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TOPIC HIGHLIGHT

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Are there ways to attenuate arterial calcification and improve cardiovascular outcomes in chronic kidney disease?

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Abstract

The risk of cardiovascular mortality among patients with end-stage renal disease is several times higher than general population. Arterial calcification, a marker of atherosclerosis and a predictor of cardiovascular mortality, is common in chronic kidney disease (CKD). The presence of traditional cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, and advanced age cannot fully explain the high prevalence of atherosclerosis and arterial calcification. Other factors specific to CKD such as hyperphosphatemia, excess of calcium, high dose active vitamin D and prolonged dialysis vintage play important roles in the development of arterial calcification. Due to the significant health risk, it is prudent to attempt to lower arterial calcification burden in CKD. Treatment of hyperlipidemia with statin has failed to lower atherosclerotic and arterial calcification burden. Data on diabetes and blood pressure controls as well as smoking cessation on cardiovascular outcomes in CKD population are limited. Currently available treatment options include non-calcium containing phosphate binders, low dose active vitamin D, calcimimetic agent and perhaps bisphosphonates, vitamin K and sodium thiosulfate. Preliminary data on bisphosphonates, vitamin K and sodium thiosulfate are encouraging but larger studies on efficacy and outcomes are needed.

Key words: Vascular calcification; Coronary calcification; Hemodialysis; Dialysis; Chronic kidney disease

Core tip: Arterial calcification is common in chronic kidney disease (CKD). Factors specific to CKD such as hyperphosphatemia, excess of calcium and high dose vitamin D therapy play important roles in the development of arterial calcification. Statin is ineffective in lowering the calcification burden. Data on diabetes and blood pressure controls and smoking cessation on cardiovascular outcomes in CKD population are limited. Available treatment strategies include non-calcium containing phosphate binders, low dose active vitamin D and calcimimetic agent. Preliminary data on bisphosphonates, vitamin K and sodium thiosulfate are encouraging but larger studies on efficacy and outcomes are needed.

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INTRODUCTION

Cardiovascular disease is the leading cause of death in

chronic kidney disease (CKD) population. The risk of cardiovascular mortality among those with end-stage renal disease is several times higher than general population[1]. Arterial calcification, a marker of atherosclerosis and a predictor of cardiovascular mortality, is common in CKD[2]. The presence of arterial calcification leads to an increase in arterial stiffness and a decrease in coronary perfusion resulting in cardiac hypertrophy and myocardial ischemia. Young adults who have been on hemodialysis for a long period of time have the prevalence of coronary artery calcification (CAC) that is at least ten times higher than those of the same age whose kidney function are normal[3]. Moreover, an inverse relationship between the estimated glomerular filtration rate and the degree of CAC was observed[4]. The presence of traditional cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, and advanced age cannot fully explain the high prevalence of atherosclerosis and arterial calcification in CKD[5]. Along with common cardiovascular risk factors, other factors specific to CKD population such as hyperphosphatemia, excess of calcium from calcium-containing phosphate binders and high calcium concentration in dialysis solution, high dose active vitamin D used in the treatment of hyperparathyroidism and prolonged dialysis vintage have been shown to positively influence the development of arterial calcification[3,6].

MINERAL METABOLISM IN CKD

In early CKD, the kidney's ability to excrete phosphate load is impaired resulting in a release of fibroblast growth factor 23 (FGF-23) whose action is to stimulate renal phosphate excretion in order to maintain neutral phosphate balance[7]. FGF-23, in the presence of its obligatory co-receptor klotho, binds to FGF receptors causing a decrease in phosphate reabsorption in the proximal tubules and a suppression of 1,25 dihydroxyvitamin D (1,25-OH_2-D) synthesis[8]. Continued phosphate retention and decreased 1,25-OH-D levels later on lead to an increase in parathyroid hormone (PTH) secretion. The accumulation of FGF-23 together with PTH work in concert to enhance renal phosphate excretion. As CKD advances, these compensatory mechanisms fail and phosphate retention ensues evidenced by the development of hyperphosphatemia[9]. Accumulation of PTH also enhances bone resorption giving rise to an increase in circulating calcium, bone loss and fracture. On the other hand, elevated FGF-23 has been linked to cardiac hypertrophy, vascular calcification, congestive heart failure and increased mortality[10-13].

