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

Thanh-Mai Vo, Sinee Disthabanchong

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 and high dose vitamin D therapy 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 the calcification burden. Data on diabetes and blood pressure controls as well as smoking cessation on cardiovascular outcomes in CKD population are limited. Available treatment strategies 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.

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.
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[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-OH2-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]. Kidney transplanta- tion 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[21,22]. 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[23,24]. 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[25,26]. 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 has linked the amount of calcium intake derived from calcium-containing phosphate binders to the severity of vascular calcification. Never 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. In hemodialysis patients, sevelamer attenuates the progression of CAC and aortic calcification compared to calcium (Table 1). In two randomized controlled trials in incident hemodialysis patients, those who were treated with calcium had a higher risk of death compared to sevelamer. However, a randomized study in prevalent hemodialysis patients did not show survival benefit associated with sevelamer use. 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. 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. 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. 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. Long-term use of lanthanum in renal failure can result in an accumulation in various organs but without any obvious harmful effects. Similar to sevelamer, the use of lanthanum in moderate CKD can lower FGF-23 levels. In both uremic rats and dialysis patients, lanthanum attenuated the development of vascular calcification. 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. 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. Increased severity of vascular calcification has been observed in hemodialysis and peritoneal dialysis patients with low normal magnesium levels. 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. 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 dialedyzed against 0.5 mm magnesium dialysate and experienced no serious adverse events. FGF-23 levels also decreased in the magnesium group. Furthermore, a small observational study in 7 hemodialysis patients showed stabilization of CAC score after 18 mo of being on calcium-magnesium phosphate binder.

**Iron-based phosphate binders**
Recently food and drug administration (FDA) approved iron-based phosphate binder in the United States is sucralfate. 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. 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. Iron deficiency can increase FGF-23 levels and therefore iron-based phosphate binders can lower FGF-23 levels. In uremic rats, sucralfate oxyhydroxide prevented the development of vascular calcification. 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[5] | HD | 114 | RCT | Sevelamer vs calcium | 12 | ↓ CAC and AC |
| Chertow et al[9] | HD | 200 | RCT | Sevelamer vs calcium | 12 | ↓ CAC |
| Kakuta et al[20] | HD | 183 | RCT | Sevelamer vs calcium | 12 | ↓ CAC |
| Suki et al[14] | HD | 2103 | RCT | Sevelamer vs calcium | 19 | ↓ mortality |
| Block et al[13] | Incident HD | 127 | RCT | Sevelamer vs calcium | 44 | ↓ mortality |
| Di Iorio et al[6] | Incident HD | 466 | RCT | Sevelamer vs calcium | 24 | ↓ mortality |
| Block et al[16] | Non-dialysis CKD | 148 | RCT | Sevelamer, lanthanum, calcium vs placebo | 9 | ↓ CAC and AC |
| Di Iorio et al[6] | Non-dialysis CKD | 212 | RCT | Sevelamer vs calcium | 24 | ↓ mortality |
| Lemons et al[26] | Non-dialysis CKD | 38 | RCT | Rosuvastatin, sevelamer vs no drug | 24 | ↔ CAC |
| Toussaint et al[9] | HD | 45 | RCT | Lanthanum vs calcium | 18 | ↓ AC |
| Wilson et al[27] | HD | 1354 | RCT | Lanthanum vs calcium | 27 | ↔ mortality |
| Spiegel et al[5] | HD | 7 | Observational | Combined magnesium-calcium | 18 | ↓ mortality |
| Kalarnt-Zadeh et al[11] | HD | 58058 | Retrospective | Paricalcitol vs no drug | 24 | ↓ mortality |
| Naves-Diaz et al[12] | HD | 16004 | Retrospective | Alfacalcidol or calcitriol vs no drug | 16 | ↓ mortality |
| Sjoji et al[15] | HD | 242 | Prospective | Alfacalcidol vs no drug | 61 | ↓ CVD mortality |
| Tentori et al[16] | HD | 38066 | Retrospective | Active vitamin D vs no drug | 60 | ↓ mortality |
| Melamed et al[26] | Incident HD and PD | 1007 | Prospective | Calcitriol vs no drug | 30 | ↓ mortality |
| Teng et al[27] | Incident HD | 51037 | Retrospective | Active D vs no drug | 24 | ↓ mortality |
| Tentori et al[16] | Incident HD | 14967 | Retrospective | Calcitriol vs paricalcitol vs doxercalciferol vs no drug | 37 | ↓ mortality in all active D groups compared to no drug |
| Kovessy et al[10] | Non-dialysis CKD | 520 | Retrospective | Calcitriol vs no drug | 24 | ↓ mortality |
| Shoben et al[19] | Non-dialysis CKD | 1418 | Retrospective | Calcitriol vs no drug | 24 | ↓ mortality |
| Sugiura et al[20] | Non-dialysis CKD | 665 | Retrospective | Alfacalcidol vs no drug | 55 | ↓ CVD events and mortality |
| Thadhani et al[21] | Non-dialysis CKD | 227 | RCT | Paricalcitol vs placebo | 48 | ↔ left ventricular mass index |
| Tamet et al[22] | Non-dialysis CKD | 196 | RCT | Paricalcitol vs placebo | 48 | ↓ left atrial volume index |
| Raggi et al[23] | HD | 360 | RCT | Cinacalcet + active D vs active D | 12 | ↓ CAC and aortic valve calcification |
| Chertow et al[9] | HD | 3883 | RCT | Cinacalcet vs placebo | 21 | ↓ CVD events or mortality |
| Hashiba et al[24] | HD | 18 | RCT | Etidronate vs no drug | 6 | ↓ AC |
| Nitta et al[25] | HD | 35 | Observational | Etidronate | 12 | ↓ CAC |
| Kawahara et al[26] | GP | 108 | RCT | Atorvastatin vs etidronate vs both | 12 | ↓ thoracic and abdominal aortic plaques in combined therapy |
| Adirekkit et al[27] | HD | 32 | Prospective | STS vs no drug | 9 | ↓ CAC |
| Mathews et al[28] | 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
progression of CAC and aortic valve calcification was associated with high dose vitamin D treatment. In nephrectomized rats, adding cinacalcet to active vitamin D helped decrease the severity of vascular calcification [71].

