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Serum Level of Vitamin K as Predicts Mortality in Iraqi COVID-19 Patients

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Abstract
Objective: The aim of the presented study is to evaluate the discriminative ability of vitamin K markers for predicting, monitoring, and a prognosis of severity patients of Covid-19.
Methods: In this case-control study, a maximum of sixty patients (30–50 years old) were included. The patients' diagnoses were made using quantitative RT-PCR and a chest X-ray or CT scan performed seven to thirteen days after the onset of symptoms. Murray ratings were utilized to categorize COVID-19 patients based on the severity of their illness. (60) individuals of the same age and gender who appeared to be in good health were included in this study as a control group in order to compare the outcomes. The measurement of serum vitamin K was applied to all patients and healthy individuals.
Results: The group of COVID-19 patients had a lower serum vitamin K level (612.32 ± 106.76 vs. 1198.95 ± 151.59 ng/ml, $P = 0.0001$) than the healthy control group. Furthermore, we discovered a negative correlation between serum vitamin K levels and COVID-19.
Conclusion: The current findings showed that, when compared to healthy controls, patients with COVID-19 had decreased vitamin K levels, particularly in severe cases. These low levels suggest that COVID-19 patients may be more likely to die. These results imply that vitamin K may be involved in the COVID-19 disease processes.
Keywords: COVID-19, vitamin K, severity, mortality

Introduction

COVID-19 has become a major global health issue, putting millions of individuals in an increasing number of countries at risk. Because COVID-19 induces endothelial of evidence-based COVID-19 therapeutic options available for both prevention and management of the illness.[1]

Additionally, preliminary findings from multiple trials seem to suggest that anticoagulant medication is linked to a decreased death rate among individuals with COVID-19 from Respiratory Infection Pathogenesis Diagnostic Measures and Current Treatment Strategy.[2]

In severe COVID-19 patients, coagulopathy and thromboembolism are common, and cardiovascular problems account for 40% of COVID-19 death demonstrating the potential function of vitamin K through modulation of coagulation.

In fact, anticoagulant therapies have been shown in several recent studies to lower mortality in severe cases. Potential pathways that could link COVID-19 to coagulopathy and where vitamin K could influence coagulation in relation to the pathophysiology of the disease (Getachew et al., 2023),[3] order to enhance illness outcomes, we investigate the possible advantages of utilizing vitamin K against COVID-19 and present the latest evidence establishing COVID-19 as a vascular disease. A recent study found a correlation between the poorest COVID-19 outcomes and a shortage in vitamin K, which is crucial for preventing blood clotting and a key role in the coagulation system.[4]

Materials and Methods

A case-control study design for Sixty individuals of patients' with COVID-19 with age (30–50 years old) were included. This patient diagnoses by using quantitative RT-PCR and a chest X-ray or CT scan performed seven to thirteen days after the onset of symptoms were collected from AL- Sadder medical city in AL-Najaf governorate. Within the period from September 2021-December 2021. Murray Score were utilized to categorize COVID-19 patients based on the severity of their illness to (33) mild, (15) sever (12) deceased patients. the same age and sex who appeared to be in good health were included in this study as a control group in order to compare the outcomes. Participants (both controls and patients) or their parents or legal guardians gave written informed permission in accordance with the most stringent ethical requirements. All local, national, and international ethical and privacy regulations were followed, and the research was approved by the institutional ethics board at the University of Karbala and Declaration of Helsinki of the World Medical Association. Serum vitamin K, D-dimer, CRP, ferritin and anthropometric data were estimated and examined for all patients and healthy individuals. vitamin K were measured through enzyme-linked immunosorbent assays (ELISA) Bioassay. Complete blood count was measured by using auto hematology analyzer.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) was utilized to analyze the observed data, which were expressed as mean ± SD. A separate t-test was employed to assess any noteworthy distinctions between the groups of sick and healthy individuals. The statistical relationship (association) between any two variables in the current study was mentioned using the Pearson correlation coefficient test. In order to indicate the strength of evidence supporting significant differences between variables, two significance levels were determined: 5% ($P \leq 0.05$) and 1% ($P \leq 0.01$).

Results and Discussions

In total, 60 patients with confirmed COVID-19 and 60 healthy subjects were enrolled in this study and Comparisons of anthropometric characteristics and Vitamin K Levels between COVID-19 Patients and the apparently control groups. In Table 1 shown a no significant in mean age, SBP, and DBP when compared between patients and control groups. But, the mean of BMI increased significantly in patients group compared the control group.

