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Bone Turnover and Vascular Calcification

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Abstract

The impaired bone mineral metabolism followed byVascular Calcification (VC) will be presentat the beginning stage of Chronic Kidney Disease (CKD). VC can be considered as two major types, which are intimal calcification, associated with atherosclerosis, and medial calcification that involves damaged vascular smooth muscle cells (VSMCs), which leads to increase vascular stiffness and decrease vascular elasticity. Many factors control the mechanisms, and they are imbalances in serum calcium and phosphate, systemic inflammation, hyperparathyroidism, increased matrix degradation, VSMC apoptosis, decreased matrix glutamate protein, etc. These will make VSMCs Trans differentiation to phenotypic osteoblastic cells. In addition, patients with CKD usually have bone turnover problems. For a high turnover status, secondary hyperparathyroidism increases calcium and phosphate release from the bone, but for a low turnover status in a dynamic bone disorder, circulating phosphate and calcium cannot enter the bone to cause serum calcium and phosphate levels to frequently maintain at high levels. This is caused by the fact that the bone can no longer buffer the increases in phosphate and calcium load, and these conditions will cause the possibility of VC. Interestingly, the VC process will secrete sclerostin, a hormone that may act not only locally in the artery wall to reduce mineralization but also destroy bone mineralization. These problems will lead to reduced bone mass with a cycle between bone turnover and VC that only leads to problems. This article will describe the complex relationship between the rate of bone turnover and VC in CKD.

Keywords: Bone turnover; Vascular calcification; Bone remodeling; Wntsignaling

Introduction

Physiological bone remodeling is a lifelong and highly coordinated process of bone resorption and formation. It involves continuous removal of old bone, replacement with a newly synthesized proteinaceous matrix, and subsequent mineralization of the matrix to form new bone. Bone remodeling is starting with bone resorption and then bone formation. The resorption and formation is essential for repair of micro-fractures and to modify the bone structure as a response to stress or other forces. Remodeling is the replacement of bone without changing its shape. However, maintaining mineral homeostasis is another essential role of bone remodeling [1]. Generally speaking, bone turnover occurs in both cortical and trabecular bone with a relative higher turnover rate in trabecular bone. Bone turnover processes basically start with osteoclast activation.

At the onset of CKD, the systemic mineral metabolism and bone composition start to change. This alteration is known as CKD-MBD. The greater the decrease in renal function, the worse the progression of CKD-MBD. It is well known that bone turnover disorder is the most common complication of CKD-MBD. The Kidney Disease: Improving Global Outcomes (KDIGO) defined the term CKD-MBD as a broader systemic disorder of mineral and bone metabolism that occurs as a result of CKD [2]. CKD-MBD is characterized by the following: (1) abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism; (2) abnormalities in bone turnover, mineralization, volume linear growth, or strength; (3) vascular or other soft-tissue calcification [2].

Normal bone remodeling

In 1990, Frost defined bone remodelingasa complex process by which old bone is continuously replaced by new tissue so that remodeling brings about bone adaption to mechanical burden and stress [3]. For adults, bone remodeling includes four consecutive phases: resorption, reversal, formation and mineralization.

Resorption

It begins with the relocation of partially differentiated mononuclear preosteoclasts, derived from hematopoietic stem cells, on the bone surface where they form multinucleated osteoclasts. The ruffled border of osteoclast secrets and synthesizes lysosomal enzymes to decompose bone minerals and fragments of collage. Some of the collagen is digested into its smallest particles aspyridinoline and deoxypyridinoline residues.

Reversal

It is a phase when mononuclear cells appear on the bone surface to help new osteoblasts adhere to resorbed surface and may provide signals for osteoblast differentiation and relocation. Osteopontin may play a key protein at the reversal site [4].

