Review article

UDC: 616.61-008.6:577.161.5
doi:10.5633/amm.2022.0209

INSIGHTS INTO THE METABOLISM AND CLINICAL SIGNIFICANCE OF VITAMIN K IN UREMIA: MORE THAN A SUPPLEMENT?

Stefanos Roumeliotis[1,2], Garyfallia Varouktsi[1,2], Ariti Tsinari[1,2], Andrej Veljković[3], Gordana Lazarević[4,5], Zoran Perišić[4,5], Jovan Hadži-Djokić[6], Gordana Kocić[3], Vassilios Liakopoulos[1,2]

Vascular calcification (VC) is a common manifestation of the enhanced Cardiovascular (CV) disease that is observed in Chronic Kidney Disease (CKD). Although the pathogenesis of VC is very complex, recently it became evident that it is the result of the imbalance between calcification promoters and inhibitors, in favor of the former. Matrix Gla Protein (MGP), a powerful inhibitor of VC depends on vitamin K to be fully activated. Epidemiologic data suggest that vitamin K deficiency is highly prevalent in CKD even at the early stages of the disease and correlates tightly with CV outcomes. In animal models, supplementation of vitamin K was accompanied with regression of VC, through activation of MGP. In this review, we aimed to present the existing data regarding the effect of vitamin K supplementation on VC and CV outcome in uremic patients.

Acta Medica Medianae 2022;61(2):72-79.

Key words: *arterial calcification, arterial stiffness, cardiovascular disease, chronic kidney disease, vascular calcification, vitamin K*

[1]Division of Nephrology and Hypertension, 1st Department of Internal Medicine, AHEPA Hospital, Thessaloniki, Greece
[2]Aristotle University of Thessaloniki, School of Medicine, Thessaloniki, Greece
[3]University of Niš, Faculty of Medicine, Department of Biochemistry, Niš, Serbia
[4]University Clinical Center Niš, Division of Cardiology, Niš, Serbia
[5]University of Niš, Faculty of Medicine, Niš, Serbia
[6]Serbian Academy of Sciences and Arts, Belgrade, Serbia

Contact: Stefanos Roumeliotis
1 St. Kyriakidi Street, 54636 Thessaloniki, Greece
E-mail: roumeliotis@auth.gr

Introduction

Cardiovascular disease (CVD) still remains the major cause of mortality and morbidity in the chronic kidney disease (CKD) population, accounting for nearly half of the deaths that occur in end stage kidney disease (ESKD) patients receiving dialysis treatment, according to the large national database of United States Renal Data System USRDS (1). Globally, the prevalence of CKD is about 11-13% of the general population but only 0.1-0.3% ends in dialysis, a percentage that is expected to rise dramatically during the next decade (2). This is due to the fact that more of patients at CKD stages 1-2 will die from CVD than progress to ESKD and require dialysis treatment (3). Traditional, Framingham risk factors can only partially explain the increased risk for CVD that is observed in the CKD population. One of the novel mechanisms that is proposed to underlie the occurrence and progression of CVD in CKD might be the calcification of the arteries and cardiac valves (4). Therefore, vascular calcification (VC) or vascular stiffness (VS) might confer to the deleterious CVD burden that is common in uremic patients.

Arterial calcification and stiffness in CKD and ESKD

VC or VS starts in the third decade of life, increases progressively as we age and is a common finding among the healthy aged. In CKD and ESKD, VC and VS start very early (5), are highly prevalent and progress along with deterioration of kidney function. The clinical importance of VC is that the presence of calcium depositions in any artery of the human body (regardless of size or site), confers a 3-4 fold increased risk for CVD morbidity and mortality (6), whereas it is suggested that "we are as old as our arteries are". VC exists in four distinct types: calcification of the media, of the intima layer, of heart valves and calciphylaxis. In CKD, any of these forms might present alone in any combination with other forms (7). Compared to age/gender-matched

controls from the general population, VC in CKD is up to 45 times more pronounced (8), whereas even at CKD stages 1 or 2, VC is detected in 50-90% of all patients (5). In ESKD, VC is more exacerbated, and is prevalent in 90% of all cases; moreover, each extra year on hemodialysis (HD) increases the risk for developing VC by 15% (9). Although VC has been identified over a century ago, the exact pathophysiological mechanisms underlying its occurrence and progression were not fully elucidated until recently.

For more than a hundred years, VC was recognized as a passive, degenerative disorder with no treatment options. This perception was overturned three decades ago, when it became evident that VC was actually an active molecular process, where the first crucial step was the transformation of vascular smooth muscle cells to osteoblastic phenotype (10). Moreover, it was found that this process was modulated by a plethora of molecules and proteins that were implicated in the process of bone formation and either enhanced or abrogated the calcification process. Thus, VC might be the result of the imbalance between calcification promoters and inhibitors, in favor of the former.

