Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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How menaquinone-7 deficiency influences mortality and morbidity among COVID-19 patients

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a viral infection known as the coronavirus disease 2019 (COVID-19). The spread of the novel COVID-19 has resulted in a pandemic, which threatens to amplify mortality and morbidity worldwide. The majority of individuals who contract this virus develop respiratory failure as a result of pneumonia and/or acute respiratory distress syndrome (ARDS), which decreases their prospect of survival. On the other hand, several observational reports indicate that individuals who develop severe SARS-CoV-2 infections often have comorbidities, namely diabetes, hypertension, and cardiovascular diseases (Gandhi et al., 2020; Guan et al., 2020).

Vitamin K is known for its role as a coagulation cofactor, and it naturally exists in two forms, vitamin K1 (phylloquinone) and vitamin K2 (menaquinone). Both vitamin subtypes act as a necessary cofactor for the carboxylation of vitamin K dependent proteins (Gla proteins). However, the two distinct forms of vitamin K are vastly different with respect to their chemical structure and pharmacokinetics that affect metabolism, bioavailability, and impact on health outcomes.

The liver uses phylloquinone to activate coagulation factors, while menaquinone plays a more dominant role in the activation of extrahepatic vitamin K-dependent proteins, such as the matrix Gla protein (MGP). Therefore, phylloquinone primarily participates in blood clotting, and menaquinone is involved in important metabolic processes, such as bone mineralisation and soft tissue decalcification (Berenjian et al., 2015).

Research suggests that greater health benefits are associated with the intake of menaquinone in comparison to phylloquinone, particularly with the consumption of menaquinone-7 (MK-7), which is an exceptional form of menaquinone due to its high bioavailability. Studies have also found that MK-7 has anti-inflammatory properties that are completely independent of its role as an enzyme cofactor. MK-7 is typically synthesised through bacterial fermentation; however, as a result of its low availability in the diet, deficiency of this vitamin is common (Mahdinia et al., 2017).

We hypothesise that manifestations of COVID-19 and comorbidities associated with the severe form of this disease could be linked to MK-7 deficiency. Therefore, this work aims to discuss how MK-7 can support the prevention and treatment of the disease during the COVID-19 pandemic.

Elastin plays a key role in providing resilience, elasticity, and deformability to dynamic tissues, namely the lungs and arteries, which has a high affinity for calcium. Vascular calcification typically initiates in the elastin fibres of the medial arterial wall. MGP is MK-7-dependent and is well-known as a calcification inhibitor in soft tissues, such as the arterial walls. Moreover, MGP plays a key role in protecting extracellular matrix proteins from possible enzymatic degradation. Elastic fibres are essential components of the extracellular matrix in the lungs, where MGP is strongly expressed.

Therefore, MGP's role in the pulmonary compartment seems to be comparable with that in the vasculature and is crucial for the protection of elastic fibres against calcification. Impaired MGP activation could be associated with elastic fibre degradation. These processes are interrelated, and partially degraded elastic fibres are more prone to mineralisation. Furthermore, the release of matrix metalloproteinases (MMPs) can enhance elastic fibre calcification, resulting in lung fibrosis (de Brouwer et al., 2016).

A profound increase in extrahepatic inactive MGP was observed in individuals with COVID-19, which is indicative of an MK-7 deficiency in these patients. In addition, a subset of pulmonary macrophages that release MMPs tends to be elevated during severe SARS-CoV-2 pneumonia, leading to elastic fibre degradation (Dofferhoff et al., 2020). Consequently, accelerated elastic fibre degradation and insufficient active MGP in COVID-19 patients suggest an interrelationship between MK-7 deficiency and COVID-19. Therefore, COVID-19 may theoretically be linked to MK-7 deficiency, which can be presumed to worsen the health outcome associated with the disease.

Interestingly, many comorbid conditions, which worsen COVID-19 clinical outcomes, are associated with a compromised level of MK-7. An MK-7 deficiency is certainly linked to vascular calcification, as it reduces the concentration of active MGP below that required for the inhibition of elastic fibre mineralisation. These damaged and calcified elastic fibres are more prone to further degradation in comparison to intact fibres. Additionally, hypertension, diabetes, and cardiovascular disease are all associated with the remodelling of elastic tissues. Therefore, MK-7 deficiency can be a risk factor for increasing the severity of the COVID-19 disease, and SARS-CoV-2 infected patients with comorbid conditions tend to develop acute manifestations. Evidence suggests that similar processes also occur in the lungs, as aforementioned. Calcification of elastic fibres makes them more susceptible to degradation following the enhanced production of MMPs by macrophages during COVID-19 infection. However, a clinical trial to assess the change in the MK-7 status of individuals before and after supplementation would be required to determine the effect of MK-7 on SARS-CoV-2 pneumonia.

Following vitamin K antagonist (VKA) initiation during atrial fibrillation in COVID-19 patients, the risk of stroke illogically increases. This may be justified by the increase in the concentration of inactive MGP (uncarboxylated MGP), which has been shown to be linked to mortality (Dofferhoff et al., 2020). Since MK-7 supplementation decreases uncarboxylated MGP (ucMGP) levels, MK-7 administration is likely to improve the health outcome of COVID-19 patients.

Furthermore, coagulopathy and venous thromboembolism tend to be common in severe SARS-CoV-2 infections, resulting in poor health outcomes and low rates of survival. The mechanisms that activate

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coagulation in COVID-19 appear to be linked to inflammatory responses rather than to the specific properties of the virus. Anticoagulants have also been shown to heighten the risk of severe COVID-19 infection (Azoulay et al., 2014). Therefore, MK-7, due to its anti-inflammatory role, which is independent of its role as an enzyme cofactor (Lal and Berenjian, 2020), could be a potential substitute to reduce the mortality rate associated with COVID-19.

MK-7 seems to be effective in the prevention and treatment of atherosclerosis, calcified arterial plaque, and inflammation. Individuals infected with SARS-CoV-2 that have such conditions are more susceptible to a severe disease course. Furthermore, it also appears that a potential relationship exists between MK-7 deficiency, lung tissue injury, and comorbidities in COVID-19 patients. However, a clinical trial is essential to evaluate whether MK-7 administration improves the health outcome or prognosis of patients with COVID-19.

Declaration of competing interest

We declare no competing interests.

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