Formation

This phase is initiated by osteoblasts, differentiated from multipotent mesenchymal stem cells, laying down in groups on the resorbed bone surface [5]. Osteoblasts synthesize new collagenous organic matrix and regulate mineralization of matrix by releasing small, membrane bound matrix vesicles that concentrate calcium and phosphate and enzymatically destroy mineralization inhibitors such as pyrophosphate or proteoglycans [6]. They synthesize type I collagen and other proteins as osteocalcin to form osteoid extracellularly, then bone mineralization occurs [7]. The serum concentration of bone-specific alkaline phosphatase and osteocalcin reflect the cellular activity of osteoblasts [8-10].

Mineralization

It starts about two weeks after the osteoid newly formed. Bone mineralization is a well regulated process for accumulation of matrix molecules, which are produced by osteocytes and are piled up in precise amounts within the fibrous matrix. For adult people, the time of resorption is probably for 2 weeks, the reversal phase may last up to 4 or 5 weeks, while formation can continue for 4 months [5]. Usually, a bone structural unit to become fully mineralized will take several years.

The Communication between Osteoclast and Osteoblast

Influence of osteoblast on osteoclast

The bone remodeling process occurs through the action of RANK/RANKL /OPG (receptor activator of nuclear factor kappa /receptor activator of nuclear factor kappa B ligand /osteoprotegerin) system. RANK, a type I membrane protein on the surface of osteoclast cells, is involved in osteoclast cell stimulation when bound with RANKL produced by osteoblasts [11]. RANK L/RANK signaling not only regulates the formation of multinucleated osteoclast cells from their precursors, but also influences their activation and survival during normal bone remodeling and in a variety of pathologic conditions [12]. OPG, the other protein secreted from osteoblast cells, is a potent inhibitor of osteoclast differentiation and protects the skeleton from excessive bone resorption by acting as a decoy receptor for RANK L and preventing RANK L from binding to its receptor, RANK [11]. Thus, the RANK L/OPG ratio is a significant determinant of bone formation.

This RANK/RANK L /OPG system is affected by hormones (such as: PTH, calcitriol, sex steroid, and glucocorticoids), cytokines, interleukins, etc. Increased PTH levels increase the quantity of osteoclasts and osteoblasts [13]. Calcitriol enhances calcium and phosphorus absorption from digestive track to help bone mineralization [14]. Both estrogen and androgen affect bone remodeling process as well. Estrogen, for example, not only act onosteoblastic lineage, but also influence on lineage, including osteoclast precursors, mature osteoclasts, and lymphocytes [15]. Glucocorticoid-induced osteoporosis may induce apoptosis of osteoblasts and osteocytes [16]. RANKL/RANK interaction provides essential signals to osteoclast progenitors, leading to osteoclast differentiation, an important step in osteoclastogenesis, and bone resorption. This process can be blocked by OPG, a decoy receptor for RANKL that protects against bone resorption and extensive deterioration [17].

Influence of osteoclast on osteoblast

Sema4D, a new signaling between osteoclast and osteoblast found by Negishi-Koga et al. [18], secreted by osteoclasts functions as a ligand to activate downstream of RhoA by binding its receptor, Plexin-B1, on osteoblasts, thus suppressing the differentiation of osteoblast. Their study demonstrated that further RANK L-induced osteoclasto genesis will also induce osteoclasts highly express Sema4D at the same time [18]. In turn, producing more Sema4D to inhibit osteoblast differentiation serves as a negative feedback loop to balance the activity of osteoclasts and osteoblasts.

Influence of osteocyte on osteoblast (Wnt signaling)

Canonical Wnt signaling is a molecular pathway known to be essential for the regulation of bone physiology. During bone remodeling, the osteocyte will secrete sclerostin, and Dickkopf-related protein-1 (DKK-1) which may inhibit osteoblast differentiation and maturation through the inhibition of Wnt signaling [19].

