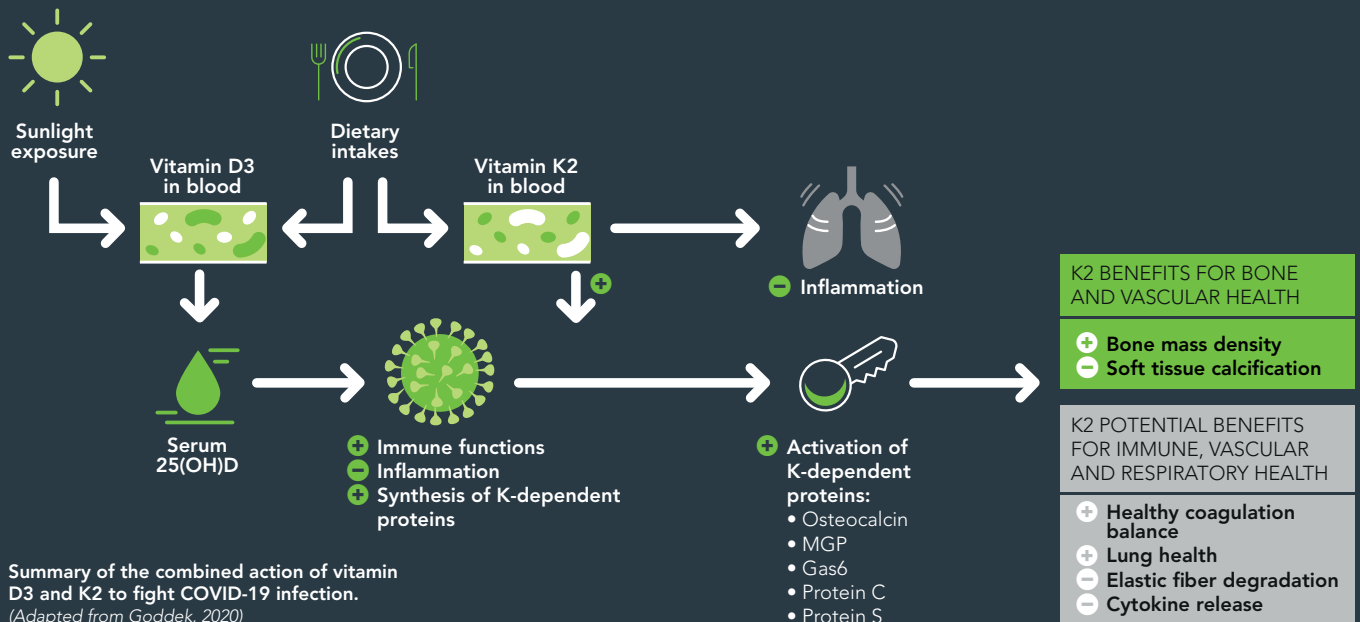


VITAMIN K2 AND D: CONTRIBUTION TO IMMUNE HEALTH



VITAMINS D AND K2 HAVE A COMMON CONNECTION TO CALCIUM

High doses of vitamin D can induce short-term hypercalcemia, a transient increase in serum calcium levels. This calcium may deposit in soft tissue, such as blood vessels or elastic fibers in the lungs, which can lead to damages.

The other way around, too little calcium is just as deleterious. Hypocalcemia seems to be common in COVID-19 patients, and was linked to more severe disease course. Vitamin D supports calcium absorption, but vitamin K2 is needed to bring this calcium to the right places.

The frequent deficiencies in vitamins D and K2 disturb the calcium balance. Calcium-binding proteins are vitamin K2-dependent. **K2VITAL® puts calcium in balance.**



CALCIUM OPERATES KEY FUNCTIONS IN THE HUMAN BODY

- Bone and teeth formation
 - Blood clotting
 - Muscle (including cardiac muscles) contraction
 - Neuronal transmission
 - Hormonal secretion
- Its metabolism is tightly regulated.



