This scientific paper is intended for health professionals.

Vitamin K2 and D: Contribution to immune health

Research update

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“From a biochemical perspective, vitamin D and vitamin K2 are different nutrients. From a functional perspective their activities occur on a continuum and are synergistic and unified.”

Dr Andrew Myers, Member of Kappa Bioscience Scientific & Medical Advisory Board (smab)

Synergy of vitamin K2 and D

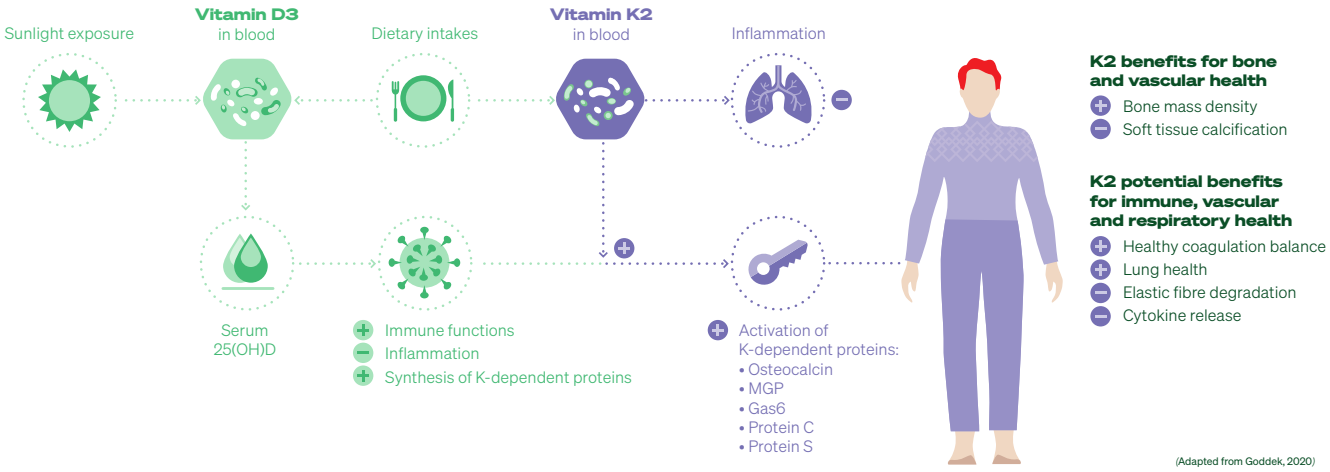
In our body’s system of calcium management, vitamin K2 finishes the job that vitamin D started with the absorption of calcium.

Unlike vitamin K1, vitamin K2-MK7 has its leading role outside the liver, maintaining calcium balance and elastic fibre elasticity and an immune-modulating function.

K2VITAL®

Puts calcium in balance.

Overview of the combined action of vitamin D3 and K2 to fight COVID-19 infection



(Adapted from Goddek, 2020)

How vitamin K deficiency promotes blood clotting and calcium disorders:

Vitamin K activates not only procoagulant but also anti-coagulant factors such as protein S. Protein S has an anti-coagulant and an anti-inflammatory effect. Half of the anticoagulant protein S is produced outside the liver in endothelial cells. While vitamin K1, absorbed via green leafy vegetables, has a half-life of about 1.5 hours, this is about 72 hours for vitamin K2 in the form of all-*trans* MK-7.

This is an adequate way to achieve stable blood levels. Moreover, it explains why vitamin K2 is much more effective than vitamin K1 for all effects outside the liver.