As revealed in Table 2 a significant decrease in the level of vitamin K and increased serum levels of ferritin and D-dimer levels in COVID-19 patients group compared with the control group.

Table 1. **General characteristics of the patients and control group**

Parameters	COVID-19 patients group Mean ± SD *N* = 60	Healthy group Mean ± SD *N* = 60	*P*-value
Sex, F/M	24/36	11/19	-
Age, (years)	56.89 ± 6. 32	56.48 ± 5.41	N.S
BMI, (kg/m^2)	28.82 ± 4.31	24.46 ± 3.11	0.001
SBP, (mmHg)	124.73 ± 7.31	123.69 ± 7.02	N.S
DBP, (mmHg)	70.15 ± 10.27	70.83 ± 6.18	N.S

N, Number of subject; Data represented as Mean ± SD; SD, Stander deviation; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; F, female; M, male; N.S, Non-significant.

In Table 3 shown decreased in levels of vitamin K but increased non significantly in sever and deceased patients groups compared mild group.

In Table 4 illustrated the significant correlation between serum vitamin K with BMI, LYM%, LNR, D-Dimer, and ferritin in patients group.

In severe COVID-19 patients, coagulopathy and thromboembolism are common, and cardiovascular problems account for 40% of COVID-19 fatalities. In individuals with COVID-19, abnormal coagulation parameters are associated with a bad prognosis. The victims' afflicted lungs also showed signs of widespread thrombosis. It is common knowledge that vitamin K is crucial to the coagulation system. The current investigation demonstrated the involvement of vitamin K by revealing a relationship between Covid verity and vitamin K deficiency.[5] Investigate the potential benefits of utilizing vitamin K against Covid-19 to enhance disease outcome. Determine the possible processes associating Covid-19 with coagulopathy, in which vitamin K may exercise its regulating role in coagulation related to disease etiology. According to one of the most popular theories, lung damage is caused by an overwhelming pro-inflammatory cytokine response that intensifies the immune response. This phenomenon is known as a "cytokine storm".[6]

There is a connection between the worst cases of coagulopathy and vitamin K deficiency. Vitamin K is crucial for preventing blood clotting and is a vital participant in the coagulation system. The results of COVID-19 were just made public.[7]

The respiratory symptoms associated with COVID-19 are diverse and can occasionally result in severe consequences.

Table 2. **Comparison of complete blood count, D-dimer, ferritin and vitamin K levels in COVID-19 patients and control group**

Parameters	Covid-19 patients group Mean ± SD *N* = 60	Healthy group Mean ± SD *N* = 60	*P*-value
PLT%	250.74 ± 57.33	257.3 ± 21.11	0.05
NEUT%	84.30 ± 7.84	45.31 ± 9.83	0.0002
LYM%	10.21 ± 2.81	23.85 ± 6.91	0.0002
NLR	8.26 ± 3.69	1.79 ± 0.87	0.0001
D-dimer (ng/mL)	3450.20 ± 1800.17	269.69 ± 88.96	0.0001
Ferritin (ng/mL)	1081.93 ± 471.46	106.7 ± 47.81	0.0001
Vitamin K (ng/mL)	612.32 ± 106.76	1198.95 ±151.59	0.0001

Data represented as mean ± SD, Standard deviation; LYM, Lymphocyte; NEUT, neutrophil; NLR, Neutrophil/Lymphocyte ratio; PLT, Platelet.

Table 3. **Comparison of serum vitamin K level in COVID-19 patients groups**

Parameters	Covid-19 patients groups			*P*-value
	Deceased *N* = 12	Severe *N* = 15	Mild *N* = 33	
Vitamin (pg/mL)	868.46 ± 157.32	796.40 ± 147.13	743.84 ± 110.79	a = 0.4 b = 0.1 c = 0.4

Data represented as Mean ± SD, standard deviation; a = *P*-value (Deceased + Severe); b = *P* -value (Deceased + Mild); c = *P* -value (Severe + Mild).