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 widespread 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 m² [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 as nephrolithiasis, metastatic calcification, tumoral calcinosis and CUA [84,85]. In a large observational study in 172 hemodialysis patients with CUA, intravenous STS therapy resulted in clinical improvement in most patients [93]. In uremic rats, parenteral administration of STS has been shown to prevent the development of vascular calcification [94]. 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 [95-97]. 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 (phyloquinone) 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 percent of ingested vitamin K1 can be converted to vitamin K2 in the body. Colonic bacteria can synthesize vitamin K2 and antioxidants that interfere with the growth of these colonic flora impair vitamin K2 production[1]. 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.

REFERENCES

1. Foley RN, Parfrey PS, Saran MK. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32: S112-S119 [PMID: 9820470]
2. Block GA, Raggi P, Bellasi A, Koivela L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 2007; 71: 438-441 [PMID: 17200680 DOI: 10.1038/sj.ki.5002059]
3. Goodman WG, Goldfin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000; 342: 1478-1483 [PMID: 10816185 DOI: 10.1056/NEJM20001513422055]
4. Budoff MJ, Rader DJ, Reilly MP, Mohler ER, Lash J, Yang W, Rosen L, Glenn M, Teal V, Feldman HI. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. Am J Kidney Dis 2011; 58: 519-526 [PMID: 21783289 DOI: 10.1053/j.jkdd.2011.04.024]
5. Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, Klag MJ. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHICoE Study. J Am Soc Nephrol 2002; 13: 1918-1927 [PMID: 12089399]
6. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant 2003; 18: 1731-1740 [PMID: 12937218]
7. Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, Appleby D, Nessel L, Bellovich K, Chen J, Hamm L, Gadebeku C, Horwitz E, Townsend RR, Anderson CA, Lash JP, Hsu CY, Leonard MB, Wolf M. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 2011; 79: 1370-1378 [PMID: 21389978 DOI: 10.1038/ki.2011.47]
8. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukushima S, Yamashita T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. JBIIR 2004; 19 (3): 429-435
9. Chatrirsak K, Vipattawat K, Assanathan M, Nongnuch A, Ingsathit A, Domrongkitchaiporn S, Sumethkul V, Ditha-Banchong S. Mineral metabolism and outcomes in chronic kidney disease stage 2-4 patients. BMC Nephrol 2013; 14: 14 [PMID: 23324569 DOI: 10.1186/1471-2369-14-14]
10. Paul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguilon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadebeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moo EOW, Kuoro O-M, Kusek JW, Koane MG, Wolf M. FGF23 induces left ventricular hypertrophy. J Clin Invest 2011; 121: 4393-4408 [PMID: 21985788 DOI: 10.1172/JCI61122]
11. Scialla J, Xie H, Rahman M, Anderson AH, Isakova T, Ojo A, Zhang X, Nessel L, Hamano T, Grunwald JE, Raj DS, Yang W, He J, Lash JP, Go AS, Kusek JW, Feldman H, Wolf M. Fibroblast growth factor 23 and cardiovascular events in CKD. J Am Soc Nephrol 2014; 25: 349-360 [PMID: 24158986 DOI: 10.1681/ASN.2013050465]
12. Jimbo R, Kakwakami-Mori F, Mu S, Hirohama D, Majtan B, Shimizu Y, Yatomi Y, Fukushima S, Fujita T, Shimosawa T. Fibroblast growth factor 23 accelerates phosphate-induced vascular calcification in the absence of Klotho deficiency. Kidney Int 2014; 85: 1103-1111 [PMID: 24088960 DOI: 10.1038/ki.2013.332]
13. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwald S, He J, Schwartz S, Lo J, Ojo A, Sondeheimer J, Hsu CY, Lash J, Leonard M, Kusek JW, Feldman H, Wolf M. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA 2011; 305: 2432-2439 [PMID: 21389978 DOI: 10.1038/ki.2011.47]
2012; Goto S, Fujii H, Hamada Y, Kobayashi A, Cebi D, Altiparmak MR, Akman C, Ataman R, 2011; Sumethkul V, Ingsathit A, Domrong 2009; 2007; 2009; Lu TS, Molostvov G, Lee C, Lam FT, Zehnder D, Lau WL, Reilly MP, Isakova T, Yang HY, Vo TM

