Matrix-GLA-Protein and Vascular Calcification: Can Diet Influence the Consequences of Matrix GLA Protein Inactivation? A Review

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Abstract
In vascular calcification, as a physiological process, intimal arterial calcification (IAC) associated with increased cardiovascular risk is distinguished from medial arterial calcification (MAC) localized mainly in the lamina elastica interna, which are not only based on different pathophysiological mechanisms. They also lead to different cardiovascular diseases. While intimal arterial calcification involves inflammation and lipid accumulation, a calcification process similar to desmal ossification plays the main role in medial arterial calcification. In this context, the phenotype change of smooth muscle cells from muscular type to synthetic form in the tunica media is considered to be of great importance, which puts the matrix GLA protein, mainly involved in bone metabolism, in the center of interest. The present review work elucidates the molecular biological basis of interaction of matrix GLA protein subunits in the pathogenesis of vascular calcifications and the influence of diet on the consequences of underactivation of matrix GLA protein.

Keywords: Matrix-GLA-protein, vascular calcification, vitamine K, diet

Introduction
Vascular calcification (VCas) a physiological process occurs much earlier in high atherogenic status, such as chronic renal failure, diabetes [and oxidative stress, and is then associated with increased cardiovascular (CV) mortality and morbidity [1-4]. This plays an important role especially in dialysis patients and patients under anticoagulant therapy. In this review work, we have described the influence of matrix GLA protein, fetuin A and their metabolites on vascular calcification and possible influence by diet.

Discussion
Previously, the phenotype change of smooth muscle cells from muscular type to synthetic form in the tunica media has been reported [5]. With the knowledge of smooth muscle cell differentiation to an osteoblastic phenotype as a crucial step for vascular calcification, the matrix GLA protein, which is mainly involved in bone metabolism, became the focus of interest [6,7]. In vascular calcification, intimal arterial calcification (IAC), previously associated with increased cardiovascular risk, has been distinguished from medial arterial calcification (MAC), which is mainly localized in the lamina elastica interna [6-11] and also manifests differently radiographically. While intimal arterial calcification shows a patchy/patchy pattern on radiographs, medial arterial calcification causes linear or annular calcifications on radiographs [10,11]. Different pathophysiological mechanisms underlie both forms of calcification, which are not only triggered by different risk factors but may lead to different cardiovascular diseases [12]. Intimal arterial calcification is characterized by inflammation and lipid accumulation, whereas medial arterial calcification is an active calcification process similar to desmal ossification [12-15]. Recent observations on explanted carotid plaques also show two distinct plaque morphologies with evidence of desmal bone tissue in calcified plaques [16]. In larger patient collectives, a risk association between medial arterial calcification and advanced age, diabetes, and renal disease has been established [17-20]. An association of medial arterial calcification with arterial hypertension and hyperlipoproteinemia could not be verified [13-15]. Comorbidity analysis for intimal arterial calcification showed only an association with nicotinamide and hyperlipoproteinemia [21]. The most potent natural inhibitor of calcification is considered to be Matrix Gla Protein (MGP); a vitamin K-dependent protein (VKDPs) secreted by both chondrocytes and smooth muscle cells [22-27].
One of the main mechanisms of action of MGP is based on direct inhibition of binding of bone morphogenetic protein-2 (BMP-2) expressed by endothelial foam cells of human atherosclerotic plaques to its receptor, as the main step to osteoblast differentiation of VSMCs within the arterial wall [28-31].

Moreover, the matrix GLA protein binds to newly formed hydroxyapatite crystals through its high binding affinity [33]. It is this binding that initiates macrophages to phagocytose the newly formed MGP matrix protein [33].

The binding and affinity of matrix GLA protein to BMP-2 are directly dependent on the concentration of free calcium ions and carboxylation state of matrix GLA protein [34,35].

The structural change of matrix GLA protein required for this binding is achieved by vitamin K-dependent γ-carboxylation of Gla residues and phosphorylation of serine residues [36-40].

Although deficiency of Matrix GLA protein leads to significant changes in the structure and function of extracellular matrix Gla and marked diffuse vascular calcification, excessive expression of matrix GLA protein has been found in atherosclerotic plaques, the severity of which is directly associated with serum levels of matrix GLA protein [41-44].