Matrix Gla Protein: The natural inhibitor of VC in need of vitamin K

Among various inhibitors of arterial calcification, Matrix Gla Protein (MGP) is the first one to be ever discovered and the most powerful of all (11). MGP is a small molecule with a molecular weight of about 12 kDa, containing 84 amino-acids, 3 serine residues and 4-5 glutamate (Glu) residues. MGP is secreted within the vessel wall and the cartilage and inhibits VC via several pathways (10): firstly, MGP exhibits high affinity to free, circulating calcium, secondly, it directly binds to calcium, phosphorus and hydroxyapatite crystals accumulated in the vessel wall and forms inactive complexes, thirdly, it stimulates the clearance and removal of these complexes from the vessels by macrophages and finally, MGP abrogates the activation of a powerful promoter of VC, bone morphogenetic protein-2, by antagonizing the binding of this molecule to its specific receptors (10, 12, 13). Moreover, there is a synergy between MGP and vitamin D regarding the metabolism of free calcium; MGP keeps the free calcium away from the vessels and vitamin D transfers it to the bones (14). Luo et al., were the first to identify the crucial clinical role of MGP (15); genetically modified rodents that could not express MGP (knockout MGP-/-), were born with natural phenotype but all died within 240 days from their birth due to excessive bleeding caused by rupture of their calcified aorta. Therefore, it became evident that without expressing MGP, life could not be sustained. Additional evidence came from genetic studies showing that mutations in the MGP gene - leading to under expression of MGP - are responsible for the Keutel syndrome, a rare condition where accelerated spontaneous calcification of cartilage, vessels and soft tissues presents (16). Following these, several genetic studies reported a tight association between single nucleotide polymorphisms of the MGP gene and VC/VS or CVD outcomes in various populations, including CKD (17-19). MGP is part of the family of vitamin-k-dependent proteins (VKDPs), which are implicated in coagulation, bone metabolism and cardiovascular health. The common characteristic of all VKDPs is the presence of Glu residues that need to undergo carboxylation, a process that need vitamin K as a cofactor. Only when the inactive Glu residues are fully carboxylated to γ-carboxyglutamate (Gla), VKDPs become biologically active. In addition, MGP has to undergo to another activation process that requires vitamin K as a cofactor, phosphorylation of its serine residues. Therefore, the initial, fully inactive MGP molecule is uncarboxylated and dephosphorylated (dp-ucMGP), which undergoes firstly carboxylation and then phosphorylated to become the fully active form. Only after undergoing these two processes, MGP possesses the ability to act as an inhibitor of VC and an important regulator of circulating calcium (20). However, dp-ucMGP cannot bind to bone morphogenetic protein-2 receptors and no longer has the ability to sweep calcium and hydroxyapatite crystals from the vessel wall (21, 22).

Warfarin, a well-known anticoagulation agent, is a vitamin K antagonist. Since MGP needs vitamin K to become active, the research team from Maastricht found that after 180 days of warfarin supplementation, rats exhibited enhanced VC, due to the impaired carboxylation of MGP (23). After the end of this period, rats were divided to receive warfarin or vitamin K in low or high concentrations for another 240 days and the authors found a 37% regression of VC in the high vitamin K group. This was the first study to show that vitamin K supplementation might prevent or even regress VC, through activation of MGP. During the past decade, dp-ucMGP has been coherently shown to be associated with subclinical, surrogate markers of VC/VS and cardiovascular outcomes in the general population (24-26), in patients with heart failure (27-29) and CVD (30, 31). Since uremia is a state of enhanced arterial calcification, several investigators aimed to explore the potential clinical importance of dp-ucMGP in CKD and ESKD. In a small cohort of pre-dialysis CKD patients, Schurgers et al., were the first to show that dp-ucMGP was correlated with the degree of VC and predicted all-cause mortality (21). In the same study, dp-ucMGP increased progressively across stages of CKD. Similarly, Roumeliotis et al., showed that in a cohort of diabetic CKD patients, dp-ucMGP predicted all-cause/CVD mortality and deterioration of kidney function, after 7 years of follow-up (32). Likewise, other small, cross-sectional studies reported a close association between dp-ucMGP and VC or VS in pre-dialysis CKD cohorts (33, 34). In ESKD, the tight association of dp-ucMGP with CVD outcomes has been repeatedly reported by several studies (35, 36). The major limitations of the forementioned studies include the small sample size, the fact that vitamin K was not directly assessed and the observational design. However, it was coherently shown that dp-ucMGP, reflecting vitamin K deficiency, was a reliable marker of VC in uremic patients.

