doi:<http://dx.doi.org/10.1155/2012/819467>.
- Yasuda K, Takeuchi Y, Hirota K. The pathogenicity of Th17 cells in autoimmune diseases. *Semin Immunopathol* 2019;41:283–97, doi:<http://dx.doi.org/10.1007/s00281-019-00733-8>.
- Yasui T, Miyatani Y, Tomita J, Yamada M, Uemura H, Miura M, et al. Effect of vitamin K2 treatment on carboxylation of osteocalcin in early postmenopausal women. *Gynecol Endocrinol* 2006;22:455–9, doi:<http://dx.doi.org/10.1080/09513590600900402>.
- Zheng Y, Sun L, Jiang T, Zhang D, He D, Nie H. TNF α promotes Th17 cell differentiation through IL-6 and IL-1 β produced by monocytes in rheumatoid arthritis [WWW Document]. *J Immunol Res* 2014;2014;., doi:<http://dx.doi.org/10.1155/2014/385352>.