Reduced Vitamin K Status and Coronavirus Disease 2019

Groothof, Dion; Post, Adrian; Gans, Reinold O B; Bakker, Stephan J L

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responses during the second epidemic wave. Our data indicate that an initial SARS-CoV-2 infection protected HCW against reinfection for at least 167 days. However, a protective neutralizing antibody level could not be determined. These findings could be used to compare the immunity developed after a natural infection with that conferred by current SARS-CoV-2 vaccines.

Notes

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Chloé Dimeglio,[1,2] Fabrice Herin,[3] Marcel Miedougé,[1] Guillaume Martin-Blondel,[2,4] Jean-Marc Soulat,[3] and Jacques Izopet[1,2]

[1]CHU Toulouse, Hôpital Purpan, Virology Laboratory, Toulouse, France; [2]INSERM UMR1291—CNRS UMR5051, Toulouse Institute for Infectious and Inflammatory Diseases (INFINITy), Toulouse, France; [3]Occupational Diseases Department, Toulouse-Purpan University Hospital, Toulouse, France; and [4]Infectious and Tropical Diseases Department, Toulouse University Hospital, Toulouse, France

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Correspondence: C. Dimeglio, Centre Hospitalier Universitaire de Toulouse, Toulouse, France (dimeglio.c@chu-toulouse.fr).

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Reduced Vitamin K Status and Coronavirus Disease 2019: An Epiphenomenon of Impaired Kidney Function?

To the Editor—Dofferhoff et al [1] recently hypothesized that enhanced thrombogenicity related to low vitamin K status is implicated in coronavirus disease 2019 (COVID-19), linking pulmonary and thromboembolic disease. This hypothesis was corroborated by the finding of markedly elevated plasma dephospho-uncarboxylated matrix Gla protein (dp-ucMGP)—a marker of poor extrahepatic vitamin K status—in hospitalized patients with COVID-19 compared with healthy controls. Furthermore, among patients, plasma dp-ucMGP was higher in those with poor outcome (ie, those who required invasive ventilation or died in-hospital) compared with good outcome (ie, those who were discharged without the need for invasive ventilation). These differences were independent of age, sex, and use of vitamin K antagonists as potential confounders. Nonetheless, there are reasons to believe that the differences in plasma dp-ucMGP between hospitalized patients with COVID-19 and healthy controls and between poor and good outcomes were driven by differences in kidney function.

Impaired kidney function is common among hospitalized patients with COVID-19 and the degree of impairment strongly relates to disease severity. Acute kidney injury is experienced by 32% to 46% of patients [2, 3], of which 80% develops within 1 day of hospitalization [3]. Interestingly, in the study by Dofferhoff et al, 3 hospitalized patients with COVID-19 versus none of the healthy controls were dialysis dependent, which may be a sign thereof.

Importantly, it has been consistently reported that there is a strong cross-sectional association between plasma dp-ucMGP and kidney function, with circulating dp-ucMGP progressively increasing with decreasing kidney function [4, 5]. In 2018, it was postulated that higher plasma dp-ucMGP is also associated with increased risk of incident chronic kidney disease (CKD) [6]. However, this study did not account for the cross-sectional association between plasma dp-ucMGP and kidney function at baseline. Indeed, a subsequent replication study showed that the prospective association between higher plasma dp-ucMGP and increased risk of incident CKD disappears if baseline kidney function is accounted for [7].

Given the strong and established association between plasma dp-ucMGP and kidney function, on the one hand, and the high prevalence of kidney dysfunction in hospitalized patients with COVID-19, on the other hand, we postulate that the observation of elevated plasma dp-ucMGP in hospitalized patients with COVID-19 may be confounded by impaired kidney function. It is imperative to know whether the observations by Dofferhoff et al [1] would remain statistically significant after baseline kidney function is accounted for. Otherwise, their findings should be interpreted with great caution, as the observed between-group differences in plasma dp-ucMGP could be an epiphenomenon of actual differences in kidney function. We therefore cordially invite the authors to report on the association of extrahepatic vitamin K status with accelerated elastic fiber degradation and thrombosis after having accounted for time-matched kidney function.

Note

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Dion Groothof,[1] Adrian Post,[1] Reinold O. B. Gans,[1] and Stephan J. L. Bakker[1]

[1]Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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Correspondence: D. Groothof, Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands (d.groothof@umcg.nl).

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Reply to Author

As suggested by Groothof et al [1], within populations there is indeed a correlation between circulating dephosphorylated-uncarboxylated Matrix Gla Protein (dp-ucMGP) and kidney function, and at first glance their request seems reasonable. However, in the context of MGP and vitamin K metabolism, it is unfounded. Correcting for kidney function would only be appropriate if elevated levels of dp-ucMGP were caused by impaired excretion. There is no evidence to suggest either that dp-ucMGP is actively excreted or that it is positively dependent on kidney function. Instead, when you consider the mechanisms of COVID-19, it is far more reasonable to think that both elevated dp-ucMGP and impaired renal function are consequences of the same systemic pathology. Namely, the interplay of inflammation and microvascular thrombosis could underlie both observations.

The authors state that it is imperative to know whether the association between elastic fiber degradation and vitamin K deficiency remains significant after correction for renal function, however, statistical analyses should not be performed blindly without knowledge of underlying pathophysiological mechanisms. Here it is unwise to rush to corrections without a better understanding of kidney pathology during SARS-CoV-2 infection. As such, we see no added value of performing this analysis at this time.

Nonstandard Abbreviation: dp-ucMGP, dephosphorylated-uncarboxylated Matrix Gla Protein.

Notes

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Jona Walk,[1] Rob Janssen,[2] and Anton S.M. Dofferhoff[1]

[1]Department of Internal Medicine, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands, and [2]Department of Pulmonary Medicine, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

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Correspondence: J. Walk, Department of Internal Medicine, Canisius-Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 SZ Nijmegen, The Netherlands (jona.walk@cwz.nl).

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