PATHOGENESIS OF ARTERIAL CALCIFICATION

Pathogenesis of arterial calcification is no longer believed to be the passive precipitation of calcium and phosphate crystals but involves a tightly regulated process of cellular transformation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells. These calcified VSMCs, instead of retaining smooth muscle cell markers, express specific osteoblast markers as well as several bone matrix proteins[14,15]. The process of calcification also has features that resemble bone matrix mineralization. For example, the formation and nucleation of mineral crystals require the presence of matrix vesicles. Dying VSMCs form apoptotic bodies which have the ability to concentrate calcium and phosphate in the same fashion as matrix vesicles[16]. Several factors related to CKD including high calcium and phosphate environment and high dose active vitamin D have been shown to promote VSMC transformation followed by matrix vesicle-mediated mineralization[17,18]. Moreover, the reduction and the alteration of function of naturally occurring calcification inhibitors such as fetuin A, matrix gla-protein, osteopontin and osteoprotegerin are also important in the development of arterial calcification in CKD[19,20]. Klotho deficiency has been observed in kidneys, parathyroid glands and other organs during the course of CKD[21,22]. In arterial wall, decreased klotho expression potentiates the development of arterial calcification[23,24]. The role of FGF-23 in arterial calcification is complex. Few studies have identified FGF receptor and its signaling pathway in the arterial wall whereas others have not[12,23,25]. Kidney transplantation can markedly improve both renal function and mineral metabolism in the long term. Several studies have demonstrated stabilization or decline in the rate of progression of arterial calcification in patients who received a kidney transplant as compared to those who remained on dialysis especially during the first 1-2 years[26-28]. However, with longer follow-up period up to 3-4 years post-transplantation, the progression becomes more evident. Overall the rate of CAC progression was estimated to be around 10% per year[29,30]. The severity of baseline calcification and the presence of hyperlipidemia were identified as independent predictors of progression in these studies. It appears that once calcification develops it probably cannot be reversed. Despite the significant improvement in kidney function and mineral metabolism, arterial calcification tends to become more severe as time passes probably triggering by the presence of common cardiovascular risk factors in kidney transplant recipients including aging, diabetes, hypertension and hyperlipidemia.

Due to the significant health risk of atherosclerosis and arterial calcification, it is prudent to attempt to lower calcification burden in CKD patients. Cardiovascular risk modification through the use of statin for hyperlipidemia has not been proved fruitful in attenuating CAC progression[31,32]. Studies on diabetes and blood pressure controls as well as smoking cessation on cardiovascular outcomes in CKD population are limited. The following review focuses on therapies that can modify CKD-related risk factors for arterial calcification which may have favorable impact on cardiovascular outcomes.

PHOSPHATE BINDERS

The purpose of phosphate binder is to bind phosphate in the ingested food and increase its elimination in the

stool. Calcium-containing phosphate binders such as calcium carbonate and calcium acetate are commonly used as phosphate binding agents since early 1980s as alternatives to aluminum hydroxide due to the high prevalence of aluminum toxicity. The use of calcium-containing phosphate binders is often limited by the development of hypercalcemia. Furthermore, over the past decade, increasing evidence have linked the amount of calcium intake derived from calcium-containing phosphate binders to the severity of vascular calcification[3,6,33]. Newer phosphate binding agents including sevelamer, lanthanum, calcium-magnesium combination and iron-based phosphate binders have been developed to overcome these limitations.

Sevelamer carbonate

Sevelamer is an ion-exchange resin that is commonly used as an alternative to calcium for phosphate binding. In addition to binding to phosphate, sevelamer has been shown to lower cholesterol, FGF-23, inflammatory markers, c-reactive protein and hemoglobin A1C and may improve endothelial function[34,35]. In hemodialysis patients, sevelamer attenuates the progression of CAC and aortic calcification compared to calcium[36-38] (Table 1). In two randomized controlled trials in incident hemodialysis patients, those who were treated with calcium had a greater risk of death compared to sevelamer[2,39]. However, a randomized study in prevalent hemodialysis patients did not show survival benefit associated with sevelamer use[40]. In non-dialysis CKD population, patients who were treated with sevelamer in order to keep serum phosphate within the normal range had better survival compared to those treated with calcium[41]. In another small randomized study in moderate CKD patients that compared calcium, sevelamer and lanthanum versus placebo revealed an increase in arterial calcification in all groups, however, the degree was highest in the calcium group[42]. It has been theorized that the use of phosphate binders in non-dialysis CKD may result in an increase in the availability of free calcium in the intestine. Similarly, when rosuvastatin, sevelamer and no drug were compared in a small randomized study in moderate CKD patients, a significant increase in CAC scores was observed in all three groups[43]. Despite the possible survival benefit, the use of phosphate binders may not be beneficial in reducing calcification burden in moderate CKD population. In order to justify the use of phosphate binders in non-dialysis CKD patients, more studies are required to confirm the beneficial or harmful effects.

