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Emanuela Anastasi , Cristiano Ialongo , Raffaella Labriola , Giampiero Ferraguti , Marco Lucarelli & Antonio Angeloni

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LETTER TO THE EDITOR

Vitamin K deficiency and covid-19

In December 2019 a novel coronavirus strain disease called COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in China and fast spread around the word [1]. In the early stages of the viral infection, gastrointestinal symptoms defined as diarrhea and nausea/vomiting have been observed in one-third of patients with COVID-19, whereas severe complications have been reported to occur in 33% of patients such as acute respiratory distress syndrome, cardiomyopathy, acute renal failure, acute respiratory injury, septic shock, and severe pneumonia [2]. The numerous studies published on viral infection and clinical management of the disease seem to indicate a greater prevalence of COVID-19 infections in males compared to females [3].

Elevated levels of the proinflammatory IL-6 have been found in COVID-19 patients admitted to intensive care units and it has been suggested that coronavirus infection in humans activates cytokine/chemokine secretion, such event has been termed '*cytokine storm*'. The onset of a *cytokine storm* has been proposed to represent an important determinant to the severity of the disease and a negative prognostic parameter for multiple organ failure and death [4].

In recent years, attention has been focused on the anti-inflammatory action of vitamin K, which is mediated by the reduction of PGE2, COX2, IL-6 [5]. When vitamin K deficiency occurs due to the presence of intestinal malabsorption or in relationship to the administration of drugs (anticoagulant or prolonged antibiotic therapy) an increase in levels of inflammatory cytokines, including IL-6 and C-reactive protein, has been observed.

In addition to the anti-inflammatory action, recent studies have shown that a high intake of vitamin K is associated with reduced coronary calcification and a decreased risk of cardiovascular diseases (CVD) [6].

Moreover, in experimental animal models, vitamin K supplementation induces a 50% reduction in atherosclerotic calcification due to the activation of a specific matrix Gla protein (MGP) capable of removing abnormal accumulation from the arteries [7].

In the clinical practice, vitamin K deficiency is a frequent complication in patients admitted in adult intensive care units (ICU) with an incidence as high as 25% [8].

Prothrombin induced by vitamin K absence-II (PIVKA-II) also known as des-γ-carboxy prothrombin, is an abnormal prothrombin molecule produced by the liver in the absence of vitamin K or in the presence of malignant cells [9].

It has recently been reported that PIVKA-II levels can be considered an early marker of vitamin K deficiency because they are detectable before others coagulation tests alteration and before the onset of clinical signs of bleeding [10].

Thus, to investigate the diagnostic role of vitamin K deficiency in the context of COVID-19 patients, we measure the serum level of PIVKA-II in a larger cohort of COVID-19 patients. To further evaluate the hypothesis of an anti-inflammatory action of vitamin K, we evaluate the correlation between IL-6 levels and vitamin K status.

Between March and April 2020, sixty-two COVID-19 positive patients, 45males (mean age 68.4 years) and 17 female (mean age 69.8 years), referred to the 'COVID-19 Intensive Care Unit' of the Policlinico Umberto I, 'Sapienza' University of Rome, were enrolled in the study.

Blood samples were collected at the first access to the emergency Department be A blood specimen withdrawn at the first admission to the Emergency Department, before starting therapy, was sent to the laboratory for the determination of PIVKA-II and IL-6 levels.

PIVKA-II serum concentrations were determined on a Lumipulse G1200 (Fujirebio-Europe, Gent, Belgium), using the LUMIPULSE G PIVKA-II kit (Fujirebio, Tokyo, Japan). PIVKA-II detection range was between 5 and 75,000 mAU/mL, with intra-assay CV of <2.4% and inter-assay CV of <10% and as a clinical cut-off we considered 48 mAU/mL. IL-6 serum concentration was quantified by Elecysis IL-6 (Roche) IL-6 detection range was between 1.5 and 5000 pg/mL, as a clinical cut-off we considered 7.0 pg/mL.

Deficiency of vitamin K assessed indirectly through the measurement of PIVKA-II levels was observed in 41 patients with almost twice the incidence in males than females (72.3% versus 36.8% respectively). However, no relationship was found between vitamin K depletion and clinical signs or symptoms of coagulation disorders, as well as with age.

On overall, for males and females the median IL-6 level was 66.2 pg/mL (IQR: 528.7 pg/mL) and 15.4 pg/mL (IQR: 29.7 pg/mL) respectively, and the median PIVKA-II level was 93 mAU/mL (IQR: 228 mAU/mL) and 50 mAU/mL (IQR: 35 mAU/mL) respectively. The prevalence of subjects with both IL-6 and PIVKA-II above their respective cut-off limits (IL-6+/PIVKA-II+) was significantly associated with the gender (Cochran–Mantel-Haenszel χ^2=13.98, $p < .001$). With respect to this, log-transformed values of the two markers showed a significant although weak non-linear trend in males (Kendall's tau = 0.22, $p < .034$) but not in females (Kendall's tau=−0.08, $p = 0.650$). These findings are summarized in Figure 1 were it is shown the scatter of IL-6 versus PIVKA-II values according to gender.