Vitamin K-the key vitamin for cardiovascular health in uremia

Vitamin K is a family of fat-soluble vitamins playing a pivotal role in coagulation, bone and calcium metabolism. Vitamin K includes two vitamers, K1 or phylloquinone and K2 or menaquinone; in turn, K2 exists in several subtypes, which differ in isoprenyl units and length of side chain. Although the subtype with the longest side chain and the best bioavailability in humans is menaquinone-7 (MK-7) (37), all K forms have the ability to act as cofactors for MGP carboxylation.

Data from large population-based studies - such as the ERGO (38), NHANES II (39), EPIC (40), PREVENT (41) and Danish Diet, Cancer and Health Study (42) - coherently showed that insufficient, dietary vitamin K intake was independently associated with all-cause mortality and CVD in the general population. CKD is a state of subclinical and underdiagnosed vitamin K deficiency which is highly prevalent even at stages 1-2 and gradually increases, as disease progresses to ESKD (43). This could be attributed to several reasons; first, CKD patients often have strict dietary recommendations to avoid green leafy vegetables (that are rich in K1 and potassium) and dietary products (that are rich in K2 and phosphorus) (44), second, the uremic environment might affect the recycling and bioavailability of vitamin K (45), third, certain drug agents that these patients receive (such as phosphate binders and proton pump inhibitors) might further reduce the availability of vitamin K (46) and finally, in uremia, the uptake and metabolism of vitamin K by lipoproteins is significantly impaired (47). In pre-dialysis CKD, in ESKD patients and in kidney transplant recipients, vitamin K deficiency is very common and has been repeatedly associated with the occurrence of CVD outcomes (21, 32, 48, 49). With this background in mind, it was attractive to hypothesize that in uremia, vitamin K supplementation might protect from VC through activation of MGP. To determine the dose of vitamin K that should be supplemented in ESKD patients, Caluwe et al. (50) and Westenfeld et al. (51) conducted two dose-finding studies in HD cohorts. Caluwe et al., divided 200 HD patients to either 360 or 720 or 1080 μg of MK-7 thrice weekly for 60 days and found that plasma dp-ucMGP was decreased by 17%, 33% and 46% in groups, respectively (50). In a study with quite similar design, Westenfeld et al., divided 53 HD patients to either 45 or 135 or 360 μg of MK-7 every day for 45 days and found that plasma dp-ucMGP was reduced by 17.9%, 36.7% and 61.1% in groups, respectively (51). These two studies showed a dose-dependent reduction of dp-ucMGP with increased dose of MK-7 and provided the rationale for interventional, clinical studies in this population. Moreover, it was shown that even a daily dose of 464 μg could not fully restore vitamin K deficiency in HD patients.

Interventional clinical trials of vitamin K supplementation in uremia

To date, seven interventional trials on patients with kidney function impairment have been completed and reported results; two in kidney transplant recipients, two in pre-dialysis CKD and three in dialysis patients. The first study was conducted by Kurnatowksa et al., in 2015 (52), in a cohort of 42 CKD patients at stages 3-5 not receiving dialysis. Patients were randomly allocated to daily, oral supplementation of either vitamin D 10 μg or combination of D with K (MK-7, 90 μg) for 270 days. After the treatment period, the authors reported that compared to the D group, patients in the D+K group exhibited a significant reduction of carotid intima media thickness (cIMT) progression, whereas a non-significant trend towards improvement of coronary artery calcification score in this group was observed. Mansour et al., conducted the KING study, the first interventional trial in kidney transplant recipients (53). In this single arm study, sixty patients received *per os* 360 μg/day of MK-7 for 60 days and at the end of the treatment period the authors found a significant, 14.2% decrease in carotid-femoral pulse wave velocity (PWV). Although these two trials were positive, the ones that followed have reported negative results to date. Oikonomaki et al., conducted a single arm study where they supplemented 52 HD patients with 200 μg/day of MK-7 for 360 days and reported no effect on the Agatston score (54). Likewise, the K4KIDNEYS was a randomized, placebo-controlled trial in a cohort of 159 pre-dialysis CKD patients showing that 400 μg/day of MK-7 for 360 days failed to show any beneficial effect on PWV or abdominal aortic calcification score (55). Similarly, the VALKYRIE study that included 132 HD patients with atrial fibrillation randomly divided to either warfarin, or rivaroxaban or rivaroxaban with vitamin K (200 μg of MK-7, thrice weekly) for 540 days, failed to show any effect of vitamin K on PWV, coronary artery calcification score or calcification of the heart valves (56). In agreement with these results, the RENAKVIT randomized, placebo-controlled trial showed that daily intake of 360 μg MK-7 for 720 days had no effect on VC or VS, in a mixed dialysis cohort of 21 patients either on HD or peritoneal dialysis treatment (57). The most recent randomized, placebo controlled trial that was published is the VIKTORIES trial (58). In this trial, ninety kidney transplant recipients were randomized to either 5 mg of menadiol diphosphate thrice weekly or placebo for 360 days but after the treatment period there was no effect of vitamin K intake on arterial stiffness assessed by MRI-based aortic distensibility or arterial calcification assessed by coronary artery calcium score.

