Tzu Chi Medical Journal 2023; 35 (1): 51-52

Editorial Comment

Editorial comment on Vitamin K and vascular calcification in chronic kidney disease: An update of current evidence – The role of Vitamin K in managing chronic kidney disease–mineral bone disorder

Cardiovascular disease poses the major cause of mortality in chronic kidney disease (CKD) patients. Vascular calcification (VC) is the most pathogenesis of cardiovascular morbidities in CKD patients. Beyond the traditional risk factors, secondary hyperparathyroidism and sequential osteodystrophy accelerate the VC by increasing the extraosseous deposition of calcium apatite [1]. The excessive osteoclastic activity with uncoupled bone formation increased the calcium and phosphorus release under the high bone turnover status, and the deficiency of calcifying inhibitors such as fetuin-A or matrix Gla protein worsens the extraosseous calcification [2]. Therefore, the nutrients supplement for enhancing bone formation and the calcifying inhibition should be regarded as the preventive strategy for lowering the incidence of cardiovascular complications in CKD subjects. Vitamin K, as the main factor for carboxylation, might be an important niche for treating CKD–mineral bone disorder (CKD–MBD) and VC. In this issue, Lin and Hsu made an extensive review of Vitamin K and VC in CKD [3].

The role of carboxylation in managing high bone turnover disorder

Secondary hyperparathyroidism is the trade-off effect of the decreased renal excretion of phosphate. The PTH activates the vigorous osteoclastogenesis of the macrophage through the interaction of the receptor activator of nuclear factor kappa-B ligand released from the osteoblast. During the activated osteoclastogenesis, several factors would decrease the survival, mineralization, and maturation of the osteoblast in CKD, and therefore, disturb the bone formation. It has been known that Vitamin D deficiency is common in CKD patients [4]. Vitamin D regulating element stimulates the formation of the pro-osteocalcin. The carboxylated pro-osteocalcin at Glu residue, in contrast to the uncarboxylated form, enhance bone mineralization, and therefore, increase bone density by binding to hydroxyapatite in the extracellular matrix of bone. Beyond the Vitamin D supplement, the supplement of factors associated with carboxylation is essential during the management of the high bone turnover disease.

The role of carboxylation in managing vascular calcification by modifying calcification inhibitors

In CKD subjects, the vessel wall confronts massive stress such as hypertension, oxidative stress originating from the protein-bounded uremic toxin, or hyperphosphatemia [1]. When confronting excessive stress, the hematopoietic cells within the endothelial layers release the extracellular vesicle (EV) to cope with cellular apoptosis. The composition of the EV reflects the further severity of the VC. The composition of EV includes calcifying inhibitors such as fetuin-A, secretory Klotho, or matrix Gla protein [5]. With sufficient calcifying inhibitors, the EV generates the circulating calcium phosphate crystallization into the calciprotein particle (CPP) with a spheric shape and smaller diameters. The scavenger receptor on the hepatic endothelial layer facilitates the clearance of calcium phosphate crystallization in a CPP manner. Among the calcifying factors, the posttranslational γ-carboxylation of matrix Gla protein further chelates the calcium, and therefore, protects the endothelium and smooth muscle layer from calcification [6]. From this aspect, the factors catalyzing carboxylation are important for preventing VC [Figure 1].

Vitamin K: As the supplement of carboxylation in uremic vascular calcification and bone formation simultaneously

Vitamin K is a posttranslational factor essential for converting γ-carboxyglutamate from peptide-bound glutamate. The transformed Vitamin K2 in the liver is delivered to extrahepatic tissue and then facilitates the carboxylation with Vitamin K-dependent protein. The natural form of Vitamin K is mostly in green leafy vegetables (Vitamin K1) and fermented dairy such as cheese (Vitamin K2) [7]. However, these foods rich in Vitamin K also contain potassium. Therefore, CKD patients might be prone to Vitamin K deficiency under the concern of hyperkalemia. Vitamin K deficiency is common in CKD patients with different stages. In addition, the protein associated with Vitamin K recycling is dysregulated in CKD subjects, and therefore, the percentage of uncarboxylated protein is more common in CKD. From the clinical evidence, the fraction of carboxylated matrix Gla protein (cMGP) was associated with VC in CKD patients. Vitamin K deficiency was also associated with fracture risk in dialysis patients or nondialysis CKD patients.