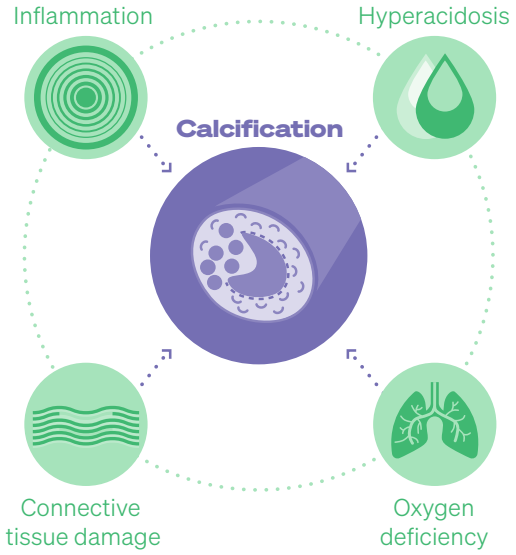
The underestimated importance of elastic fibres, MGP and vitamin K:

Elastic fibres are a critical component of the extracellular matrix and enable the normal function of respiration and blood circulation. Inflammation promotes the calcification of elastic fibres and thus leads to a vicious circle of their calcification and degradation: the affinity of elastic fibres for calcium is biochemically high. Matrix Gla proteins (MGP) are the most critical natural calcification inhibitor in connective tissue. MGP prevents calcium deposition, elastic fibre degradation, thrombosis, and inflammation in blood vessels and the lungs. Damaged and calcified elastic fibres are particularly common in diabetes mellitus type 2, hypertension, renal and cardiovascular diseases – the typical COVID risk groups. This increases the need for MGP synthesis (and thus vitamin K) to protect elastic fibres.

Degenerative processes reinforce each other and promote calcification

Inflammation
- Patients with severe COVID-19 present an overreaction of their immune system, described as the "cytokine storm"
- Besides the immune system, cytokines also activate blood clotting, which can explain the blood clot formation in COVID-19 patients

Tissue damage
- Existing CVD is associated with an increased risk of mortality from COVID-19
- COVID-19 appears to promote the development of cardiovascular disorders
- Calcification and blood clot formation put the cardiovascular and respiratory systems at risk

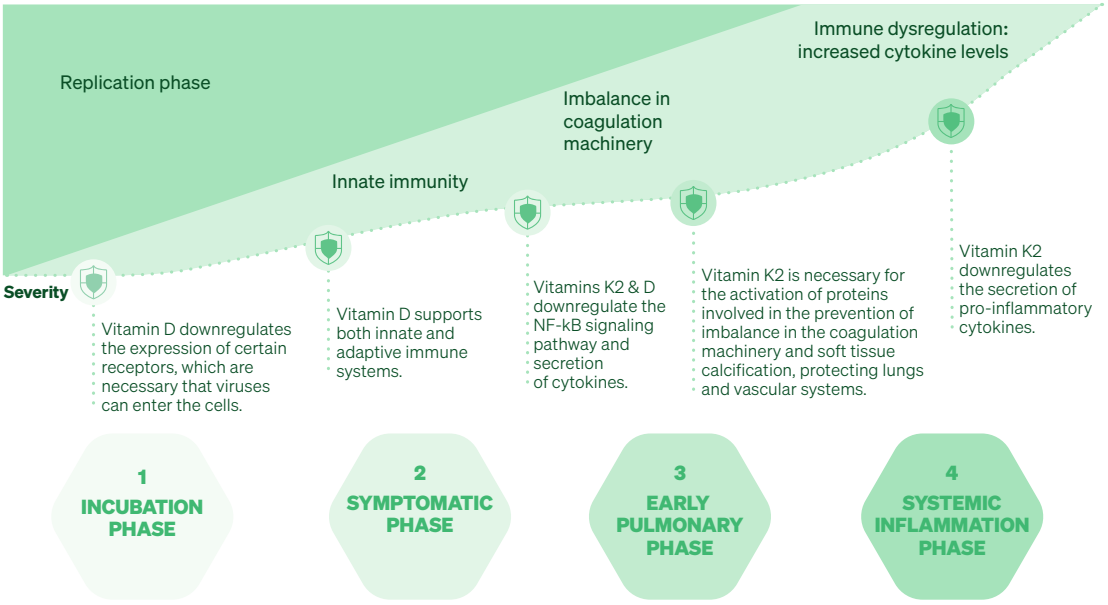


Acidosis
- Inflammatory reaction leads to a local acidosis, and the lowered pH promotes inflammation – a vicious cycle
- Acidosis fundamentally disturbs the balance in calcium metabolism