Although the existing studies are very limited, we expect with great interest the results of several, currently ongoing interventional studies in CKD populations, including the Treatment to Reduce Vascular Calcification in Hemodialysis Patients Using Vitamin K (TReVasc-HDK) (59), the Inhibit Progression of Coronary Artery Calcification with Vitamin K1 in Hemodialysis participants (iPACK-HD) (60), the Vitamin K to Slow Progression of Cardio-

vascular Disease Risk in Hemodialysis Patients (Vita-K 'n' CKD) Study (registered in clinicaltrials.gov, with reference number NCT03311321), the Vitamin K1 to Slow Progression of Vascular Calcification in HD Patients (VitaVasK) (61), the Universidad Católica de Salta-Vitamin K2 Supplementation and Vascular Calcification (UCASAL-VITK), which studies for the first time intravenous supplementation of MK-7 in HD patients (registered in clinicaltrials.gov, with reference number NCT04539418) and the Vitamin K in Peritoneal Dialysis (VIKIPEDIA) study, which will be the first to assess MK-7 supplementation in PD (registered in clinicaltrials.gov, with reference number NCT04900610).

Questions that remain, areas of debate and future directions

To date, the existing data do not support that vitamin K supplementation has beneficial effect on VC and CVD in uremic patients. However, the data are limited and derived from studies with major limitations (62). First, although the dose-finding studies by Westenfeld et al. and Caluwe et al., showed that even 464 μg/day of MK-7 failed to restore vitamin K status in HD patients, all aforementioned studies used lower dosages. Secondly, in certain studies the sample size was very small (in RENAKVIT study, only 21 patients completed the study) and thirdly, in other studies (such as the VALKYRIE study), the population included was very old where arteries are in a calcified, mummified status and probably unresponsive to treatment. Finally, in the K4KIDNEYS study the population was probably not vitamin K deficient and the treatment period was rather short.

There are still several questions that remain unanswered: should we treat CKD patients with vitamin K? With which vitamer? Which subform? Which dosage? For how long? And how to monitor the possible beneficial effect? These questions will be hopefully answered when the ongoing, interventional studies report their results.

Conclusion

VC is a common manifestation of CVD in uremia. Although its pathogenesis is very complex, MGP, a powerful inhibitor of VC depends on vitamin K to be fully activated. Epidemiologic data suggest that vitamin K deficiency is highly prevalent in CKD even at the early stages of the disease and correlates tightly with CVD outcomes. In animal models, supplementation of vitamin K (MK-7) was accompanied with regression of VC, through activation of MGP. Until to-day, the data regarding the effect of vitamin K on uremic patients remain limited. Future, larger, interventional randomized placebo-controlled trials are needed in order to draw definite conclusions.

