nutrients

MDPI

Comment

Comment on Kremer et al. Kidney Function-Dependence of Vitamin K-Status Parameters: Results from the TransplantLines Biobank and Cohort Studies. *Nutrients* 2021, *13*, 3069

Rob Janssen [1,*], Jona Walk [2] and Cees Vermeer [3]

[1] Department of Pulmonary Medicine, Canisius-Wilhelmina Hospital, Weg Door Jonkerbos 100, 6532 SZ Nijmegen, The Netherlands
[2] Department of Internal Medicine, Canisius-Wilhelmina Hospital, 6532 SZ Nijmegen, The Netherlands; jona.walk@cwz.nl
[3] Cardiovascular Research Institute CARIM, Maastricht University, 6229 ER Maastricht, The Netherlands; cees.vermeer@outlook.com
* Correspondence: rob.janssen@cwz.nl

In the article "Kidney Function-Dependence of Vitamin K-Status Parameters: Results from the TransplantLines Biobank and Cohort Studies", Kremer et al. measured plasma levels of dephosphorylated-uncarboxylated matrix Gla protein (dp-ucMGP) in patients with chronic renal failure (CRF) and correlated these with plasma creatinine [1]. MGP is a vitamin K-dependent calcification inhibitor that may undergo two activation steps—phosphorylation and carboxylation—creating four MGP variants: 1. dp-ucMGP; 2. phosphorylated-carboxylated (p-c)MGP; 3. p-ucMGP; and 4. dp-cMGP [2]. Circulating dp-ucMGP reflects vitamin K status with high and low dp-ucMGP levels representing vitamin K deficiency and sufficiency, respectively [2].

Kremer et al. demonstrated that dp-ucMGP positively correlates with creatinine in CRF patients and concluded that dp-ucMGP should therefore be corrected for kidney function [1]. However, a correlation between a biomarker and kidney function does not automatically imply that it should be corrected for creatinine. Adjustment would only be appropriate if the rise is caused by a fall in renal function. Rennenberg et al., however, demonstrated that the average renal fractional extraction of MGP is independent of kidney function in hypertensive patients [3]. Theoretically, it could be the case that MGP variants in CRF are differentially excreted in urine, but Kremer et al. did not provide convincing evidence for this [1].

The correlation between dp-ucMGP and creatinine in CRF likely reflects a mechanistic link. Vascular calcification is prevalent in CRF due to disorders in mineral metabolism and increases as the glomerular filtration rate declines [4]. Calcium deposition leads to MGP upregulation to protect blood vessels from further mineralization [5]. MGP, however, is only functional after vitamin K-dependent carboxylation [6]. Activation of synthesized MGP may lead to depletion of vitamin K stores and subsequent vitamin K deficiency, which is reflected by increased dp-ucMGP levels. Adequate levels of cMGP are crucial to maintain the patency of blood vessels [5]. In a state of vitamin K deficiency, there is insufficient cMGP activity in the kidneys, exacerbating vascular deterioration and renal failure [7].

We conclude that the correlation between dp-ucMGP and creatinine is far more likely the result of vitamin K deficiency than a function of a decreased glomerular filtration rate. Regardless of any renal influence on dp-ucMGP levels, elevated dp-ucMGP levels should, in our opinion, be normalized by vitamin K administration and not through adjusting for creatinine.

check for updates

Citation: Janssen, R.; Walk, J.; Vermeer, C. Comment on Kremer et al. Kidney Function-Dependence of Vitamin K-Status Parameters: Results from the TransplantLines Biobank and Cohort Studies. *Nutrients* 2021, *13*, 3069. *Nutrients* **2022**, *14*, 2439. https://doi.org/10.3390/nu14122439

Academic Editor: Evangelia Dounousi

Received: 3 February 2022
Accepted: 24 May 2022
Published: 13 June 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author Contributions: Writing—original draft preparation, R.J.; writing—review and editing, J.W. and C.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: R.J. discloses a patent on vitamin K in COVID-19 (WO 2021/206560). R.J. and J.W. have a scientific collaboration with Kappa Bioscience AS, a manufacturer of vitamin K2 (MK-7). C.V. declares no competing interest.

References

1. Kremer, D.; Groothof, D.; Keyzer, C.A.; Eelderink, C.; Knobbe, T.J.; Post, A.; van Londen, M.; Eisenga, M.F.; TransplantLines Investigators; Schurgers, L.J.; et al. Kidney Function-Dependence of Vitamin K-Status Parameters: Results from the TransplantLines Biobank and Cohort Studies. *Nutrients* **2021**, *13*, 3069. [CrossRef] [PubMed]
2. Wei, F.F.; Trenson, S.; Verhamme, P.; Vermeer, C.; Staessen, J.A. Vitamin K-Dependent Matrix Gla Protein as Multifaceted Protector of Vascular and Tissue Integrity. *Hypertension* **2019**, *73*, 1160–1169. [CrossRef] [PubMed]
3. Rennenberg, R.J.; Schurgers, L.J.; Vermeer, C.; Scholte, J.B.; Houben, A.J.; de Leeuw, P.W.; Kroon, A.A. Renal handling of matrix Gla-protein in humans with moderate to severe hypertension. *Hypertens. Res.* **2008**, *31*, 1745–1751. [CrossRef] [PubMed]
4. Palit, S.; Kendrick, J. Vascular calcification in chronic kidney disease: Role of disordered mineral metabolism. *Curr. Pharm. Des.* **2014**, *20*, 5829–5833. [CrossRef] [PubMed]
5. Price, P.A.; Buckley, J.R.; Williamson, M.K. The amino bisphosphonate ibandronate prevents vitamin D toxicity and inhibits vitamin D-induced calcification of arteries, cartilage, lungs and kidneys in rats. *J. Nutr.* **2001**, *131*, 2910–2915. [CrossRef] [PubMed]
6. Schurgers, L.J.; Cranenburg, E.C.; Vermeer, C. Matrix Gla-protein: The calcification inhibitor in need of vitamin K. *Thromb. Haemost.* **2008**, *100*, 593–603. [PubMed]
7. Roumeliotis, S.; Roumeliotis, A.; Dounousi, E.; Eleftheriadis, T.; Liakopoulos, V. Vitamin K for the Treatment of Cardiovascular Disease in End-Stage Renal Disease Patients: Is there Hope? *Curr. Vasc. Pharmacol.* **2021**, *19*, 77–90. [CrossRef] [PubMed]