kidney transplantation: relationship with osteoprotegerin

rad G. Evolution of coronary artery calcifications following

Bargnoux AS, Wolf M. Fibroblast growth factor 23 is not associated with

Crouthamel MH, Chavkin NW, Rahman M, Wahl P, Amaral

Changes of coronary calcification after kidney transplantation: a cross-sectional study.

Kidney Int 2004; 66: 226-229 [PMID: 15569318 DOI: 10.1111/j.1523-1755.2004.660015.x]

Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Böhm R, Metzger T, Wanner C, Jahnchen-Dechent W, Floege J. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lanec 2003; 361: 827-833 [PMID: 12624205 DOI: 10.1001/s0140-6736(03)12710-9

Shanahan CM, Cary NR, Salisbury JR, Proudfoot D, Weissberg PL, Edmonds ME. Medial localization of mineralization-regulating proteins in association with Mönckeberg’s sclerosis: evidence for smooth muscle cell-mediated vascular calcification. Circulation 1999; 100: 2168-2167 [PMID: 10571976]

Koh N, Fujimori T, Nishiguchi S, Tamori A, Shiomi S, Nakatani T, Sugimura K, Kishimoto T, Kinoshita S, Kuroki T, Nabeshima Y. Severely reduced production of klotho in human chronic renal failure patients. Biochem Biophys Res Commun 2001; 280: 1015-1020 [PMID: 11162628 DOI: 10.1006/bbrc.2000.4226]

Komaba H, Goto S, Fuji H, Hamada Y, Kobayashi A, Shibuuya K, Tominaga Y, Otsuki N, Nibu K, Nakagawa K, Tsugawa N, Okano T, Kitazawa R, Fukagawa M, Kita T. Depressed expression of Klotho and FGF receptor 1 in hyperparathyroid glands from uremic patients. Kidney Int 2010; 77: 232-238 [PMID: 19890272 DOI: 10.1038/ki.2009.414]

Lim K, Lu TS, Molostov G, Lee C, Lam FT, Zehnder D, Hsiao LL. Vascular klotho deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. Circulation 2012; 125: 2243-2255 [PMID: 22926235 DOI: 10.1161/CIRCULATIONAHA.111.053405]

Hu MC, Shi M, Zhang J, Quinones H, Griffith C, Kuro-o M, Moe OW. Klotho deficiency causes vascular calcification in chronic kidney disease. J Am Soc Nephrol 2011; 22: 124-136 [PMID: 21115613 DOI: 10.1681/ASN.2009121311]

Scialla JJ, Lau WL, Reilly MP, Isaková T, Yang HY, Crouthamel MH, Chavkin NW, Rahman M, Wahl P, Amaral AP, Hamano T, Master SR, Nessel L, Chai B, Xie D, Kallem RR, Chen J, Lash JP, Kusek JW, Budoff MJ, Giaccelli CM, Wolf M. Fibroblast growth factor 23 is not associated with and does not induce arterial calcification. Kidney Int 2013; 83: 1159-1168 [PMID: 23389416 DOI: 10.1038/ki.2013.3]

Oschatz E, Benesch T, Kodras K, Hoffmann U, Haas M. Changes of coronary calcification after kidney transplantation. Am J Kidney Dis 2006; 48: 507-513 [PMID: 16660198]

Bargnoux AS, Dupuy AM, Garrigue V, Jaussent I, Galhide G, Badieu S, Savicar I, Deloize S, Vernhet H, Cristol JP, Moukad G. Evolution of coronary artery calcifications following kidney transplantation: relationship with osteoprotegerin

levels. Am J Transplant 2009; 9: 2571-2579 [PMID: 19775319 DOI: 10.1111/j.1600-6143.2009.02814.x]