In the group of male patients we observed, concomitantly with a severe vitamin K deficiency higher values of IL-6 (Figure 1), we propose that the two observations might be mechanistically related. Interestingly the outcome of COVID-19 infection in patients admitted in an intensive

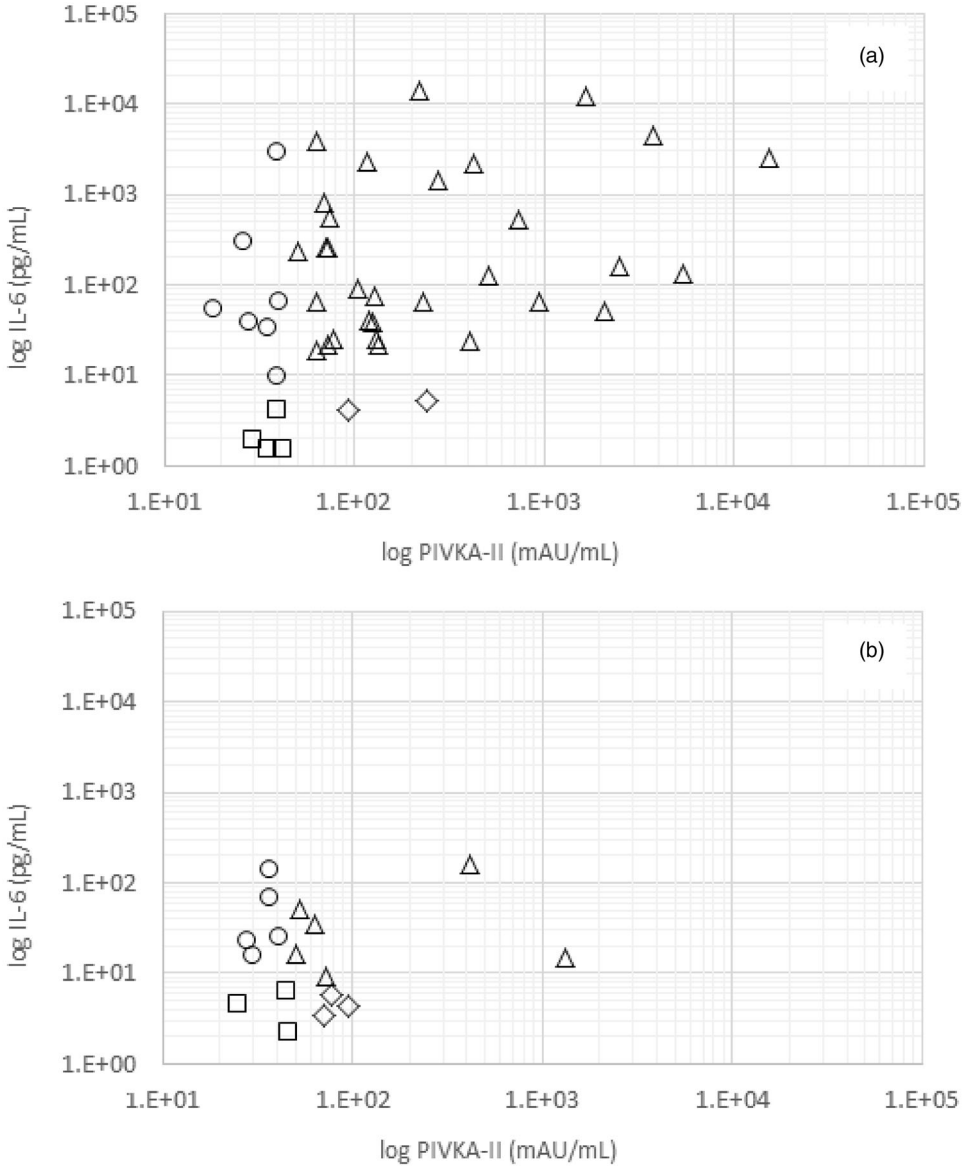

Figure 1. Scatterplot of IL-6 versus PIVKA-II levels in COVID-19-19 affected patients. Data are shown separately for males (a) and females (b) in log-transformed scale and grouped according to whether markers were both above their respective cutoff (△ IL-6+/PIVKA-II+), both below (≤IL-6-/PIVKA-II-) or alternate (◇ IL-6-/PIVKA-II+, ○ IL-6+/PIVKA-II-).

care unit is known to be more severe in men than women and this may be related to the greater IL-6 and lower vitamin K level in the male gender.

We postulate that the vitamin K deficiency arising during the early phases of the COVID-19 infection may contribute to the activation of the Th2 storm with increased production of IL-6.

Although an *in vitro* study has shown that IL-6 is capable of inducing the production of PIVKA-II, subsequent studies in patients with inflammatory liver disease did not report an increased PIVKA-II production [10].

Summarizing, the results of this study suggest that vitamin K deficiency is frequently observed in COVID-19 patients and that the deficit is greater in males than in females. In addition, in male patients, vitamin K deficiency is associated with a greater IL-6 level in the general circulation.

In conclusion, we propose that vitamin K deficiency could support both cytokine storm Th2 by increasing pro-inflammatory cytokines such as IL-6, which is involved in the building up of the inflammatory response recruiting both cellular and humoral components. Besides, it can also contribute to those events involved in vascular calcification leading to thrombosis and disseminate intravascular coagulation (DIC), which feature the microvascular damage observed in COVID patients

The results of this study highlight the role of Vitamin K as a possible modifiable risk factor for a more severe evolution of COVID-19 in infected patients with clinical symptoms. While a cause-effect relationship has not be established, our findings support further investigating the role of vitamin K in this clinical setting.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Marco Lucarelli http://orcid.org/0000-0002-5538-2494

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Emanuela Anastasi
Department of Molecular Medicine, Policlinico Umberto I, Rome, Italy
emanuela.anastasi@uniroma1.it

Cristiano Ialongo, Raffaella Labriola, Giampiero Ferraguti, Marco Lucarelli and Antonio Angeloni
Department of Experimental Medicine, Policlinico Umberto I, 'Sapienza' University, Rome, Italy

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