References

1. Renal U. Data System. USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007.2011.
2. McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD incidence and prevalence in the United States through 2030. Journal of the American Society of Nephrology. 2019;30(1): 127-35. [CrossRef] [PubMed]
3. Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol. 2005;16(2):489-95. [CrossRef] [PubMed]
4. Roumeliotis A, Roumeliotis S, Panagoutsos S, Theodoridis M, Argyriou C, Tavridou A, et al. Carotid intima-media thickness is an independent predictor of all-cause mortality and cardiovascular morbidity in patients with diabetes mellitus type 2 and chronic kidney disease. Ren Fail. 2019;41(1):131-8. [CrossRef] [PubMed]
5. Porter CJ, Stavroulopoulos A, Roe SD, Pointon K, Cassidy MJ. Detection of coronary and peripheral artery calcification in patients with chronic kidney disease stages 3 and 4, with and without diabetes. Nephrology Dialysis Transplantation. 2007;22(11): 3208-13. [CrossRef] [PubMed]
6. Rennenberg RJ, Kessels AG, Schurgers LJ, van Engelshoven JM, de Leeuw PW, Kroon AA. Vascular calcifications as a marker of increased cardiovascular risk: a meta-analysis. Vasc Health Risk Manag. 2009; 5(1):185-97. [CrossRef] [PubMed]
7. Roumeliotis S, Mallamaci F, Zoccali C. Endothelial Dysfunction in Chronic Kidney Disease, from Biology to Clinical Outcomes: A 2020 Update. J Clin Med. 2020;9(8). [CrossRef] [PubMed]
8. O'neill WC, Lomashvili KA. Recent progress in the treatment of vascular calcification. Kidney international. 2010;78(12):1232-9. [CrossRef] [PubMed]
9. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, et al. Cardiac calcification in adult hemodialysis patients: A link between end-stage renal disease and cardiovascular disease? Journal of the American College of Cardiology. 2002;39(4):695-701. [CrossRef] [PubMed]
10. Roumeliotis S, Roumeliotis A, Dounousi E, Eleftheriadis T, Liakopoulos V. Biomarkers of vascular calcification in serum. Advances in clinical chemistry. 2020;98:91-147. [CrossRef] [PubMed]
11. Roumeliotis S, Dounousi E, Salmas M, Eleftheriadis T, Liakopoulos V. Vascular Calcification in Chronic Kidney Disease: The Role of Vitamin K- Dependent Matrix Gla Protein. Front Med (Lausanne). 2020;7:154. [CrossRef] [PubMed]
12. Bostrom K, Tsao D, Shen S, Wang Y, Demer LL. Matrix GLA protein modulates differentiation induced by bone morphogenetic protein-2 in C3H10T1/2 cells. J Biol Chem. 2001;276(17):14044-52. [CrossRef] [PubMed]
13. Zebboudj AF, Imura M, Bostrom K. Matrix GLA protein, a regulatory protein for bone morphogenetic protein-2. J Biol Chem. 2002;277(6):4388-94. [CrossRef] [PubMed]
14. Van Ballegooijen AJ, Pilz S, Tomaschitz A, Grübler MR, Verheyen N. The synergistic interplay between vitamins D and K for bone and cardiovascular health: a narrative review. International journal of endocrinology. 2017;2017. [CrossRef] [PubMed]
15. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature. 1997;386(6620):78-81. [CrossRef] [PubMed]
16. Hur DJ, Raymond GV, Kahler SG, Riegert-Johnson DL, Cohen BA, Boyadjiev SA. A novel MGP mutation in a consanguineous family: review of the clinical and molecular characteristics of Keutel syndrome. Am J Med Genet A. 2005;135(1):36-40. [CrossRef] [PubMed]
17. Brancaccio D, Biondi ML, Gallieni M, Turri O, Galassi A, Cecchini F, et al. Matrix GLA protein gene polymorphisms: clinical correlates and cardiovascular mortality in chronic kidney disease patients. Am J Nephrol. 2005;25(6):548-52. [CrossRef] [PubMed]
18. Roumeliotis S, Roumeliotis A, Panagoutsos S, Giannakopoulou E, Papanas N, Manolopoulos VG, et al. Matrix Gla protein T-138C polymorphism is associated with carotid intima media thickness and predicts mortality in patients with diabetic nephropathy. J Diabetes Complications. 2017;31(10):1527-32. [CrossRef] [PubMed]
19. Sheng K, Zhang P, Lin W, Cheng J, Li J, Chen J. Association of Matrix Gla protein gene (rs1800801, rs1800802, rs4236) polymorphism with vascular calcification and atherosclerotic disease: a meta-analysis. Sci Rep. 2017;7(1):8713. [CrossRef] [PubMed]
20. Schurgers LJ, Spronk HM, Skepper JN, Hackeng TM, Shanahan CM, Vermeer C, et al. Post-translational modifications regulate matrix Gla protein function: importance for inhibition of vascular smooth muscle cell calcification. J Thromb Haemost. 2007;5(12): 2503-11. [CrossRef] [PubMed]
21. Schurgers LJ, Barreto DV, Barreto FC, Liabeuf S, Renard C, Magdeleyns EJ, et al. The circulating inactive form of matrix gla protein is a surrogate marker for vascular calcification in chronic kidney disease: a preliminary report. Clin J Am Soc Nephrol. 2010;5(4):568-75. [CrossRef] [PubMed]
22. Schurgers LJ, Cranenburg EC, Vermeer C. Matrix Gla-protein: the calcification inhibitor in need of vitamin K. Thromb Haemost. 2008;100(4):593-603. [PubMed]
23. Schurgers LJ, Spronk HM, Soute BA, Schiffers PM, DeMey JG, Vermeer C. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood. 2007;109(7):2823-31. [CrossRef] [PubMed]
24. Dalmeijer GW, van der Schouw YT, Vermeer C, Magdeleyns EJ, Schurgers LJ, Beulens JW. Circulating matrix Gla protein is associated with coronary artery calcification and vitamin K status in healthy women. J Nutr Biochem. 2013;24(4):624-8. [CrossRef] [PubMed]
25. Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women. A double-blind randomised clinical trial. Thromb Haemost. 2015;113(5):1135-44. [CrossRef] [PubMed]