Mazzaferro S, Pasquali M, Taggi F, Baldinelli M, Conte C, Muci ML, Pirozzi N, Carbone I, Francone M, Pugliese F. Progression of coronary artery calcification in renal transplantation and the role of secondary hyperparathyroidism and inflammation. Clin J Am Soc Nephrol 2009; 4: 685-690 [PMID: 19211668 DOI: 10.2215/CJN.03930808]

Maréchal C, Coche E, Goffin E, Dragean A, Schlieper G, Nguyen P, Floege J, Kanaan N, Devuyst O, Jadoul M. Progression of coronary artery calcification and thoracic aorta calcification in kidney transplant recipients. Am J Kidney Dis 2012; 59: 250-269 [PMID: 21944666 DOI: 10.1053/j.kid.2011.07.019]

Seyahi N, Cebi D, Altıparmak MR, Akman C, Ataman R, Pekmezci S, Serdenegcti K. Progression of coronary artery calcification in renal transplant recipients. Nephrol Dial Transplant 2012; 27: 2101-2107 [PMID: 21965591 DOI: 10.1093/ndt/gfr558]

Schmermund A, Achenbach S, Budde T, Buziashiyli V, Förster A, Friedrich G, Henein M, Kerkhoff G, Knollmann F, Kukharzuk V, Lahiri A, Leischik R, Mosborge W, Schaeff M, Siffert W, Steinhegen-Thiessen E, Sinaiyin V, Vego A, Wiedeking B, Erbel R. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of coronary artery atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation 2006; 113: 427-437 [PMID: 16415377 DOI: 10.1161/CIRCULATIONAHA.105.568147]

Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E. The st. Francis Heart Study randomized clinical trial. J Am Coll Cardiol 2005; 46: 166-172 [PMID: 15992652 DOI: 10.1016/j.jacc.2005.02.089]

Direrrekiat S, Sumethkul V, Ingsathit A, Domrongkitchaiporn S, Phakdeeikitcharoent K, Kantachuevsi S, Kittayakara C, Klyprayong P, Disthabanchong S. Sodium thiosulfate delays the progression of coronary artery calcification in haemodialysis patients. Nephrol Dial Transplant 2010; 25: 1923-1929 [PMID: 20083471 DOI: 10.1093/ndt/gfp755]

Vlassara H, Uribarri J, Cai W, Goodman S, Pyzik R, Post J, Grojean F, Woodward M, Striker GE. Effects of sevelamer on HbA1c, inflammation, and advanced glycation end products in diabetic kidney disease. Clin J Am Soc Nephrol 2012; 7: 934-942 [PMID: 22461535 DOI: 10.2215/CJN.12991211]

Guida B, Cataldi M, Riccio E, Grumetto L, Pota A, Borrelli S, Memoli A, Barbato F, Argentino G, Salerno G, Memoli B. Plasma p-cresol lowering effect of sevelamer in peritoneal dialysis patients: evidence from a Cross-Sectional Observational Study. PloS One 2013; 8: e73558 [PMID: 24015307 DOI: 10.1371/journal.pone.0073558]

Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002; 62: 245-252 [PMID: 12081584 DOI: 10.1046/j.1523-1755.2002.00434.x]

Kakuta T, Tanaka R, Hyodo T, Suzuki H, Kanai G, NagaoKA M, Takahashi H, Hirawa N, Oogushi Y, Miyata T, Kobayashi H, Fukagawa M, Saito A. Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients. Am J Kidney Dis 2011; 57: 422-431 [PMID: 21239096 DOI: 10.1053/j.kid.2010.10.055]

Braun J, Asmus HG, Holzer H, Brunchorst R, Krause R, Schulz W, Neumayer HH, Raggi P, Bonner J. Long-term comparison of a calcium-free phosphate binder and calcium carbonate in dialysis patients with cardiovascular calcification. Clin Nephrol 2004; 62: 104-115 [PMID: 15356967]

Di Iorio B, Molony D, Bell C, Cucciendi E, Bellizzi V, Russo
D. Bellasi A. Sevelamer versus calcium-based phosphate binders in moderate-to-severe end-stage renal disease: a randomized, controlled, double-blind, placebo-controlled study. *Journal of the American Society of Nephrology* 2007; 18: 2567-2571 [PMID: 21436379 DOI: 10.1093/asn/jgl444]

40 Wilson R, Zhang P, Smyth M, Pratt R. Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. *Curr Med Res Opin* 2009; 25: 3021-3028 [PMID: 19485495 DOI: 10.1111/j.1473-0399.2009.02998]

41 Maier JA. Low magnesium and atherosclerosis: an evidence-based link. *Mol Aspects Med* 2003; 24: 137-146 [PMID: 12537993]