SYNERGY OF VITAMIN K2 AND D

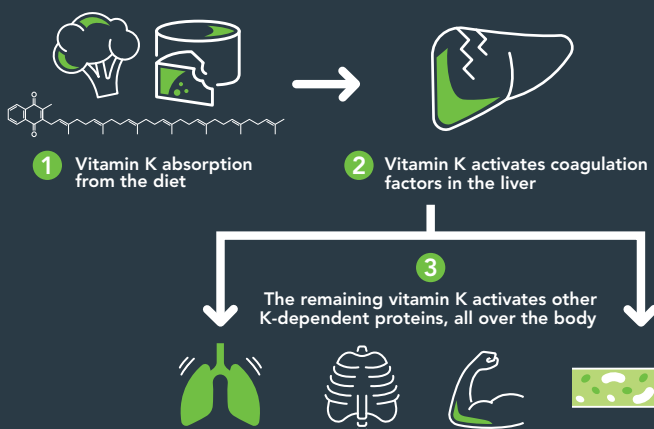
On the one hand, to support calcium-balance through increased expression and activation of calcium-binding proteins.
On the other hand, to support a healthy balance between pro- and anticoagulation, support proper functioning of the immune system.

TRIAGE THEORY

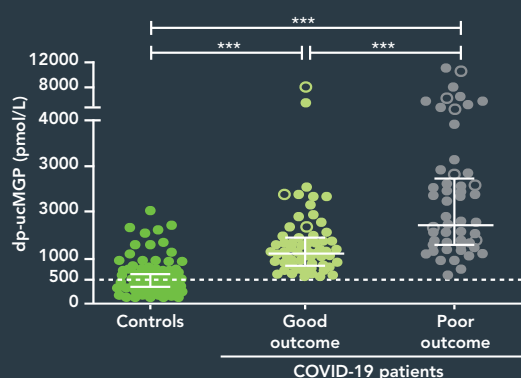
The triage theory posits that some functions of micro-nutrients are restricted during shortage:

short-term survival prevails over "less essential" functions

In case of vitamin K insufficiency, supply will be preferentially transported to the liver, to activate pro-coagulant factors, at the expense of extrahepatic vitamin K-dependent proteins. Involved in **bone formation, tissue protection against calcification, anti-coagulation and anti-inflammation functions**, these are yet crucial for the proper functioning of our body.

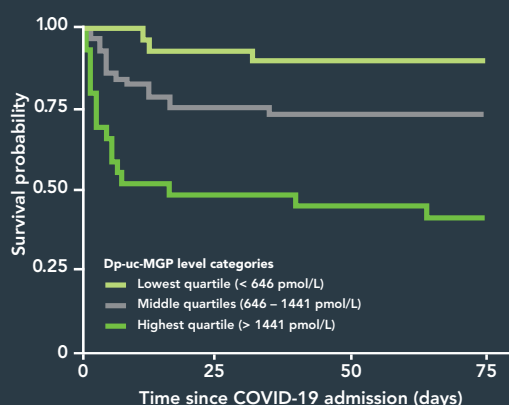


CORRELATION: VITAMIN K STATUS VS. COVID-19 OUTCOME ⁽¹⁾



dp-ucMGP: Inactive vitamin K (VK) dependent protein (extrahepatic), high level shows a low vitamin K status. **Open circles:** VK antagonist user

KAPLAN-MEIER PLOT OF 90-DAYS CUMULATED RISK OF DYING STRATIFIED BY LEVELS OF VITAMIN K STATUS ⁽²⁾



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

VITAMIN K STATUS IN COVID-19 PATIENTS

A strong correlation was found between lower vitamin K status and worse disease outcomes in COVID-19 patients. Whether preexisting, or due to increased need in times or crisis – or both –, vitamin K deficiency puts our health at risk. Double-blind, randomized, placebo-controlled clinical trials are now needed to investigate the benefits of supplementation with vitamin K2.

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

One clinical trial has already started, in the Canisius Wilhelmina Hospital, the Netherlands:

[recruiting] Double-blind, randomized, placebo-controlled clinical trial: 40 patients, hospitalized with COVID-19, will receive 999 mcg of K2VITAL® vitamin K2 MK-7 daily for 2 weeks. Desmosine and dp-ucMGP levels will be measured and compared within the two groups.



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

“ 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. Considering that vitamin K is important for regulating lung health and blood clotting, vitamin K deficiency during COVID-19 may make both those problems worse.”

(1) Adapted from Dofferhoff, A. S., Pijls, L., 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*.

