

Editorial Focus

Matrix-Gla protein and vascular calcification: The negative role of oral anticoagulant therapy

Mario Cozzolino

Renal Division, S. Paolo Hospital, University of Milan, Milan, Italy

With great interest I read the article by Koos et al. (1) on the association between low circulating inactive Matrix-Gla Protein (ucMGP) levels and the degree of calcification in patients with aortic valve disease published in this issue of *Thrombosis and Haemostasis*. The authors' results support one of the potential mechanisms involved in vascular calcification (VC): the treatment with oral anticoagulant inhibits MGP activation and local expression by impairing vitamin K production. I found the manuscript to be of real interest, and I would like to discuss why these results may be important for the clinical point of view, in particular for chronic kidney disease (CKD) patients.

It is a fact that CKD patients are more prone to develop accelerated atherosclerotic vascular disease. These subjects develop extensive medial calcification, which causes increased arterial stiffness and elevated cardio-vascular disease that induces higher morbidity and mortality (2). A mounting number of VC risk factors are involved in CKD patients: age, gender, inflammation, mineral metabolism abnormalities, and diabetes. In addition to these well-known factors, over the last decade new pathogenetic tools have emerged which better our understanding of the physiopathology of VC. In fact, although not completely elucidated, it is now clear that the process of calcification is not merely a passive deposition of calcium-phosphate crystals; rather it is a well ordered process, involving cell activity and some specific protein synthesis (3). Accordingly, several (bone-related) proteins are now certified for their capacity to induce or inhibit the process of extraskelatal calcification and the potential role of the "protective" proteins associated with reduced VC needs to be better clarified. In particular, MGP represents one of the most important regulatory key factors in preventing VC.

What is MGP and why should its measurement be important? MGP is a member of the vitamin K-dependent protein family with unique structural and physical properties. During the first two months of life, MGP-deficient mice develop diffuse arterial calcification, osteoporosis, and pathological fractures (4). Due to its properties as an extracellular matrix protein with a high affinity for calcium and phosphate, MGP plays an important role

in the prevention of both VC and the pathogenesis of osteoporosis (5). Binding bone morphogenetic protein-2 (BMP-2), MGP elicits an inhibitory mechanism on mineralization (6). The localization of MGP and other bone matrix proteins, such as osteopontin, has been investigated by Canfield et al. (7), in calcified atherosclerotic arteries and in normal vessel walls. While MGP was not detected in normal blood vessels, its expression was enhanced at loci of arterial calcification, such as atherosclerotic and calciphylactic lesions. Therefore, the MGP localization in calcified arteries suggests an etiopathogenic role for this inhibitory protein on the development of VC (7).

Recently, Jono et al. (8) reported an association between serum MGP levels and coronary artery calcification, detected by EBCT, in 115 subjects with suspected coronary artery disease and normal renal function. Patients with coronary artery calcification had lower serum MGP levels compared to those with no calcium in the coronary tree, suggesting the potential role of MGP on prevention of VC (8). Moreover, in the present issue Koos et al. (1) show the association between low serum MGP levels and aortic valve calcification in patients with CKD, indicating that this population has a major risk for VC. In addition, patients treated with oral anticoagulants over a long period of time have lower serum MGP levels. Why? Because it has been shown that the oral anticoagulant, such as warfarin, suppresses γ -carboxylation of MGP in aortic vessels of rats compared to untreated animals. An association between polymorphisms of the MGP gene and myocardial infarction in low risk individuals has been described as well (9). Potentially, the definition of polymorphisms of the MGP gene represents a critical step in understanding pathogenic mechanisms of VC in CKD and dialysis patients. Furthermore, altered MGP gene polymorphism may be a negative prognostic factor for cardiovascular events in CKD patients (10).

What do we know about the role of MGP, vitamin K, and oral anticoagulant in CKD and/or haemodialysis (HD) patients? These new results by Koos et al. can give us some answers. Three decades ago, the nephrology community thought that vitamin K was actively involved in the VC pathogenesis. By inhibiting the

Correspondence to:
Mario Cozzolino, MD PhD
Renal Division, S. Paolo Hospital, University of Milan
Via A. di Rudini, 8 – 20142 – Milan, Italy
Tel: +39 02/81844381, Fax: +39 02/89129989
E-mail: mariocozzolino@hotmail.com

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modification of MCP, it was hypothesised that warfarin prevented VC in HD patients (11–12). New experimental and clinical studies have completely rebutted this hypothesis. Paul Price's group has extensively investigated the mechanisms by which proteins inhibit VC. They showed the existence of a high-molecular-weight complex of a calcium-phosphate mineral phase and the two inhibitory proteins fetuin-A and MGP in the circulation of rats treated with the bone-active bisphosphonate etidronate (11). Furthermore, Price postulated that uremic conditions associated with hyperphosphatemia and hypercalcemia may tend to make the complex unstable and decrease serum fetuin-A and MGP levels (12).

Although pathogenetically involved in VC, none substance can be defined as "the marker" of this important clinical condi-

tion. Actually, if we consider the complexity of the calcification process, this is not a great surprise. However, it is possible to speculate that, in the near future, contemporary assessment of several markers like MGP, will enable us to recognise those patients or clinical conditions in which the bioactive process of calcification is almost invariably triggered. In fact, circulating ucMGP may be used as a biomarker to identify those patients at risk for developing VC. Moreover, significantly lower ucMGP levels were observed in HD patients compared to healthy controls. In conclusion, I believe that clinicians should be aware of the potential risk of prescribing oral anticoagulant therapy in CKD patients, not only for increased bleeding risk but also for promoting VC.

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