42 Ishimura E, Okuno S, Kitakami K, Tsuchida T, Yamakawa T, Shioi A, Inaba M, Nishizawa Y. Significant association between the presence of peripheral vascular calcification and lower serum magnesium in hemodialysis patients. *Clinical Nephrology* 2007; 68: 222-227 [PMID: 17964989]

43 Montezano AC, Zimmerman D, Yusuf H, Burger D, Chignalia AZ, Wadhera V, Van Leuwen FN, Touyz RM. Vascular smooth muscle cell differentiation to an osteogenic phenotype involves TRPM7 modulation by magnesium. *Hypertension* 2010; 56: 453-462 [PMID: 20696983 DOI: 10.1161/HYPERTENSIONAHA.110.152058]

44 Louvet L, Büchel J, Steppan S, Passlick-Deetjen J, Massey ZA. Magnesium prevents phosphate-induced calcification in human aortic vascular smooth muscle cells. *Nephrol Dial Transplant* 2013; 28: 869-878 [PMID: 23229924 DOI: 10.1093/ndt/gfs520]

45 de Schutter TM, Behets GJ, Gery P, Peter ME, Steppan S, Gundlach L, Passlick-Deetjen J, D’Haese PC, Neven E. Effect of a magnesium-based phosphate binder on medial calcification in a rat model of uremia. *Kidney Int* 2013; 83: 1109-1117 [PMID: 23466515 DOI: 10.1038/ki.2013.34]

46 de Francisco AL, Leidig M, Covic AC, Ketteler M, Benedyk-Lorenz E, Mirescu GM, Scholz C, Ponce P, Passlick-Deetjen J. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in hemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. *Nephrol Dial Transplant* 2010; 25: 3707-3717 [PMID: 20530499 DOI: 10.1093/ndt/gfq292]

47 Covic A, Passlick-Deetjen J, Kroczyk M, Büchges-Seraphin B, Ghenu A, Ponce P, Marzrell B, de Francisco AL. A comparison of calcium acetate/magnesium carbonate and sevelamer hydrochloride effects on fibroblast growth factor-23 and bone markers: post hoc evaluation from a controlled, randomized study. *Nephrol Dial Transplant* 2013; 28: 2383-2392 [PMID: 23787550 DOI: 10.1093/ndt/gft182]

48 Spiegel DM, Farmer B. Long-term effects of magnesium carbonate on coronary artery calcification and bone mineral density in hemodialysis patients: a pilot study. *Hemodial Int* 2009; 13: 453-459 [PMID: 19469885 DOI: 10.1111/j.1525-139X.2009.00364.x]

49 Wüthrich RP, Conchol M, Covic A, Gaillard S, Chong E, Tumlin JA. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. *J Am Soc Nephrol* 2013; 8: 280-289 [PMID: 23124782 DOI: 10.2215/CJN.08230811]

50 Yokoyama K, Hirakata H, Akiba T, Sawada K, Kumagai Y. Effect of oral JTT-751 (ferric citrate) on hyperphosphatemia and phosphate binder PA21 in hemodialysis patients. *Clinical J Am Soc Nephrol* 2013; 8: 79-87 [PMID: 23566203 DOI: 10.2215/JNNR.540729]

51 Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res* 2013; 28: 1793-1803 [PMID: 23505075 DOI: 10.1002/jbmr.1923]

52 Phan O, Maillard M, Peregues C, Mordasini D, Stehle JC, Funk F, Burnier M. PA21, a new iron-based non-calcium phosphate binder, prevents vascular calcification in chronic renal failure rats. *Journal of Nephrology Renovasc Dis* 2013; 6: 79-87 [PMID: 23566203 DOI: 10.2215/JNNR.540729]

53 Icardi A, Paolotti E, De Nicola L, Mazzaferrro S, Russo R, Cozzolino M. Renal anaemia and EPO hyporesponsiveness associated with vitamin D deficiency: the potential role of inflammation. *Nephrol Dial Transplant* 2013; 28: 1672-1679 [PMID: 23468534 DOI: 10.1093/ndt/gft021]

54 de Borst MH, Hajhosseiny R, Tamez H, Wenger J, Thadhani R, Goldsmith D. Active vitamin D treatment for reduction of residual proteinuria: a systematic review. *J Am Soc Nephrol* 2013; 24: 1863-1871 [PMID: 23929770 DOI: 10.1681/ASN.2013030203]

55 Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the
Vo TM et al. Therapies for arterial calcification in chronic kidney disease

renal-angiotensin system. *Clin Invest* 2002; 110: 229-238 [PMID: 12122115 DOI: 10.1172/JCI15219]

67 Sprague SM, Llach F, Amdahl M, Taccetta C, Battile D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int* 2003; 63: 1485-1490 [PMID: 12631565 DOI: 10.1046/j.1523-1755.2003.00878.x]