(2) Linneberg, A., Kampmann, F. B., Israelsen, S. B., Andersen, L. R., Joergensen, H. L., Sandholt, H., ... & Benfield, T. (2020). Low vitamin K status predicts mortality in a cohort of 138 hospitalized patients with COVID-19. (preprint)

INFLAMMATION AND THE CYTOKINE STORM

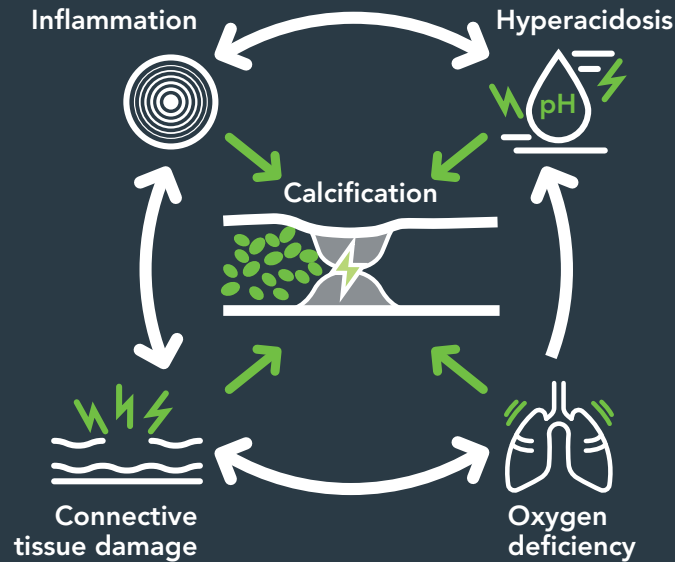
- Patients with severe COVID-19 present an overreaction of their immune system, described as the "cytokine storm"
- Besides the immune system, cytokines also activate blood clotting, which can explain the blood clot formation in COVID-19 patients.

- ✓ Vitamins D and K2 both can lower inflammation
- ✓ Vitamin K2 regulates blood clotting

TISSUE DAMAGE

- Existing CVD are 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

- ✓ Vitamin K2 puts calcium in balance and regulates blood clotting



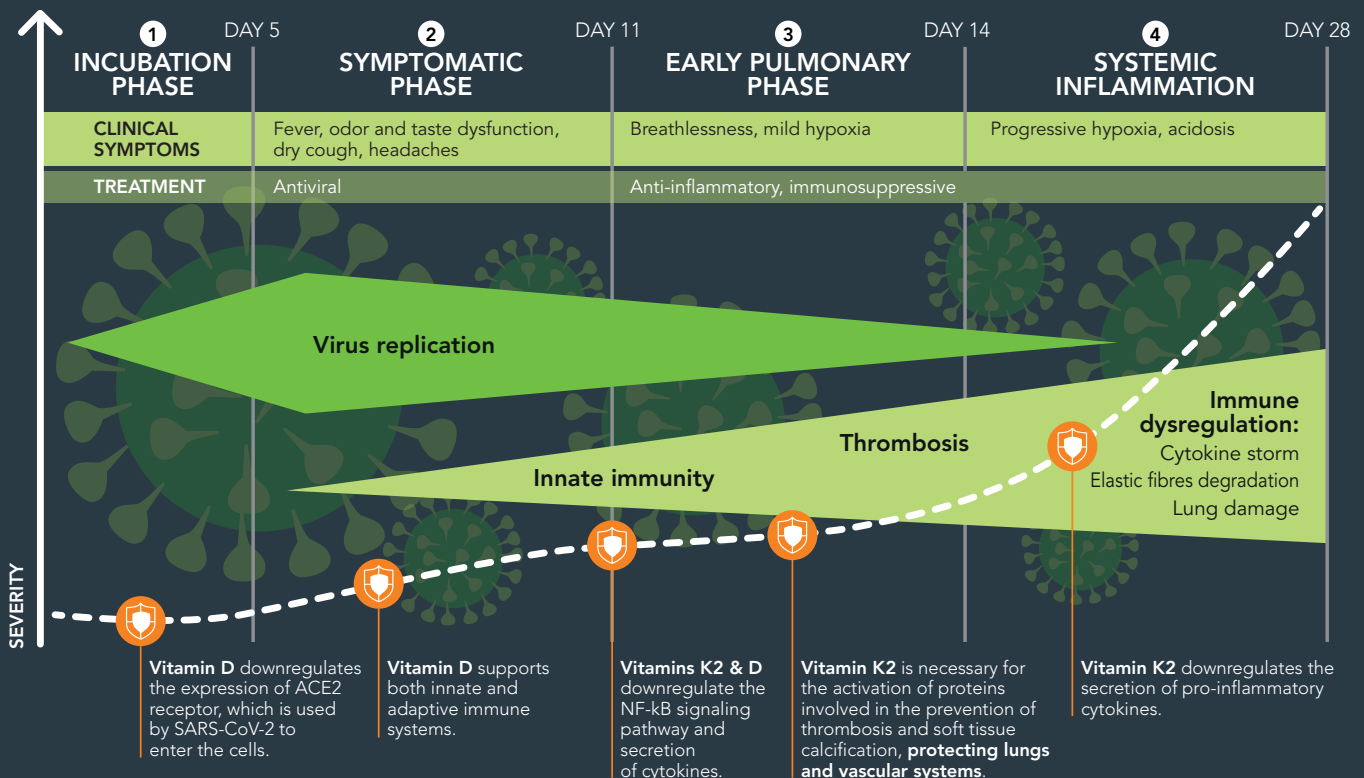
Vitamin D might have both favorable anti-inflammatory and unfavorable pro-calcification effects during COVID-19. Vitamin K might compensate for the latter.