26. van den Heuvel EG, van Schoor NM, Lips P, Magdeleyns EJ, Deeg DJ, Vermeer C, et al. Circulating uncarboxylated matrix Gla protein, a marker of vitamin K status, as a risk factor of cardiovascular disease. Maturitas. 2014;77(2):137-41. [CrossRef] [PubMed]
27. Ueland T, Dahl CP, Gullestad L, Aakhus S, Broch K, Skardal R, et al. Circulating levels of non-phosphorylated undercarboxylated matrix Gla protein are associated with disease severity in patients with chronic heart failure. Clin Sci (Lond). 2011;121(3):119-27. [CrossRef] [PubMed]
28. Ueland T, Gullestad L, Dahl CP, Aukrust P, Aakhus S, Solberg OG, et al. Undercarboxylated matrix Gla protein is associated with indices of heart failure and mortality in symptomatic aortic stenosis. J Intern Med. 2010;268(5):483-92. [CrossRef] [PubMed]
29. Hashmath Z, Lee J, Gaddam S, Ansari B, Oldland G, Javaid K, et al. Vitamin K status, Warfarin use, and arterial stiffness in heart failure. Hypertension. 2019; 73(2):364-70. [CrossRef] [PubMed]
30. Parker BD, Schurgers LJ, Brandenburg VM, Christenson RH, Vermeer C, Ketteler M, et al. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. Ann Intern Med. 2010;152(10):640-8. [CrossRef] [PubMed]
31. Dalmeijer GW, van der Schouw YT, Magdeleyns EJ, Vermeer C, Verschuren WM, Boer JM, et al. Circulating desphospho-uncarboxylated matrix gamma-carboxyglutamate protein and the risk of coronary heart disease and stroke. J Thromb Haemost. 2014;12(7): 1028-34. [CrossRef] [PubMed]
32. Roumeliotis S, Roumeliotis A, Stamou A, Leivaditis K, Kantartzi K, Panagoutsos S, et al. The association of dp-ucMGP with cardiovascular morbidity and decreased renal function in diabetic chronic kidney disease. International journal of molecular sciences. 2020;21(17):6035. [CrossRef] [PubMed]
33. Puzantian H, Akers SR, Oldland G, Javaid K, Miller R, Ge Y, et al. Circulating Dephospho-Uncarboxylated Matrix Gla-Protein Is Associated With Kidney Dysfunction and Arterial Stiffness. Am J Hypertens. 2018; 31(9):988-94. [CrossRef] [PubMed]
34. Thamratnopkoon S, Susantitaphong P, Tumkosit M, Katavetin P, Tiranathanagul K, Praditpornsilpa K, et al. Correlations of Plasma Desphosphorylated Uncarboxylated Matrix Gla Protein with Vascular Calcification and Vascular Stiffness in Chronic Kidney Disease. Nephron. 2017;135(3):167-72. [CrossRef] [PuMed]
35. Delanaye P, Krzesinski JM, Warling X, Moonen M, Smelten N, Medart L, et al. Dephosphorylated-uncarboxylated Matrix Gla protein concentration is predictive of vitamin K status and is correlated with vascular calcification in a cohort of hemodialysis patients. BMC Nephrol. 2014;15:145. [CrossRef] [PubMed]
36. Fain ME, Kapuku GK, Paulson WD, Williams CF, Raed A, Dong Y, et al. Inactive Matrix Gla Protein, Arterial Stiffness, and Endothelial Function in African American Hemodialysis Patients. Am J Hypertens. 2018. [CrossRef] [PubMed]
37. Card DJ, Shearer MJ, Schurgers LJ, Gomez K, Harrington DJ. What's in a name? The pharmacy of vitamin K. Br J Haematol. 2016;174(6):989-90. [CrossRef] [PubMed]
38. Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, van der Meer IM, et al. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. J Nutr. 2004;134(11):3100-5. [CrossRef] [PubMed]
39. Cheung CL, Sahni S, Cheung BM, Sing CW, Wong IC. Vitamin K intake and mortality in people with chronic kidney disease from NHANES III. Clin Nutr. 2015; 34(2):235-40. [CrossRef] [PubMed]
40. Nimptsch K, Rohrmann S, Kaaks R, Linseisen J. Dietary vitamin K intake in relation to cancer incidence and mortality: results from the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg). Am J Clin Nutr. 2010;91(5):1348-58. [CrossRef] [PubMed]
41. Riphagen IJ, Keyzer CA, Drummen NEA, de Borst MH, Beulens JWJ, Gansevoort RT, et al. Prevalence and Effects of Functional Vitamin K Insufficiency: The PREVEND Study. Nutrients. 2017;9(12). [CrossRef] [PubMed]
42. Bellinge JW, Dalgaard F, Murray K, Connolly E, Blekkenhorst LC, Bondonno CP, et al. Vitamin K Intake and atherosclerotic cardiovascular disease in the danish diet cancer and health study. Journal of the American Heart Association. 2021;10(16):e020551. [CrossRef] [PubMed]
43. Roumeliotis S, Roumeliotis A, Gorny X, Mertens PR. Could Antioxidant Supplementation Delay Progression of Cardiovascular Disease in End-Stage Renal Disease Patients? Curr Vasc Pharmacol. 2021;19(1):41-54. [CrossRef] [PubMed]
44. Cranenburg EC, Schurgers LJ, Uiterwijk HH, Beulens JW, Dalmeijer GW, Westerhuis R, et al. Vitamin K intake and status are low in hemodialysis patients. Kidney Int. 2012;82(5):605-10. [CrossRef] [PubMed]
45. McCabe KM, Booth SL, Fu X, Ward E, Adams MA, Holden RM. Vitamin K metabolism in a rat model of chronic kidney disease. American Journal of Nephrology. 2017;45(1):4-13. [CrossRef] [PubMed]
46. Neradova A, Schumacher SP, Hubeek I, Lux P, Schurgers LJ, Vervloet MG. Phosphate binders affect vitamin K concentration by undesired binding, an in vitro study. BMC Nephrol. 2017;18(1):149. [CrossRef] [PubMed]
47. Kaesler N, Schreibing F, Speer T, de la Puente-Secades S, Rapp N, Drechsler C, et al. Altered vitamin K biodistribution and metabolism in experimental and human chronic kidney disease. Kidney International. 2022;101(2):338-48. [CrossRef] [PubMed]
48. Keyzer CA, Vermeer C, Joosten MM, Knapen MH, Drummen NE, Navis G, et al. Vitamin K status and mortality after kidney transplantation: a cohort study. Am J Kidney Dis. 2018;65(3):474-83. [CrossRef] [PubMed]
49. Schlieper G, Westenfeld R, Kruger T, Cranenburg EC, Magdeleyns EJ, Brandenburg VM, et al. Circulating nonphosphorylated carboxylated matrix gla protein predicts survival in ESRD. J Am Soc Nephrol. 2011; 22(2):387-95. [CrossRef] [PubMed]
50. Caluwe R, Vandecasteele S, Van Vlem B, Vermeer C, De Vriese AS. Vitamin K2 supplementation in haemodialysis patients: a randomized dose-finding study. Nephrol Dial Transplant. 2014;29(7):1385-90. [CrossRef] [PubMed]
51. Westenfeld R, Krueger T, Schlieper G, Cranenburg EC, Magdeleyns EJ, Heidenreich S, et al. Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. Am J Kidney Dis. 2012;59(2):186-95. [CrossRef] [PubMed]
52. Kurnatowska I, Grzelak P, Masajtis-Zagajewska A, Kaczmarska M, Stefanczyk L, Vermeer C, et al. Effect of vitamin K2 on progression of atherosclerosis and vascular calcification in nondialyzed patients with chronic kidney disease stages 3-5. Pol Arch Med Wewn. 2015;125(9):631-40. [CrossRef] [PubMed]
53. Mansour AG, Hariri E, Daaboul Y, Korjian S, El Alam A, Protogerou AD, et al. Vitamin K2 supplementation and