In contrast, significant low uncarboxylated MPG was found in patients with severe coronary artery disease (CAD) [28]. However, plasma levels of uncarboxylated MPG correlated with calcium deposition in abdominal aorta, common carotid, and coronary arteries [45].

While no clear correlation between serum ucMGP level and CHD was found in female patients, this association was also absent in elderly patients with carotid intima-media thickness (cIMT) [46].

However, in patients with stable CHD, low plasma ucMGP concentrations were associated with mortality [47].

Carboxylated matrix GLA protein is of great importance in the prophylaxis of calciaphlyaxis. In patients requiring dialysis, a 0.1 decrease in serum cMGP was associated with a twofold risk of developing calciaphlyaxis [48].

These patients have significantly higher plasma ucMGP levels compared with the general population [49-51]. In children requiring dialysis, the association between ucMGP and vascular calciaphlyaxis was absent [52].

The association between different matrix GLA protein forms and cardiovascular disease and comorbidities is even more evident in female patients. Whereas previous studies have found an association between dephosphorylated uncarboxylated matrix Gla protein (dpucMGP) and arterial calcification in the general population, other research groups have demonstrated a clear correlation between dpucMGP levels and increases in aortic and femoro-popliteal pulse wave velocities [53-62].

Only after menopause did serum dpucMGP levels correlate with carotid intima-media-thickness (cIMT) and endothelial dysfunction score [60]. However, detailed data analysis showed that in female patients, only circulating dephosphorylated uncarboxylated matrix Gla protein (dpucMGP) and not uncarboxylated matrix Gla protein or (ucMGP) or dephosphorylated carboxylated matrix Gla protein dpucMGP correlated with the coronary artery calcium score (CAC) [62].

Plasma level-related mortality and fatal and nonfatal cardiovascular outcomes showed a significant correlation with dpucMGP plasma level in patients with advanced aortic stenosis, heart failure, type 2 diabetes mellitus, chronic peripheral arterial disease, and chronic renal failure, especially in patients with chronic renal failure and advanced aortic stenosis [63-71].

Similarly, other studies showed an association between cardiovascular and all-cause mortality, heart failure, and relevant graft dysfunction after renal transplantation with plasma dp-ucMGP [72,73].

The retinal microcirculation is little known and little considered, but of great interest. The matrix GLA protein significantly regulates the structural integrity of the trabecular meshwork and retinal ganglion cells [74-77].

The reduced retinal arteriolar diameter and arteriole-to-venule diameter ratio induced by doubling of plasma dp-ucMGP levels correlates directly with coronary artery disease, resulting mortality, and lacunar [78-82].

Observational studies showed a beneficial effect of high vitamin K intake on cardiovascular morbidity [83]. However, a distinction must be made between vitamin K1 uptake, represented by plasma levels of circulating phylloquinone, and vitamin K2 uptake, represented by dephosphorylated uncarboxylated matrix Gla protein (dp-ucMGP) [84-87].

Hepatic vitamin K-dependent proteins have been implicated as serine proteases in the coagulation system [88-91]. As an extrahepatic vitamin K-dependent protein, osteocalcin regulates bone formation and mineralization [92], with osteocalcin reflecting bone turnover [93].

Total uncarboxylated MGP (t-ucMGP), consisting of phosphorylated MGP is sequestered at sites of arterial calcification [94].

With the increasing knowledge of vitamin-dependent matrix GLA proteins, vitamin K research has been shifted from blood coagulation to cardiovascular disease, osteoporosis, diabetes, and cancer, giving importance to nutrition in the context of key molecular biological functions of GLA [95].

Hepatic vitamin K deficiency with consecutive coagulation disorders is a rarity compared with extrahepatic forms, especially in children, patients over 40 years of age, and chronic insufficiency, regardless of the stage of the disease [96-102].

In previous case studies, antepartum administration of vitamin K to pregnant women reduced the incidence of neonatal hemorrhage [103].

The originally used water-soluble vitamin K3 was replaced by intramuscular administration of vitamin K1 because of serious side effects including hematologic toxicities such as hemolytic anemia [104-107].

Anticoagulant therapy with vitamin K antagonists, which is widely used worldwide, inevitably leads to suboptimal carboxylation of Gla proteins due to their mode of action, which has pronounced negative effects on the cardiovascular system [108-111].