68 Mizobuchi M, Finch JL, Martin DR, Slatopolsky E. Differential effects of vitamin D receptor activators on vascular calcification in uremic rats. *Kidney Int* 2007; 72: 709-715 [PMID: 17597697 DOI: 10.1038/sj.ki.5002406]

69 Mathew S, Lund RJ, Chaudhary LR, Geurs T, Hruska KA. Vitamin D receptor activators can protect against osteoporosis. *J Am Soc Nephrol* 2008; 19: 1509-1519 [PMID: 18448587 DOI: 10.1681/ASN.20070809092]

70 Hansen D, Rasmussen K, Danilenisen H, Meyer-Hofmann H, Bacevicus E, Lauridsen TG, Madsen JK, Tougaard BG, Markmann P, Thye-Roenn P, Nielsen JE, Kreiner S, Brand L. No difference among alfacalcidol and paricalcitol in the treatment of secondary hyperparathyroidism in hemodialysis patients: a randomized crossover trial. *Kidney Int* 2011; 80: 841-850 [PMID: 21832679 DOI: 10.1111/j.1523-1755.2011.12266]

71 Lau WL, Leaf EM, Hu MC, Takeo MM, Kuro-o M, Moe OW, Giachelli CM. Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet. *Kidney Int* 2012; 82: 1261-1270 [PMID: 22932118 DOI: 10.1038/ki.2012.322]

72 Lomashvili KA, Wang X, O'Neill WC. Role of local versus systemic vitamin D receptors in vascular calcification. *Arterioscler Thromb Vasc Biol* 2014; 34: 146-151 [PMID: 24202304 DOI: 10.1161/ATVBAHA.133.320255]

73 Panizo S, Barrios-Vázquez S, Naves-Díaz M, Carrillo-López R, Monney P, Nguyen HV, Pyykkö H, Descombes E. Rapid improvement of calciphylaxis after intravenous pamidronate therapy in a patient with chronic renal failure. *Nephrol Dial Transplant* 2012; 27: 784-790 [PMID: 21730210 DOI: 10.1093/ndt/gfr384]

74 Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Fleoje J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012; 367: 2482-2494 [PMID: 23121574 DOI: 10.1056/NEJMoa1205624]

75 Monney P, Nguyen HV, Pyykkö H, Descombes E. Rapid improvement of calciphylaxis after intravenous pamidronate therapy in a patient with chronic renal failure. *Nephrol Dial Transplant* 2012; 21: 2130-2132 [PMID: 22317761 DOI: 10.1093/ndt/gfr391]

76 Shiraiishi N, Kitamura K, Miyoshi T, Adachi M, Kohda Y, Nonoguchi H, Misumi S, Maekawa Y, Murayama T, Tomita M, Tomita K. Successful treatment of a patient with severe calcific ureteric arteriolyopathy (calciphylaxis) by etidronate disodium. *Am J Kidney Dis* 2006; 48: 151-154 [PMID: 16797398 DOI: 10.1053/j.ajkd.2006.04.062]

77 Lomashvili KA, Monier-Faugere MC, Wang X, Malluche HH, O'Neill WC. Effect of bisphosphonates on vascular calcification and bone metabolism in experimental renal failure. *Kidney Int* 2009; 75: 617-625 [PMID: 19129793 DOI: 10.1038/ki.2008.646]

78 Nitta K, Akita T, Suzuki K, Uchida K, Watanabe R, Majima K, Aoki T, Nishi E. Effects of cyclic intermittent etidronate therapy on coronary artery calcification in patients receiving long-term hemodialysis. *Am J Kidney Dis* 2004; 44: 680-688 [PMID: 15384019]

79 Hashiba H, Aizawa S, Tamura K, Shigematsu T, Kogo H. Inhibitory effects of etidronate on the progression of vascular calcification in hemodialysis patients. *Ther Apher Dial* 2004; 8: 241-247 [PMID: 15154878 DOI: 10.1111/j.1528-8661.2004.00136.x]

80 Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Effect of alendronate on vascular calcification in CKD stages 3 and 4: a pilot randomized controlled trial. *Am J Kidney Dis* 2010; 56: 57-68 [PMID: 20347511 DOI: 10.1053/j.jkd.2009.12.039]

81 Tankó LB, Qin G, Alexandersen P, Bagger YZ, Christiansen C. Effective doses of ibandronate do not influence the 3-year progression of aortic calcification in elderly osteoporotic women. *Osteoporos Int* 2005; 16: 184-190 [PMID: 15197541 DOI: 10.1007/s00198-005-1662-x]

82 Kawahara T, Nishikawa M, Kawahara C, Inazu T, Sakai K, Suzuki G. Atorvastatin, etidronate, or both in patients at risk for arterial calcification in chronic kidney disease. *Kidney Int* 2007; 71: 1483-1490 [PMID: 17387306 DOI: 10.1038/ki.2006.137]