Hypoxia and oxygen deficiency
- Patients with severe COVID-19 may have extremely low oxygen levels without respiratory distress. Caused by ARDS, this silent hypoxia explains the sudden, rapid deterioration of patients' health

Dr. med. L.M. Jacob, 2021, viewed 31 March 2022 at https://vitamind.science/vitamin-k-und-covid-19/

Could deficiencies in vitamins D and K play a role in COVID-19 disease?



Specific roles of vitamins D and K2 in the body's immune response

Inflammation

- **Vitamin K2** activates proteins involved in inflammation prevention. (Protein C, Gas 6, GRP).
- **Vitamin K2 and D** downregulate the NF-kB signaling pathway and secretion of pro-inflammatory cytokines (IL-1ß, IL-6, TNF-α).
- **Vitamins K2 and D** thus improve inhibition of the inflammatory cascade, which can lead to the cytokine storm, one cause of severe disease development in COVID-19 patients.

Simes et al. 2020; Desai et al. 2021; Xia et al. 2012; Pan et al. 2016

Blood clotting

- **Vitamin K2** activates anti-coagulant factors such as protein S and protein C.
- **Low activation of protein S results in a higher risk for thrombosis**. The immune and inflammatory responses to SARS-CoV-2 infection can increase the need for vitamin K2 to protect against thrombosis.
- **Active protein S also shows anti-inflammatory effects** by reducing IL-6, among others.

Janssen et al. 2020; Suleiman et al. 2013

Lung health

- **Calcium** deposits on elastic fibres call for an increased need for MGP to protect the fibres from further calcification and degradation.
- **Vitamin D can promote synthesis of matrix Gla protein** (MGP – the most critical natural calcification inhibitor in connective tissue), but vitamin K2 is crucial for its activation.
- **Active MGP helps remove calcium from soft tissues.**

van Ballegooijen et al. 2017; Dofferhoff et al. 2020

While vitamin K1 has a half-life of about 1.5 hours, vitamin K2 all-*trans* MK-7 has 72 hours.

This is the way to achieve effective, stable blood levels. Moreover, it explains why vitamin K2 is much more effective than vitamin K1 for all effects outside the liver (extrahepatic). Therefore, vitamin K2 as MK-7 may be more suitable than vitamin K1 for supplementation to activate pulmonary MGP and endothelial protein.
(S. Theuwissen et al. 2012 / Janssen and Walk, 2020)

In case of vitamin K insufficiency, supply will be preferentially transported to the liver to activate procoagulant factors at the expense of extrahepatic vitamin K-dependent proteins.
(Triage Theory)

Vitamin K status in COVID-19 patients

"Although more research is needed, we found data in our study suggesting that vitamin K deficiency may be the missing link between lung damage and thrombosis in COVID-19."

Dr. Rob Janssen of the Department of Pulmonary Medicine, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands and corresponding author of the study

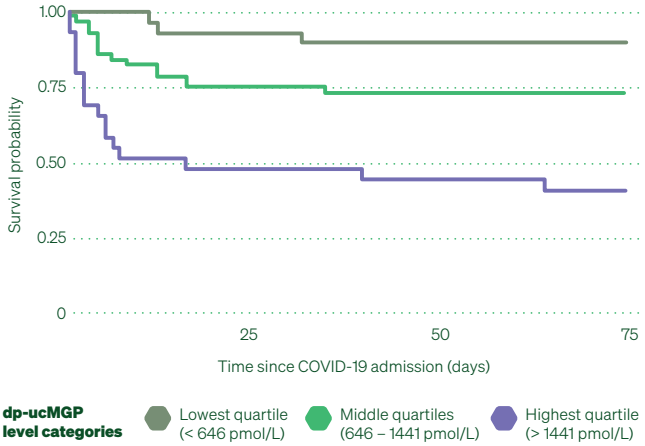
A growing number of studies show that COVID-19 patients have severely reduced vitamin K status – the more severe the COVID-19 course, the more severe the vitamin K deficiency.