arterial stiffness among renal transplant recipients-a single-arm, single-center clinical trial. J Am Soc Hypertens. 2017;11(9):589-97. [CrossRef] [PubMed]
54. Oikonomaki T, Papasotiriou M, Ntrinias T, Kalogeropoulou C, Zabakis P, Kalavrizioti D, et al. The effect of vitamin K2 supplementation on vascular calcification in haemodialysis patients: a 1-year follow-up randomized trial. Int Urol Nephrol. 2019. [CrossRef] [PubMed]
55. Witham MD, Lees JS, White M, Band M, Bell S, Chantler DJ, et al. Vitamin K supplementation to improve vascular stiffness in CKD: the K4Kidneys randomized controlled trial. Journal of the American Society of Nephrology. 2020;31(10):2434-45. [CrossRef] [PubMed]
56. De Vriese AS, Caluwé R, Pyfferoen L, De Bacquer D, De Boeck K, Delanote J, et al. Multicenter randomized controlled trial of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: the Valkyrie Study. Journal of the American Society of Nephrology. 2020;31(1):186-96. [CrossRef] [PubMed]
57. Levy-Schousboe K, Frimodt-Møller M, Hansen D, Peters CD, Kjærgaard KD, Jensen JD, et al. Vitamin K supplementation and arterial calcification in dialysis: results of the double-blind, randomised, placebo-controlled RenaKvit trial. Clinical Kidney Journal. 2021. [CrossRef] [PubMed]
58. Lees JS, Rankin AJ, Gillis KA, Zhu LY, Mangion K, Rutherford E, et al. The ViKTORIES trial: A randomized, double-blind, placebo-controlled trial of vitamin K supplementation to improve vascular health in kidney transplant recipients. American Journal of Transplantation. 2021. [CrossRef] [PubMed]
59. Sabrina-Wong-Peixin Haroon B-C, Tai L-HL, Lynette Teo AD, Leon Schurgers B-WT, Priyanka Khatri C-CO, Sanmay Low X-EY, et al. Treatment to reduce vascular calcification in hemodialysis patients using vitamin K (Trevasc-HDK): a study protocol for a randomized controlled trial. Medicine. 2020;99(36). [CrossRef] [PubMed]
60. Holden RM, Booth SL, Day AG, Clase CM, Zimmerman D, Moist L, et al. Inhibiting the progression of arterial calcification with vitamin K in HemoDialysis patients (iPACK-HD) trial: rationale and study design for a randomized trial of vitamin K in patients with end stage kidney disease. Canadian journal of kidney health and disease. 2015;2(1):17. [CrossRef] [PubMed]
61. Krueger T, Schlieper G, Schurgers L, Cornelis T, Cozzolino M, Jacobi J, et al. Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): a rationale and study protocol. Nephrol Dial Transplant. 2014;29(9):1633-8. [CrossRef] [PubMed]
62. Roumeliotis S, Roumeliotis A, Eleftheriadis T, Liakopoulos V. Letter to the Editor regarding "Six months vitamin K treatment does not affect systemic arterial calcification or bone mineral density in diabetes mellitus 2". European Journal of Nutrition. 2021:1-2. [CrossRef] [PubMed]