(Walk and Janssen, 2020) preprint

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.

COULD DEFICIENCIES IN VITAMINS D AND K PLAY A ROLE IN COVID-19 DISEASE?





VITAMIN K2 AS MK-7 MAY BE MORE SUITABLE THAN VITAMIN K1 FOR SUPPLEMENTATION

In SARS-CoV-2-infected patients, low vitamin K2 status could modify COVID-19 pathogenesis due to limited prevention of thrombosis formation, limited prevention of elastic fiber damage in the lungs and limited inhibition of the inflammatory cascade, possibly leading to increased cytokine release.

A more significant proportion of vitamin K2 than K1 is directly transported to extrahepatic tissues after absorption from the gut. Therefore, Vitamin K2 as MK-7 may be more suitable than vitamin K1 for supplementation in COVID-19 patients to activate pulmonary MGP and endothelial protein S. *Theuwissen et al. 2012 / Janssen and Walk, 2020*

HOW COULD VITAMINS D AND K2 MK-7 POTENTIALLY HELP?

BOTH VITAMINS PLAY KEY ROLES FOR MANY METABOLIC FUNCTIONS, INCLUDING:



INFLAMMATION

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

Chen et al., 2016; Pan et al., 2016; Reddi et al., 1995; Xia et al., 2012



BLOOD CLOTTING

- + **Vitamin K2** activates protein S and protein C, which regulate coagulation.
- **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.

Castoldi et al., 2008; Dahlbäck, 2018; Majid et al., 2020; Padda et al., 2020; Suleiman et al., 2013



LUNG HEALTH

- + **Vitamin D can promote synthesis of matrix Gla protein (MGP)**, but vitamin K2 is crucial for its activation.
- + **Active MGP helps remove calcium from soft tissues.**
- + **Calcium deposits on elastic fibers call for an increased need for MGP** to protect the fibers from further calcification and degradation, to protect the lungs against damages.

Berenjian, 2015; Berenjian, 2020; De Brouwer et al., 2020; Dofferhoff et al., 2020

VITAMIN K1 OR K2: WHERE ARE THE DIFFERENCES?

Most of our dietary intake in vitamin K comes under the phylloquinone (K1) form: widely present in leafy green vegetables. Menaquinones (K2) originate from animal products and fermented foods. There are several menaquinones: MK-4 and MK-7 are the most prevalent and most studied ones.

Although their biological function is similar, their differences lie in bioavailability, and tissue distribution.

Bioavailability: K1 < K2 MK-4 < K2 MK-7

Half-life: K1 = K2 MK-4 < K2 MK-7

Tissue distribution: K2 have a higher extrahepatic potential than K1



HIGH BIOAVAILABILITY

Vitamin K2 as *trans*-Menaquinone-7 (MK-7) has shown high bioavailability, the longest K vitamin half-life, and significant transport to extrahepatic tissues via LDL particles.

Theuwissen et al. 2012 / Janssen and Walk, 2020