Kappa Bioscience is preparing an international research program, rallying scientific teams in Europe and the US.

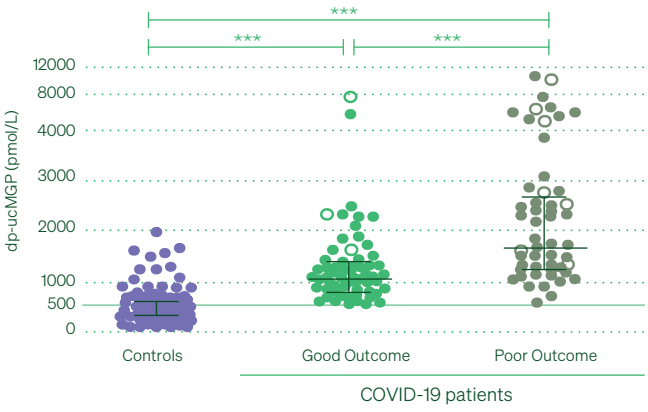
One clinical trial has been completed in the Canisius Wilhelmina Hospital. Results are not published yet.

Kaplan-Meier plot of 90-days cumulated risk of dying stratified by levels of vitamin K status

Lower dephosphorylated-uncarboxylated matrix Gla protein (dp-ucMGP) level reflects higher vitamin K status.



Correlation: vitamin K status vs. COVID-19 outcome

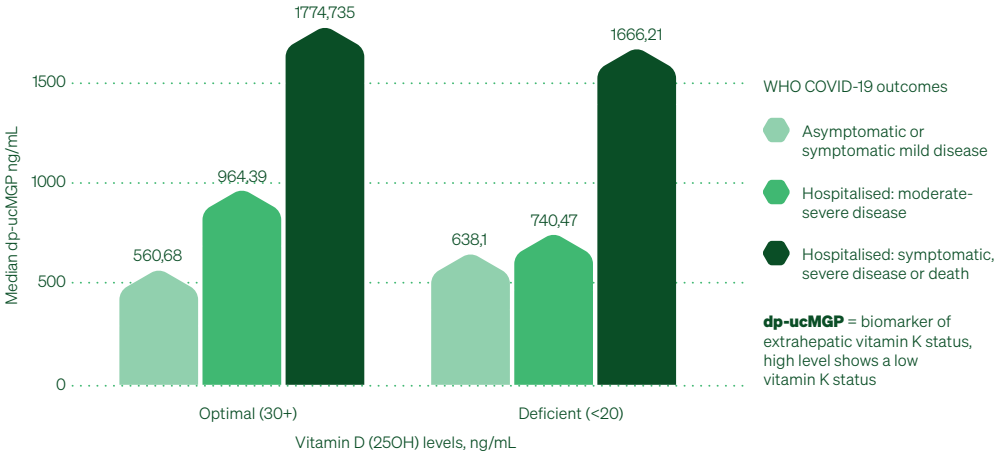


dp-ucMGP: inactive vitamin K (VK) dependent protein (extrahepatic), high level shows a low vitamin K status

Open circles: VK antagonist user

Adapted from Dofferhoff, A. S., Piscaer, I., Schurgers, L. J., Visser, M. P., van den Ouweland, J. M., de Jong, P. A., ... & Maassen, C. (2020). Reduced Vitamin K Status as a Potentially Modifiable Risk Factor of Severe Coronavirus Disease 2019. Clinical Infectious Diseases.