Lanthanum carbonate

Lanthanum is a rare earth element that is as effective as aluminum and better than sevelamer in binding phosphate[44]. Long-term use of lanthanum in renal failure can result in an accumulation in various organs but without any obvious harmful effects[45,46]. Similar to sevelamer, the use of lanthanum in moderate CKD can lower FGF-23 levels[47]. In both uremic rats and dialysis patients, lanthanum attenuated the development of vascular calcification[48,49]. The data on patient-level outcomes are limited. A follow-up data on dialysis patients who were enrolled in the phase 3 study did not show survival benefit associated with lanthanum treatment. However, in a subgroup of patients > 65 years of age, those who received lanthanum carbonate appeared to have better survival compared to standard therapy[50]. The efficacy of lanthanum depends largely on the pills being chewed thoroughly prior to swallowing. Recently the company has developed the oral powder form that may work better in patients with problems with mastication.

Combined calcium acetate-magnesium carbonate

Both intracellular and extracellular magnesium are vital in preventing inflammation and oxidative stress. Decreased magnesium concentration is associated with impaired endothelial function, vasospasm and atherogenesis[51]. Increased severity of vascular calcification has been observed in hemodialysis and peritoneal dialysis patients with low normal magnesium levels[52]. *In vitro* studies and *in vivo* study in rodents demonstrated that increasing magnesium concentrations were protective against vascular calcification through upregulation of anti-calcification proteins[53-55]. In a study of 204 hemodialysis patients over a 24-wk follow-up, the European formulation of combined calcium-magnesium phosphate binder (calcium acetate 435 mg/magnesium carbonate 235 mg) was as efficacious as sevelamer in reducing serum phosphate without the side effect of increased serum ionized calcium. A small but significant increase in serum magnesium was observed. All patients were dialyzed against 0.5 mm magnesium dialysate and experienced no serious adverse events[56]. FGF-23 levels also decreased in the magnesium group[57]. Furthermore, a small observational study in 7 hemodialysis patients showed stabilization of CAC score after 18 mo of being on calcium-magnesium phosphate binder[58].

Iron-based phosphate binders

Recently food and drug administration (FDA) approved iron-based phosphate binder in the United States is sucroferric oxyhydroxide. Another preparation of iron-based phosphate binder, ferric citrate, is currently under review by the FDA. These drugs are as efficacious as sevelamer in lowering serum phosphate[59,60]. The use of iron-based phosphate binder is associated with an increase in serum ferritin and percent transferrin saturation leading to lesser requirement of intravenous iron and erythropoiesis-stimulating agents in dialysis patients[61]. Iron deficiency can increase FGF-23 levels and therefore iron-based phosphate binders can lower FGF-23[62]. In uremic rats, sucroferric oxyhydroxide prevented the development of vascular calcification[63]. More information regarding iron-based phosphate binders should become available within the next year.

ACTIVE VITAMIN D

Active vitamin D are primarily used for the treatment of

Table 1 Studies related to therapies that may influence arterial calcification and patient outcomes

