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Commentary

Matrix Gla-Protein (MGP) Not Only Inhibits Calcification in Large Arteries But Also May Be Renoprotective: Connecting the Dots

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Many lines of evidence have established that chronic kidney disease (CKD) is associated with a substantially increased risk of cardiovascular disease (CVD) (Epstein, 2015). In the majority of cases, the risk of CVD exceeds the risk of progression to end-stage kidney disease. Consequently, the "holy grail" of investigative interest is a search to elucidate mechanisms that may promote and mediate this association and potential interventions that may abrogate or attenuate CVD risk in CKD.

We and others have emphasized that although occlusive atherosclerotic arterial disease undoubtedly occurs, the CVD associated with CKD is characterized by arteriosclerosis, resulting in arterial stiffness that in turn promotes structural heart disease (Epstein, 2015; Moody et al., 2013). Aortic stiffening exposes the left ventricle to the ravages of increased systolic pressures, leading to ventricular hypertrophy and fibrosis that may progress to cardiac failure.

Epidemiological studies have established that arterial stiffness constitutes an important risk factor for cardiovascular events and mortality in patients with CKD at all stages (Townsend, 2015). The mechanisms that promote arterial stiffening in CKD are incompletely defined, and the optimal interventions for attenuating arterial stiffness remain to be elucidated.

Among the proteins involved in modulating vascular calcium metabolism, it has been hypothesized that the vitamin K-dependent matrix Gla- (γ-carboxyglutamate) protein (MGP) plays a dominant role. MGP is a local natural calcification inhibitor secreted primarily by chondrocytes and vascular smooth muscle cells in the arterial tunica media (Schurgers et al., 2010; Liu et al., 2015; Wei et al., 2016). MGP requires vitamin K to be activated. Inactive MGP, known as desphospho-uncarboxylated MGP (dp-ucMGP), can be measured in plasma and has been associated with various cardiovascular markers, cardiovascular outcomes, and mortality (Liu et al., 2015). MGP acts as a strong inhibitor of soft tissue calcification. As an illustration, MGP knockout mice develop massive vascular calcification in their first weeks of life and die within 2 months of vessels' rupture (Luo et al., 1997).

To acquire its full calcification inhibitory activity, MGP needs to undergo two post-translational modifications: glutamate carboxylation and serine phosphorylation. Both modifications are not exerted completely, so theoretically, four different MGP conformations can be found: unmodified and inactive as dp-ucMGP, only phosphorylated, only carboxylated, and finally fully modified and active as phosphorylated and carboxylated MGP. In essence, high levels of plasma dp-ucMGP are a proxy for vitamin K deficiency (Schurgers et al., 2010; Liu et al., 2015; Wei et al., 2016).

Previous studies by the Leuven and Maastricht groups demonstrated that in patients with diabetes (Liabeuf et al., 2014), renal dysfunction (Schurgers et al., 2010), or macrovascular disease (Liu et al., 2015), dp-ucMGP behaves as a circulating biomarker associated with cardiovascular risk, more severe vascular illness, and higher mortality. In the recent Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO), the investigators demonstrated that circulating dp-ucMGP predicted total and cardiovascular mortality (Liu et al., 2015). In contrast to dp-ucMGP, total uncarboxylated MGP (t-ucMGP) is not a marker of vitamin K status, but rather reflects arterial calcification, with lower values being associated with more widespread calcium deposits. In accord with these formulations, vitamin K supplementation has been shown to reduce aortic pulse wave velocity in healthy postmenopausal women.

Whereas previous research on MGP has focused on macrovascular complications, several lines of evidence suggest that renal microvascular traits including glomerular filtration or microalbuminuria might also be affected. As examples, MGP is abundantly expressed in the kidney with MGP immunoreactivity being associated with the epithelium of Bowman's capsule and the proximal tubules (Fraser and Price, 1988). Furthermore mineral nanoparticles containing calcium phosphate and calcification inhibitors are present in kidneys of patients with end-stage renal disease, but not healthy controls, and probably precede ectopic renal calcification (Wong et al., 2015). Moreover, calcification of the arterial wall is the hallmark of renal impairment and may involve arterioles with a diameter as small as 10 to 500 μm (Lanzer et al., 2014). Consequently, the authors postulated that renal

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microvascular traits, such as glomerular filtration or microalbuminuria, might be adversely affected by deficient vitamin-K dependent activation of MGP, as exemplified by circulating dp-ucMGP.

In the present study published in this issue of *EBioMedicine*, Wei et al. (2016) tested their hypothesis in white people enrolled in the FLEMENGHO study and sought to replicate the findings in white and black participants enrolled in the South African study regarding the influence of sex, age and ethnicity on insulin sensitivity and cardiovascular function (SAfrEIC). The authors demonstrated that among Flemish and white and black Africans, for a doubling of dp-ucMGP, estimated glomerular filtration rate (eGFR) decreased by 1.5 ($P = 0.023$), 1.0 ($P = 0.56$), 2.8 ($P = 0.0012$) and 2.1 ($P < 0.0001$) mL/min/1.73 m^2 in Flemish, white Africans, black Africans and all participants combined. The odds ratios for moving up one CKD stage were 1.17 ($P = 0.033$), 1.03 ($P = 0.87$), 1.29 ($P = 0.12$) and 1.17 ($P = 0.011$), respectively. The authors interpreted their results by indicating that in the general population, eGFR decreases and CKD risk increases with higher dp-ucMGP, a marker of vitamin K deficiency. In summary, the authors confirmed the inverse association of eGFR with dp-ucMGP in black South Africans and all South Africans combined.

The potential relevance of these observations is implicit. This study emphasizes the nexus of vitamin K deficiency and CKD, and the compelling need for attention to adequate vitamin K stores. These epidemiological findings support the concept that active MGP might not only inhibit calcification in large arteries, which was previously documented (Knapen et al., 2015), but conceivably might also be protective for renal function. Consequently the present observations potentially highlight new therapeutic approaches for promoting renal health, by increasing the dietary intake of vitamin K, either by supplementation or by increasing the intake of nutrients rich in vitamin K. A caveat is in order — as the authors emphasize, circulating levels of vitamin K are rarely measured in clinical practice, because of the complexity of the assay and because plasma levels only reflect dietary intake over few hours without any indication of functionality, whereas what really counts is the tissue level of active carboxylated MGP. Therefore the focus should be on increasing the intake of nutrients rich in vitamin K. Examples could include supplementation with biologically enriched fermented vegetable or dairy products. Natural food sources of vitamin K include vegetables such as spinach, asparagus, broccoli, beans and soybeans, and eggs.

In conclusion, the current findings by Wei et al. (2016) serve to extend the protective role of vitamin K from the macrocirculation to the microcirculation as exemplified by renal function, and possibly suggest a potential for prevention by vitamin K supplementation.

Disclosure

The author has no conflict of interest to this topic or this paper.

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