As carboxylated osteocalcin and cMGP are essential for preventing the complications of renal osteodystrophy, Vitamin K supplement should provide clinical benefits in CKD patients. Few clinical trials demonstrated the Vitamin K supplement on the hard outcome in CKD patients. However, the supplement of Vitamin D analog or calcimimetics was associated with higher OC and MGP levels in dialysis patients [8]. Such evidence might suggest that the supplement of Vitamin D in CKD could play a conjunctive role in correcting the defecting carboxylation by Vitamin K deficiency.

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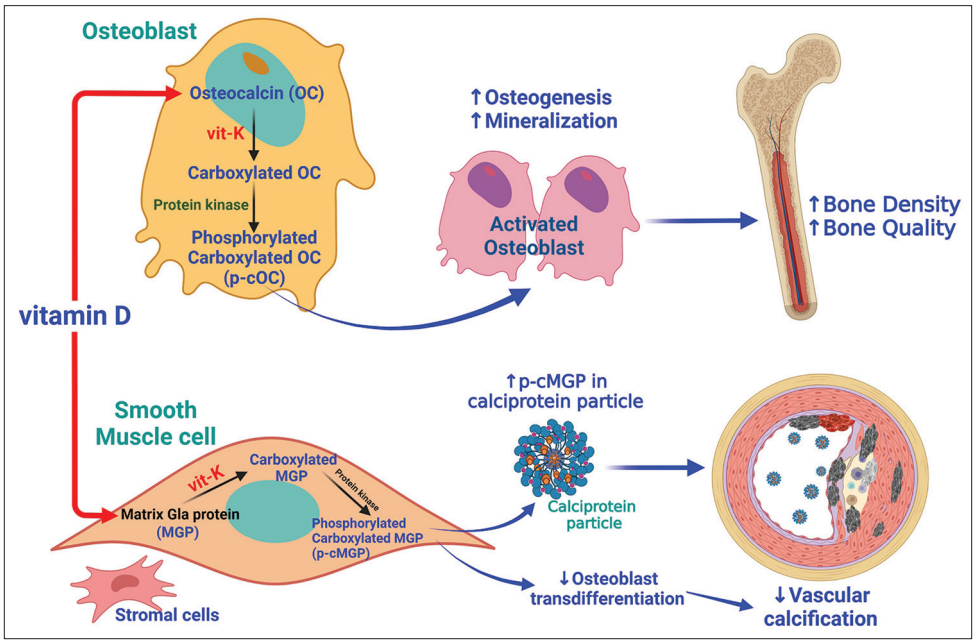

Figure 1: Vitamin K plays a conjunction role with Vitamin D in managing CKD–MBD and vascular calcification. Vitamin D promotes the synthesis of OC in osteoblasts and MGP in vascular smooth cells or stromal cells. Vitamin K-dependent carboxylation facilitates the carboxylation of OC in osteoblasts and the MGP in smooth muscle cells. Phosphorylated cOC increases bone density and bone quality and hence decreases extra-bony calcium deposition. The abundance of phosphorylated cMGP in CPPs further chelates the calcium in the serum. The calcium-enriched CPPs would be then excreted by the liver. CKD–MBD: Chronic kidney disease-mineral bone disorder, MGP: Matrix Gla protein, cOC: Carboxylated osteocalcin, cMGP: Carboxylated matrix Gla protein, CPP: Calciprotein particle, OC: Osteocalcin

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Submission: 25-Jul-2022 **Acceptance:** 16-Aug-2022
Web Publication: 09-Nov-2022

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_206_22

How to cite this article: Hou YC, Lu KC. Editorial comment on Vitamin K and vascular calcification in chronic kidney disease: An update of current evidence – The role of Vitamin K in managing chronic kidney disease–mineral bone disorder. Tzu Chi Med J 2023;35(1):51-2.