Ref.	Subjects	*n*	Study type	Intervention	Follow-up (mo)	Results
Braun *et al*[38]	HD	114	RCT	Sevalamer *vs* calcium	12	↓ CAC and AC
Chertow *et al*[36]	HD	200	RCT	Sevelamer *vs* calcium	12	↓ CAC
Kakuta *et al*[37]	HD	183	RCT	Sevelamer *vs* calcium	12	↓ CAC
Suki *et al*[40]	HD	2103	RCT	Sevelamer *vs* calcium	19	↔ mortality
Block *et al*[2]	Incident HD	127	RCT	Sevelamer *vs* calcium	44	↓ mortality
Di Iorio *et al*[39]	Incident HD	466	RCT	Sevelamer *vs* calcium	24	↓ mortality
Block *et al*[42]	Non-dialysis CKD	148	RCT	Sevelamer, lanthanum, calcium *vs* placebo	9	↑ CAC and AC
Di Iorio *et al*[41]	Non-dialysis CKD	212	RCT	Sevelamer *vs* calcium	24	↓ mortality
Lemos *et al*[43]	Non-dialysis CKD	38	RCT	Rosuvastatin, sevelamer *vs* no drug	24	↔ CAC
Toussaint *et al*[49]	HD	45	RCT	Lanthanum *vs* calcium	18	↓ AC
Wilson *et al*[50]	HD	1354	RCT	Lanthanum *vs* calcium	27	↔ mortality
Spiegel *et al*[58]	HD	7	Observational	Combined magnesium-calcium	18	↔ CAC
Kalanter-Zadeh *et al*[111]	HD	58058	Retrospective	Paricalcitol *vs* no drug	24	↓ mortality
Naves-Diaz *et al*[112]	HD	16004	Retrospective	Alfacalcidol or calcitriol *vs* no drug	16	↓ mortality
Shoji *et al*[113]	HD	242	Prospective	Alfacalcidol *vs* no drug	61	↓ CVD mortality
Tentori *et al*[114]	HD	38066	Retrospective	Active vitamin D *vs* no drug	60	↓ mortality
Melamed *et al*[115]	Incident HD and PD	1007	Prospective	Calcitriol *vs* no drug	30	↓ mortality
Teng *et al*[116]	Incident HD	51037	Retrospective	Active D *vs* no drug	24	↓ mortality
Tentori *et al*[117]	Incident HD	14967	Retrospective	Calcitriol *vs* paricalcitol *vs* doxercalciferol *vs* no drug	37	↓ mortality in all active D groups compared to no drug
Kovesdy *et al*[118]	Non-dialysis CKD	520	Retrospective	Calcitriol *vs* no drug	24	↓ mortality
Shoben *et al*[119]	Non-dialysis CKD	1418	Retrospective	Calcitriol *vs* no drug	24	↓ mortality
Sugiura *et al*[120]	Non-dialysis CKD	665	Retrospective	Alfacalcidol *vs* no drug	55	↓ CVD events and mortality
Thadhani *et al*[75]	Non-dialysis CKD	227	RCT	Paricalcitol *vs* placebo	48	↔ left ventricular mass index
Tamez *et al*[76]	Non-dialysis CKD	196	RCT	Paricalcitol *vs* placebo	48	↓ left atrial volume index
Raggi *et al*[80]	HD	360	RCT	Cinacalcet + active D *vs* active D	12	↓ CAC and aortic valve calcification
Chertow *et al*[83]	HD	3883	RCT	Cinacalcet *vs* placebo	21	↔ CVD events or mortality
Hashiba *et al*[88]	HD	18	RCT	Etidronate *vs* no drug	6	↓ AC
Nitta *et al*[87]	HD	35	Observational	Etidronate	12	↓ CAC
Kawahara *et al*[91]	GP	108	RCT	Atorvastatin *vs* etidronate *vs* both	12	↓ thoracic and abdominal aortic plaques in combined therapy
Adirekkiat *et al*[33]	HD	32	Prospective	STS *vs* no drug	9	↓ CAC
Mathews *et al*[98]	HD	22	Observational	STS	5	↓ CAC

n: Number of patients; HD: Hemodialysis; PD: Peritoneal dialysis; CKD: Chronic kidney disease; RCT: Randomized controlled trial; CAC: Coronary calcification; AC: Aortic calcification; CVD: Cardiovascular disease; STS: Sodium thiosulfate.