83 L. No difference between alfacalcidol and paricalcitol in the treatment of secondary hyperparathyroidism in hemodialysis patients: a randomized crossover trial. *Kidney Int* 2011; 80: 841-850 [PMID: 21832679 DOI: 10.1111/j.1523-1755.2011.12266]

84 Duranton F, Rodríguez-Ortiz ME, Duny U, Rodriguez M, Daüres JP, Argüelles A. Vitamin D treatment and mortality in chronic kidney disease: a systematic review and meta-analysis. *Am J Nephrol* 2013; 37: 239-248 [PMID: 23467111 DOI: 10.1159/000346846]

85 Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Sunyaga MI, Herzog C, Cunningham J, Abu-Alfa AK, Messa P, Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCay LC, Zani VJ, Olson KA, Drüeke TB, Goodman WG. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; 350: 1516-1525 [PMID: 15071126 DOI: 10.1056/NEJMoa031653]

86 De Schutter TM, Behets GJ, Jung S, Neven E, D’Haeze PC, Querfeld U. Restoration of bone mineralization by cinacalcet is associated with a significant reduction in calcitriol-induced vascular calcification in uremic rats. *Calcif Tissue Int* 2012; 91: 307-315 [PMID: 22926202 DOI: 10.1007/s00223-012-9635-0]

87 Raggi P, Chertow GM, Torres PU, Csáky B, Nasso A, Nossuli K, Moustafa M, Goodman WG, Lopez N, Downey G, Dehmel B, Fleoje J. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant* 2011; 26: 1527-1539 [PMID: 21480300 DOI: 10.1093/ndt/gfr725]

88 Ureña-Torres P, Bridges I, Christiano C, Cournoyer SH, Cooper K, Farouk M, Kopyt NP, Rodriguez M, Zehnder D, Covic A. Efficacy of cinacalcet with low-dose vitamin D in incident hemodialysis subjects with secondary hyperparathyroidism. *Nephrol Dial Transplant* 2013; 28: 1241-1254 [PMID: 23328710 DOI: 10.1093/ndt/gft686]

89 Koizumi M, Komaba H, Nakanishi S, Fujimori A, Fukagawa M. Cinacalcet treatment and serum FGF23 levels in haemodialysis patients with secondary hyperparathyroidism. *Nephrol Dial Transplant* 2012; 27: 680-688 [PMID: 21730210 DOI: 10.1093/ndt/gfr384]
high risk for atherosclerotic aortic plaques: a randomized, controlled trial. 
Circulation 2013; 127: 2327-2335 [PMID: 23658438 DOI: 10.1161/CIRCULATIONAHA.113.015344]

92 Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? Kidney Int 2013; 83: 377-383 [PMID: 23325075 DOI: 10.1038/ki.2012.425]

93 Kyriakopoulou G, Kontogianni K. Sodium thiosulfate treat- ment of tumoral calcinosis in patients with end-stage renal disease. Ren Fail 1990; 12: 213-219 [PMID: 2108084]

94 Asplin JR, Donahue SE, Lindeman C, Michalenka A, Strutz KL, Bushinsky DA. Thiosulfate reduces calcium phosphate nephrolithiasis. J Am Soc Nephrol 2009; 20: 1246-1253 [PMID: 19369406 DOI: 10.1681/ASN.2008070754]

95 Christie M, Roscoe J, Cher J, Inparajah M, Vaughan-Neil T, Nagai G, Ng P, Fung J, Ting R, Tam P, Sikaneta T. Treatment of a hemodialysis patient with pulmonary calcification-associated progressive respiratory failure with sodium thio- sulfate. Transplantation 2013; 96: e1-e2 [PMID: 23807461 DOI: 10.1097/TP.0b013e3182858502]

96 Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Laceron E, Fagundes-Abraham L. Sodium thiosulfate therapy for calcific uremic arteriolopathy. Clin J Am Soc Nephrol 2013; 8: 1162-1170 [PMID: 23520341 DOI: 10.2215/CJN.09880912]

97 Pasch A, Schaffner T, Hueynd-Do U, Frey BM, Frey FJ, Farese S. Sodium thiosulfate prevents vascular calcifications in ure- mic rats. Kidney Int 2008; 74: 1444-1453 [PMID: 18816888]

98 Mathews SJ, de Las Fuentes L, Podaralla P, Cabellon A, Zheng S, Bierhals A, Speece K, Slatopolsky E, Davila-Roman VG, Delmex JA. Effects of sodium thiosulfate on vascular calcification in end-stage renal disease: a pilot study of feasibility, safety and efficacy. Am J Nephrol 2013; 33: 131-138 [PMID: 21242673 DOI: 10.1159/000323530]

99 Mataic D, Bastani B. Intraperitoneal sodium thiosulfate for the treatment of calciphylaxis. Ren Fail 2006; 28: 361-363 [PMID: 16771254]