Table 4. **The correlations between vitamin K level with clinical parameters in COVID-19 patients group**

Parameters	*r*	*P*-value
Age, (years)	–0.341	0.064
BMI, (kg/m^2)	–0.372	0.040
SBP, (mmHg)	0.283	0.280
DBP, (mmHg)	0.209	0.245
PLT%	0.323	0.065
NEUT%	–0.325	0.071
LYM%	0.376	0.037
NLR	–0.370	0.041
D-dimer, (ng/mL)	–0.487	0.001
Ferritin, (ng/mL)	–0.467	0.001

r, Pearson correlation coefficient; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; LYM, lymphocyte; NEUT, neutrophil; NLR, neutrophil/lymphocyte ratio; PLT, Platelet.

Like other serious respiratory conditions, severe Covid-19 infections include pneumonia, acute lung injury (ALI), ARDS, and sepsis, which can result in multiple organ failure and even death.[8] Research has demonstrated that as soon as nine days from the commencement, ARDS can develop and the respiratory symptoms can get worse.[9] Even in asymptomatic individuals, computed tomography (CT) scans revealed lung damage defined by a pulmonary ground glass opacification, suggesting that the multitude of problems resulting from Covid-19 are still not well understood.[10]

The increased synthesis of pro-inflammatory cytokines due to an enhanced immune response is what causes the cytokine storm. While information indicates that a Covid-19 infection may change an individual's innate and adaptive immunity (Rabaan, et al., 2021),[11] Immune response in the respiratory system is believed to be primarily regulated by myeloid cells and respiratory epithelial cells.[12] Significant infiltration of inflammatory immune cells, predominantly neutrophils and macrophages, is seen in the lungs of severe Covid-19 patients.[13] Increased immune cell infiltration and buildup (neutrophils, macrophages) raise the risk of atherosclerotic plaque rupture and subsequent cardiovascular problems. There have been reports of macrophage infiltration of the lungs with Covid-19 infections.[14] Pro-inflammatory cytokines such as IL-6 Interleukin-1 and TNF are thought to be produced by macrophages, reported to be hyper-induced during Covid-19 infection and are found to be positively correlated with disease severity relating to cytokine storms.[15]

A bad prognosis for their illness is linked to impaired coagulation markers, which are seen in patients with severe Covid-19. Similarly, people with Covid-19 exhibit elevated levels of fibrinogen compared to normal.

In addition, plasma levels of the procoagulation protein, von Willebrand factor is also increased in Covid-19 patients.[16] Levels of D-dimer and fibrin degradation product, which can reflect the occurrence of thrombosis and is associated with a diagnosis of disseminated intravascular coagulation (DIC), are found to be significantly enhanced in severe Covid-19 cases Although, the prevalence of DIC in Covid-19 is still in debate (Iba, et al., 2020),[17] pulmonary microthrombi formation is clearly observed in Covid-19. Pulmonary embolism, strokes and heart attacks can be a direct consequence of thrombosis. Indeed, pulmonary embolism is observed in 50% of Covid-19 patients admitted to ICU, adequate oxygenation and ventilation are recommended for Covid-19 patients with ARDS.[18]

Studies demonstrate that Covid-19 can infect endothelial cells, cells which represent one third of the total cells in lungs (Zeng, et al., 2012)[19] and hence can contribute directly to thrombosis via endothelial cell lysis. Damage to the endothelial wall exposes the subendothelial collagen that is involved in platelet adhesion, activation and ultimately coagulation (Levi, et al., 2009).[20] Secretion of factors involved in coagulation by the endothelial cells is also altered. The concept of reducing mortality in Covid-19 patients by administering anticoagulant medication is widely recognized (Norooznezhad, et al., 2021).[21] In actuality, the coagulation process necessitates tight supervision because it is a delicate balance between procoagulation and anticoagulation components. Thrombophilia or coagulopathy may result from dysregulation in either direction. Two of the most important components in this process are proteins C and S (Enjeti, et al., 2018).[22] Interestingly, a low protein C activity is found in severe and aged Covid-19 patients favoring a hypercoagulability state.[23] Vitamin K is a crucial "switch" in the equilibrium of the coagulation and anticoagulation processes. The activation of both hepatic and extra-hepatic vitamin K-dependent proteins (VKDPs), such as pro-thrombin and clotting factors VII, IX, and X, which are important components of blood coagulation, is in fact facilitated by vitamin K.[24] However, through VKDPs, vitamin K can also activate important anticoagulants that result in the production of proteins C, S, and Z.[25] In addition to being crucial for blood coagulation, vitamin K may also have immune-modulatory and anti-vascular calcification properties. Research indicates that the anti-inflammatory effects of K2 form are more powerful than those of K1 (Ohsaki et al. 2010),[26] form according to K2 functions as an immunosuppressive substance to regulate the expression of numerous pro-inflammatory cytokines, including TNF, IL-1, and IL-1, and to inhibit the release of IL-6. It may also hinder the growth and activation of T cells. Furthermore, it has been demonstrated that vitamin K activates extra-hepatic VKDPs like matrix-Gla protein (MGP).[27] Furthermore, patients with pre-conditions such as diabetes, hypertension and cardiovascular disease which are known to be associated with vitamin K deficiency are prompt to develop a more severe Covid-19 disease. This is especially true for those with chronic kidney disease (CKD), a group that has a higher percentage of severe Covid-19 cases.[28]