Pregledni rad

UDC: 616.61-008.6:577.161.5
doi:10.5633/amm.2022.0209

UVIDI U METABOLIZAM I KLINIČKI ZNAČAJ VITAMINA K KOD UREMIJE: VIŠE OD SUPLEMENTA?

Stefanos Roumeliotis[1,2], Garyfallia Varouktsi[1,2], Ariti Tsinari[1,2], Andrej Veljković[3], Gordana Lazarević[4,5], Zoran Perišić[4,5], Jovan Hadži-Đokić[6], Gordana Kocić[3], Vassilios Liakopoulos[1,2]

[1]Odeljenje za nefrologiju i hipertenziju, Prvi departman interne medicine, AHEPA bolnica, Solun, Grčka
[2]Aristotelov univerzitet u Solunu, Medicinski fakultet, Solun, Grčka
[3]Univerzitet u Nišu, Medicinski fakultet, Katedra za biohemiju, Niš, Srbija
[4]Univerzitetski klinički centar Niš, Klinika za kardiologiju, Niš, Srbija
[5]Univerzitet u Nišu, Medicinski fakultet, Katedra Interna medicina i zdravstvena nega, Niš, Srbija
[6]Srpska akademija nauka i umetnosti, Beograd, Srbija

Kontakt: Stefanos Roumeliotis
Kyriakidi 1, 54636 Solun, Grčka
E-mail: roumeliotis@auth.gr

Vaskularna kalcifikacija (VK) je česta manifestacija pojačane kardiovaskularne bolesti, koja je primećena kod hronične bolesti bubrega (HBB). Iako je patogeneza kradiovaskularnih bolesti kompleksna, u poslednje vreme postalo je evidentno da je posledica disbalansa između promotera kalcifikacije i njenih inhibitora, u korist promotera kalcifikacije. Matriks Gla protein (MGP), moćan inhibitor vaskularne kalcifikacije, zavisi od vitamina K, kako bi bio aktiviran u potpunosti. Epidemiološki podaci sugerišu na to da je prevalencija deficita vitamina K visoka kod hronične bolesti bubrega, čak i u ranim fazama bolesti i u korelaciji je sa kardio-vaskularnim bolestima, kao posledicom. Kod životinja, suplementacijom vitanom K postignuta je regresija kardiovaskularne bolesti, pomoću aktivacije MGP. U ovom pregledu, cilj je da predstavimo postojeće podatke o efektima suplementacija vitamina K na vaskularnu kalcifikaciju i kardiovaskularne bolesti, kod bolesnika sa uremijom.

Acta Medica Medianae 2022;61(2):72-79.

Ključne reči: *arterijska kalcifikacija, ukočenost arterija, kardiovaskularne bolesti, hronična bolest bubrega, vaskularna kalcifikacija, vitamin K*