hyperparathyroidism in CKD. In addition to lowering PTH, active vitamin D also stimulates calcium and phosphate absorption in the gastrointestinal tract and therefore can result in worsening hypercalcemia and hyperphosphatemia. Active vitamin D also reduces proteinuria, augments the response to erythropoietin and suppresses renin-angiotensin system[64-66]. The parent drug of active vitamin D is calcitriol or 1, 25-dihydroxyvitamin D3. The closely related analogs to calcitriol are alfacalcidol (1-alpha hydroxyvitamin D3) and doxercalciferol (1-alpha hydroxyvitamin D2). Both require 25-hydroxylation process in the liver prior to becoming active forms. Similar to the parent compound, alfacalcidol and doxercalciferol can precipitate hypercalcemia and hyperphosphatemia especially if given in high doses. Paricalcitol or 19-Nor-1-25-dihydroxyvitamin D2 was developed specifically for the treatment of hyperparathyroidism in CKD. Paricalcitol appears to act preferentially in the parathyroid glands and less so in the gastrointestinal tract[67]. In rodents with uremia, administration of calcitriol and doxercalciferol resulted in an increase in aortic calcification, whereas paricalcitol did not[68]. However when testing different doses of calcitriol and paricalcitol, both active vitamin D in high doses induced a similar degree of aortic calcification. Interestingly, in this study, lower doses of both calcitriol and paricalcitol seemed to be protective against vascular calcification[69]. The calcemic and phosphatemic effects of all forms of active vitamin D have been confirmed in a recent randomized crossover trial in hemodialysis patients that showed similar incidences of hyperphosphatemia and hypercalcemia among patients who received alfacalcidol or paricalcitol[70]. The increase in calcium and

phosphate load as a result of active vitamin D induced calcium and phosphate absorption is likely responsible for the development of vascular calcification. On the other hand, the direct effect of vitamin D on vascular wall appears to be positive. Active vitamin D can stimulate klotho and osteopontin expression in the arterial wall. Both of which help prevent vascular calcification[71]. This finding can probably explain the protective effect of low dose active vitamin D on vascular calcification. The development of vascular calcification associated with the use of active vitamin D is the result of systemic accumulation of calcium and phosphate rather than the local effect on arterial wall[72]. Therefore, low doses of active vitamin D that do not augment calcium and phosphate load may actually be protective against vascular calcification[23,69].

As for the beneficial effect of vitamin D on renin-angiotensin system, a study in rats with renal failure demonstrated that active vitamin D treatment could prevent left ventricular hypertrophy and myocardial fibrosis[73]. In an observational study in hemodialysis patients, treatment of hyperparathyroidism with intravenous calcitriol led to a decline in renin, angiotensin II and atrial natriuretic peptide levels associated with a decrease in left ventricular hypertrophy[74]. However, a recent randomized study in moderate CKD patients revealed only a non-significant trend toward a decrease in left ventricular mass index in the group of patients that received paricalcitol[75]. Nevertheless, subsequent analysis did demonstrate a significant decrease in left atrial volume index[76]. The lack of clear benefit of active vitamin D on cardiac hypertrophy may be related to the increase in FGF-23 in response to active vitamin D treatment. As for survival benefit of active vitamin D therapy in hemodialysis patients, several retrospective and observational studies have revealed a decrease in all-cause and cardiovascular mortality among patients who received active vitamin D regardless of PTH levels[77]. Details of these studies can be found in Table 1. The benefit seemed to be more pronounced in the low-dose range and among patients who received paricalcitol. At the present time, there is no published prospective randomized study that evaluates the effect of active vitamin D on survival in CKD population.

CALCIMIMETIC

Calcimimetic allosterically activates calcium-sensing receptors, thus can suppress PTH secretion without elevating serum calcium. Calcimimetic is used as an add-on to active vitamin D and phosphate binder in the treatment of hyperparathyroidism in CKD[78]. Currently, cinacalcet is the only calcimimetic drug available for this purpose. In nephrectomized rats, adding cinacalcet to active vitamin D helped decrease the severity of vascular calcification associated with high dose vitamin D treatment[79]. In a randomized study in 360 hemodialysis patients, the rate of progression of CAC and aortic valve calcification was reduced when cinacalcet was added to low dose active vitamin D compared to larger and varying doses of active vitamin D therapy alone[80,81]. Cinacalcet therapy also decreases FGF-23 levels[82]. However, significant benefits in terms of overall survival or cardiovascular events were not observed in a large randomized controlled trial in 3883 hemodialysis patients after 5 years of follow-up[83].