Researchers have now noticed a connection between Covid-19 results and vitamin K levels. One of the main indicators of poor outcomes for patients with sepsis brought on by an infection is coagulopathy. Tang et al. observed coagulopathy in 183 consecutive patients, which is linked to a poor outcome in patients with severe Covid-19.[29]

Additionally, it appears that low vitamin K levels are linked to increased elastin breakdown thereby causing lung tissue degeneration and making breathing harder for Covid-19 users.[30] Low vitamin K levels are thought to be related to Covid-19 severity since patients with severe disease are more likely to have co-morbidities such type II diabetes,

cardiovascular disease, or hypertension, all of which are linked to lower vitamin K levels.[31]

A low prophylactic dose of low molecular heparin (LMWH), an anticoagulant, was suggested to be given to all Covid-19 patients requiring hospitalization as long as no contraindications such as active bleeding was recorded.[32] While studies have shown beneficial effect of LMWH on Covid-19 patients in terms of reduce mortality in clinical practice severely infected patients still continue to clot and fail to response adequately to both prophylactic and therapeutic doses. This might be resulting from the fact that Covid-19 patients present with low levels of anti-thrombin and higher levels of fibrinogen, which contribute to heparin resistance.[33]

Furthermore, due to the risk of venous thromboembolism, pulmonary embolism and renal insufficiency resulting from Covid-19 the use of unfractioned heparin (UFH) might be a better choice of anticoagulant.[34]

In order to minimize laboratory testing frequency monitoring during this pandemic, the patient taking vitamin K antagonist (VKA) must be switched to direct oral anticoagulants (DOAC) for coagulation medication. It is not appropriate for patients who have anti-phospholipid syndrome or mechanical heart valves (Chighizola, , et al., 2018).[35] Giving vitamin K tablets to patients when they are admitted to the intensive care unit (ICU) may help lower the risk of vitamin K shortage and subsequent consequences, as there is a risk of vitamin K deficiency in these patients.[36]

Ironically, vitamin K can both preserve arterial flexibility and stop arterial calcification from developing a process that is known to induce cardiovascular disease. This is possible through activation of MGP. Elastic fibers are essential components of the extracellular matrix (ECM) and are vital in lung fibrosis. Vitamin K-dependent MGP shields these fibers against mineralization. It has been discovered that pulmonary illness patients with low vitamin K status had higher elastin breakdown.[37]

According to recent reports, there may be a connection between severe cases of Covid-19 and low levels of vitamin K. Given its low toxicity in humans and its variety of unique functions in regulating blood clotting, elastin degradation, immunomodulation, and vascular health management, vitamin K is a desirable treatment that can be used either therapeutically or prophylactically as a supplement to improve the outcomes of Covid-19 disease.[23]

Conclusion

The decreased serum level of vitamin K in COVID-19 patients group may be return to to increased elastin breakdown thereby causing lung tissue degeneration and making breathing harder for Covid-19. Health care providers may be able to identify Covid-19 patients early on for treatment if vitamin K level correlations are found in the patients. These correlations may also help define the pathophysiology, clarify the pathogenesis, improve clinical prognosis prediction, and better guide thromboprophylaxis and treatment for Covid-19 patients. Different immunoregulatory pathways that are involved in the pathophysiology of COVID-19 were suggested by the cytokine levels that were found in the COVID-19 group compared to the control group. To precisely grasp the molecular mechanism underlying this disease, however, more research must be done.

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Conflicts of Interest

No conflicts of interest regarding the publication of this article.

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