An improved vitamin K status exerts a protective effect on vascular calcification, and led to vitamin K1 supplementation. However, the results of such studies are highly controversial. While some studies, especially in female postmenopausal patients after vitamin K1 supplementation showed an unchanged atherosclerotic index in the carotid comm. artery, in some studies these were even decreased [112,113].

The protective effect of vitamin K1 supplementation is particularly evident in dialysis patients. In such patients, both a reduction of dp-ucMGP plasma levels and reduced arterial stiffness could be achieved [114-119].

A similar effect was achieved in patients with vitamin K2 (MK-7) supplementation. Dialysis patients in particular have a high prevalence of both vitamin K deficiency and cardiovascular disease [119,120].
In a recent study, vitamin D3 supplementation was found to reduce plasma dp-ucMGP levels\textsuperscript{[121]}. As in previous studies, this may suggest that vitamin D metabolism is closely related to that of vitamin K\textsuperscript{[122-125]}.

The mutual interaction between the two vitamins also stems from the fact that binding of vitamin D to a vitamin D response element of the promoter of the MGP gene increases MGP expression two- to threefold\textsuperscript{[123,126]}. However, vitamin D can also lead to increased MGP secretion by directly stimulating the synthesis of vitamin K-dependent proteins, which in turn causes relative vitamin K deficiency\textsuperscript{[127]}.

However, prolonged vitamin D supplementation even at low doses (up to 400 IU/day) resulted in an increased risk of hypercalciuria, kidney stones, hypercalcemia, and vascular lesions\textsuperscript{[128-133]}. The evaluation of several meta-analyses of randomized controlled trials also failed to prove a beneficial effect on musculoskeletal fractures by vitamin D supplementation\textsuperscript{[134-136]}.

The interactions between lipid and bone metabolism and the regulation of vascular calcification by MPG is the basis of the developments of new diets to influence MPG\textsuperscript{[137,138]}.

The effects of reduced carboxylated MGP (cMGP) and γ-glutamyl carboxylase (GGCX) in atherosclerotic aortic plaques in the presence of reduced expression of vitamin K epoxide reductase complex, subunit 1-gene (Vkor-gen) could be at least partially ameliorated by a high-fat diets\textsuperscript{[138-141]}.

Another complex may also be affected by MPG. The fetuin-mineralization complexes known from animal studies, consisting of MGP (2%), fetuin-A (80%), and calcium and phosphorus ions (18%) inhibit mineral growth, aggregation, and deposition\textsuperscript{[142-148]}.

Fetuin-A itself may inhibit VSMC-related calcification via inhibition of apoptosis of VSMCs, promotion of clearance of apoptotic bodies released by VSMCs, and inhibition of intracellular mineralization of matrix vesicles of VSMCs\textsuperscript{[149-155]}.

Several experimental studies have demonstrated the potent cytotoxic and procalcific Ca-phosphate crystals in the absence of fetuin-A\textsuperscript{[156,157]}. A decrease in systemic fetuin-A increases systemic calciprotein particles and procalcification of calciprotein particles, thus promoting vascular calcification\textsuperscript{[158-162]}.

The negative influence of low-protein diet on fetuin a derived from the animal experiments could only lead to an increase in vascular calcification with an increased calcium-phosphate load\textsuperscript{[150]}.

**Conclusion**

Vascular calcification represents a multifactorial process consisting of highly complex, interrelated pathophysiological pathways, the influence of diet on which requires further research. The long-term efficacy of new anticoagulants compared with vitamin antagonists can only be assessed after appropriate evaluation of prospective studies.

**List of abbreviations**

IAC: Intimal arterial calcification  
MAC: Medial arterial calcification  
VCas: Vascular calcification  
CV: Cardiovascular  
MGP: Matrix Gla Protein (MGP)  
VKDP: Vitamin K-dependent protein  
BMP-2: bone morphogenetic protein-2  
VSMCs: Vascular smooth muscle cells  
CAD: Coronary artery disease  
cIMT: Carotid intima-media thickness  
dpucMGP: Dephosphorylated uncarboxylated matrix Gla protein  
ucMGP: Uncarboxylated matrix Gla protein  
t-ucMGP: Total uncarboxylated MGP  
GGCX : γ-glutamyl carboxylase

**Conflicts of Interest**

There is no conflict of interest regarding the publication of this paper.

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MM and SF have structured and written the paper. JK and JPA did the proofreading and fine-tuning of the paper. All authors read and approved the final manuscript.

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