BISPHOSPHONATES

Bisphosphonates are synthetic analogs of inorganic pyrophosphate that have the ability to suppress bone resorption and therefore are commonly used in the treatment and prevention of osteoporosis in general population. The other important property of inorganic pyrophosphate is inhibition of calcium and phosphate crystal deposition in the bone matrix. Oral etidronate and intravenous pamidronate have been utilized in the treatment of calcific uremic arteriolopathy (CUA), a condition of wide spread small-vessel calcification that results in progressive cutaneous ulcer due to ischemia[84,85]. In uremic rats, daily pamidronate or etidronate therapies prevented aortic calcification[86]. In hemodialysis patients, oral and parenteral etidronate have been shown to delay the progression of CAC and aortic calcification[87,88]. However, this anti-calcification effect was not observed with the newer generation bisphosphonates including alendronate and ibandronate[89,90]. A recent randomized study in general population with hypercholesterolemia revealed the combined regimen of daily atorvastatin and etidronate reduced atherosclerotic plaque burden in thoracic and abdominal aorta[91]. It was suggested that etidronate was responsible for the regression of calcified plaques in abdominal aorta while atorvastatin attenuating the non-calcified plaques in thoracic aorta. Worsening adynamic bone disease with the use of bisphosphonates in the setting of CKD is of concern, thus recent Kidney Disease Improving Global Outcomes recommendation advised against prescribing bisphosphonates in patients with an eGFR < 30 mL/min per 1.73 m^2[92].

SODIUM THIOSULFATE

Sodium thiosulfate (STS) is a reducing, chelating and anti-oxidant agent that is useful as an antidote in cyanide poisoning. STS also has the ability to chelate calcium in precipitated minerals forming calcium thiosulfate that is more soluble than calcium oxalate and calcium phosphate. Thus its use has been expanded in conditions with increased calcification burden such has nephrolithiasis, metastatic calcification, tumoral calcinosis and CUA[93-96]. In a large observational study in 172 hemodialysis patients with CUA, intravenous STS therapy resulted in clinical improvement in most patients[96]. In uremic rats, parenteral administration of STS has been shown to prevent the development of vascular calcification[97]. Twice weekly intravenous STS therapy in hemodialysis patients was able to delay the rate of progression of CAC after six months compared to the non-treatment group but with a significant decline in hip bone mineral density in one study[33,98]. Long-term intravenous or intraperitoneal

STS therapy in dialysis patients are well tolerated with minimal side effects[33,96,99]. The mechanism by which STS reduces calcification burden is poorly understood. It has been suggested that mechanisms other than calcium chelation are responsible for the decreased calcification burden[94,100].

VITAMIN K

There are two types of naturally occurring vitamin K: vitamin K1 (phylloquinone) found mostly in green leafy vegetables and vegetable oils and vitamin K2 (menaquinone) found in animals, bacteria, and fermented food such as cheese and natto. Five to twenty five percent of ingested vitamin K1 can be converted to vitamin K2 in the body. Colonic bacteria can synthesize vitamin K2 and antibiotics that interfere with the growth of these colonic flora impair vitamin K2 production[101]. Vitamin K is required as a co-factor in the process of gamma-carboxylation of several extracellular matrix proteins turning inactive uncarboxylated proteins into active carboxylated forms. Prothrombin, coagulation factors 7, 9 and 10 require vitamin K1 for their carboxylation processes; whereas, osteocalcin and matrix gla-protein require vitamin K2[102]. Osteocalcin is important in bone mineralization; therefore, menaquinone is used in the treatment of osteoporosis. Matrix gla-protein is a calcification inhibitor that plays important role in the prevention of arterial calcification. Warfarin, an antagonist to vitamin K, not only inhibits coagulation but long-term use can also promote arterial calcification[103]. Vitamin K deficiency is common in end-stage renal disease patients and the accumulation of inactive form of matrix gla-protein is associated with an increase in the severity of arterial calcification and mortality[104,105]. High menaquinone intake is also associated with reduced CAC and coronary heart disease in general population[106,107]. Vitamin K1 or K2 supplementation especially in high doses can significantly decrease the amount of inactive matrix gla-protein in hemodialysis patients[108]. In CKD rats treated with warfarin, high dietary vitamin K1 can blunt the development of vascular calcification[109]. The favorable impact of vitamin K1 on vascular calcification is likely depending on the conversion of vitamin K1 to vitamin K2 in the body. A prospective randomized controlled trial to evaluate the effect vitamin K1 supplementation on the progression of CAC (VitaVasK trial) in hemodialysis patients is currently ongoing[110].

In conclusion, the currently available treatment options for arterial calcification in CKD include non-calcium containing phosphate binders, low doses of active vitamin D, calcimimetic agent and perhaps bisphosphonates, vitamin K and STS. Preliminary data on bisphosphonates, vitamin K and STS are encouraging but larger studies on efficacy and outcomes are needed.

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