100 Lei Y, Grover A, Sinha A, Vyavahare N. Efficacy of re- versal of aortic calcification by chelating agents. Calcif Tissue Int 2013; 93: 426-435 [PMID: 23963635 DOI: 10.1007/ s00223-013-9780-0]

101 Shearer MJ, Fu X, Booth SL, Fu X, Shobeiri N, Pang JJ, Adams MA, Holden RM. Dietary vitamin K and therapeutic warfar- in alter the susceptibility to vascular calcification in experimental chronic kidney disease. Kidney Int 2013; 83: 835-844 [PMID: 23344475 DOI: 10.1016/j.kid.2012.427]

102 Krueger T, Schlieper G, Schurgers L, Cornelis T, Cazzolino M, Jacobi J, Jadoul M, Ketteler M, Lemp RJ, Stenvinkel P, Westenfeld R, Wiecek A, Reinartz S, Hilgers RD, Fleoje J. Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): a rationale and study protocol. Nephrol Dial Transplant 2013 Nov 26; Epub ahead of print [PMID: 24285427 DOI: 10.1093/ndt/gft464]

103 McCabe KM, Booth SL, Fu X, Shobeiri N, Pang JJ, Adams MA, Holden RM. Dietary vitamin K and therapeutic warfar- in alter the susceptibility to vascular calcification in experimen- tal chronic kidney disease. Kidney Int 2013; 83: 835-844 [PMID: 23344475 DOI: 10.1016/j.kid.2012.427]

104 Naves-Diaz M, Alvarez-Hernandez D, Passlick-Deehtjan J, Guinsburg A, Marelli C, Rodriguez-Puyol D, Cannata-Andia JB. Oral active vitamin D is associated with improved sur- vival in hemodialysis patients. Kidney Int 2008; 74: 1070-1078 [PMID: 18633342 DOI: 10.1016/j.ki.2008.343]

105 Shoji T, Shinohara K, Kimoto E, Emoto M, Tahara H, Koya- ma H, Inaba M, Fukumoto S, Ishimura E, Miki T, Tabata T, Nishizawa Y. Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis popula- tion (see comment). Nephrol Dial Transplant 2004; 19: 179-184

106 Tentori F, Albert JM, Young EW, Blayney MJ, Robinson BM, Pisoni RL, Akiba T, Greenwood RN, KImata N, Levin NW, Piera LM, Saran R, Wolfe RA, Port FK. The survival advantage for haemodialysis patients taking vitamin D is questioned: findings from the Dialysis Outcomes and Prac- tice Patterns Study. Nephrol Dial Transplant 2009; 24: 963-972 [PMID: 19029478 DOI: 10.1093/ndt/gfn922]

107 Melamed ML, Eustace J, Plantinga L, Jaar BG, Fink NE, Coresh J, Klag MJ, Powe NR. Changes in serum calcium, phosphat, and PTH and the risk of death in incident dialy- sis patients: a longitudinal study. Kidney Int 2006; 70: 351-357 [PMID: 16738556 DOI: 10.1038/sj.ki.5001542]

108 Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernán MA, Camargo CA, Thadhani R. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. J Am Soc Nephrol 2005; 16: 1115-1125 [PMID: 15728786 DOI: 10.1681/ASN.2004070573]

109 Tentori F, Hunt WC, Stidley CA, Rohrscheib MR, Bedrick EJ, Meyer KB, Johnson HK, Zager PG. Mortality risk among hemodialysis patients receiving different vitamin D ana- logues. Kidney Int 2006; 70: 1858-1865 [PMID: 17021609 DOI: 10.1038/sj.ki.5001685]

110 Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar- Zadeh K. Association of activated vitamin D treatment and mortality in chronic kidney disease. Arch Intern Med 2008; 168: 397-405 [PMID: 18299405 DOI: 10.1001/archi- termed.2007.110]

111 Shoben AB, Rudser KD, de Boer H, Young B, Kestenbaum B. Association of oral calcitriol with improved survival in non- dialyzed CKD. J Am Soc Nephrol 2008; 19: 1613-1619 [PMID: 18463168 DOI: 10.1681/ASN.2007111164]
Sugiura S, Inaguma D, Kitagawa A, Murata M, Kamimura Y, Sendo S, Hamaguchi K, Nagaya H, Tatekatsu M, Kurata K, Yuzawa Y, Matsuo S. Administration of alfacalcidol for patients with predialysis chronic kidney disease may reduce cardiovascular disease events. Clin Exp Nephrol 2010; 14: 43-50 [PMID: 19882205 DOI: 10.1007/s10157-009-0233-z]

P- Reviewers: Aramwit P, Papagianni A  S- Editor: Ji FF  L- Editor: A  E- Editor: Wu HL