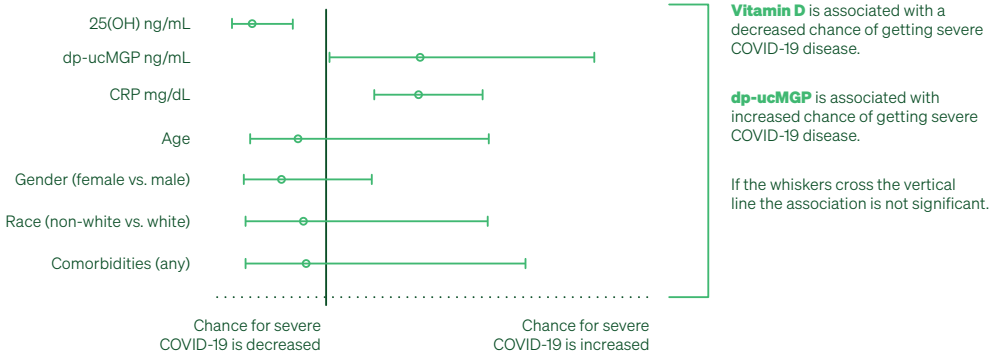
Vitamins D and K are associated with immune health



Adapted from Desai A.P. et al. Open Forum Infectious Diseases 2021. Volume 8, Issue 10, October 2021

Participants with sufficient vitamin D (>30 ng/mL= 75 nmol/L), as well as those who were vitamin D deficient (<20 ng/mL = 50 nmol/L), had the worse vitamin K status and experienced the most severe COVID-19 disease outcomes.
(Desai et al., 2021)

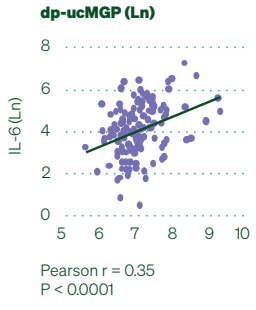
Association of dp-ucMGP (vitamin K status) and 25(OH)D (vitamin D status) with COVID-19 disease severity



Data is adjusted for confounders, like age, gender and more. Adapted from Desai A.P. et al. Open Forum Infectious Diseases 2021. Volume 8, Issue 10, October 2021

Early in acute COVID-19, both vitamin K and vitamin D deficiency were independently associated with worse COVID-19 disease severity, suggesting a potential synergistic interplay between these two vitamins in COVID-19.
(Desai et al., 2021)

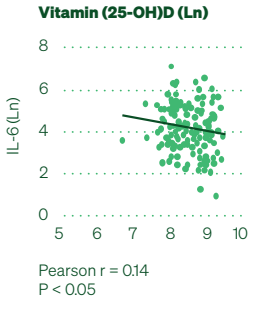
Vitamins D and K in relation to inflammatory response and elastic fibre degradation in COVID-19



Pearson r = 0.35
P < 0.0001

- dp-ucMGP levels were associated with IL-6 levels. In contrast, 25(OH)D levels were only borderline statistically significant correlated with IL-6.
- A significant association was also found between IL-6 and elastic fibre degradation.
- Contrary to vitamin K status, 25(OH)D did not correlate with elastic fibre degradation.

dp-ucMGP = biomarker of extrahepatic vitamin K status, high level shows a low vitamin K status



Pearson r = 0.14
P < 0.05

"It can be hypothesized that vitamin D supplementation puts an excessive burden on already depleted vitamin K stores during COVID-19, with subsequent destructive consequences for elastic fibres." Visser M.P.J. et al. 2022

The reason for a severe COVID-19 infection is partly an excessive inflammatory response, and IL-6 plays a key role there. dp-ucMGP associates with IL-6 as a central component of the destructive inflammatory processes in COVID-19.
(Visser et al., 2021)

If you have any thoughts, questions, or you'd like to talk about any of the information in this document, we're here to hear you out.

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Kappa Bioscience AS
Silurveien 2, Building B · 0380 Oslo, Norway

Kappa Bioscience Europe GmbH
Friesenweg 22 · 22763 Hamburg, Germany
Office +49 40 6094087-0
info@kappabio.com · www.kappabio.com · www.k2vital.com