Influence of resorted bone matrix on osteoblast

In addition, the active transforming growth factor-β1 (TGF-β1) and insulin-like growth factor-1 (IGF-1), secreted from bone matrix during bone resorption process, promotes directly the migration of bone marrow mesenchymal stem cells that form pre-osteoblasts and functions as a primary coupling factor in bone remodeling[20, 21]. In fact, the TGF-β1 and IGF-1matricellular couples of bone resorption and formation and it is also signaling between progenitors. For example, RANKL present on the osteoblastic cell surface binds its cell membrane receptor RANK on osteoclast progenitors to stimulate osteoclastogenesis [22].

Bone Turnover in CKD

The effects of uremic toxin

In addition, CKD patients accumulate uremic substances in their body because of impaired kidney function. These uremic substances, called uremic toxins (UTx), have been reported to injure various organs. Indoxyl sulfate (IS) is one of the uremic toxins, and is derived from tryptophan. It is excreted mainly from the proximal renal tubules into urine through organic anion transporter 1 (OAT1) and organic anion transporter 3 (OAT3) channel [23]. Decreased renal clearance as occurs chronic renal failure will increase IS levels in the blood, so levels are approximately 30 times higher in patients with CKD stage 4-5 (not yet on dialysis) patients, and 80 times higher in patients before initiation of dialysis than in healthy persons [24].

Mozar et al. [25] confirmed that IS directly inhibits osteoclast differentiation and activity. Furthermore, Kim et al. illustrated that IS inhibits osteoblast differentiation and induces apoptosis via the caspase (cysteine asparate protease) pathway [23,26]. IS may deteriorate the outcomes of low bone turnover diseases and attenuate

the chemical composition of bone in patients with CKD. Oral administration of the indole-absorbing agent, AST-120 prevents the progression of VC [27] and improves the low bone turnover status in patients with CKD [28].

The Effects of PTH

The effects of high PTH

In CKD patients, the effect of high levels of PTH on bone results in the high-turnover bone disease, such as: osteitis fibrosa, with excessive osteoclastic bone resorption and bone marrow fibrosis [29].

The effects of low PTH

In contrast, low-turnover bone disease is common in patients with CKD, especially in dialysis patients under high dose of active vitaminD3 [30].Osteomalacia, aluminum-induced bone disease, and a dynamic bone disease are all low-turnover bone diseases. Osteomalaciais also related to reduce active vitamin D and chronic metabolic acidosis [31]. Aluminum ingestioncauses the reducing both osteoclast resorption and osteoblast formation surfaces. Moreover, chronic low dose aluminum exposure with high intake of vitamin D reduces PTH synthesis and secretion in dialysis patients, who may present with a dynamic bone disease rather than osteomalacia [32].

Vascular Calcification in CKD

In patients with CKD, cardiovascular disease remains the leading cause of morbidity and mortality. Examination of CKD patients who have VC reveals two different but overlapping arterial pathologies; atherosclerosis and arteriosclerosis [33]. The presence of VC in the dialysis population is multifactorial, but hyperphosphatemia and over calcium load (ingested calcium-containing oral phosphate binders) are the main contributions to VC. Especially, hyperphosphatemia stimulatesosteogenic/chondrogenic differentiation, vesicle release, apoptosis of VSMC, loss of inhibitors, and extracellular matrix degradation to drive VC [34].

Atherosclerosis and Arteriosclerosis (Table 1)

Inflammation, thickening, and calcification on the intimal layer of vascular is called atherosclerosis [35] that occurs preferentially in medium-sized arteries and usually results in occlusion. By contrast, arteriosclerosis is calcification of the media layer, which usually leads to thickening of the medial layer and is most commonly found in elastic arteries to increased arterial stiffness [36], and may lead to left ventricular hypertrophy [37]. Arteriosclerosis, common in patients with diabetes, renal failure, and advanced aging [38,39], is not principally an inflammatory process but associated with apoptosis of VSMCs [40].

Layer of vascular wall	Intima	Media
Features of histology	Atherosclerosis lipid-laden plaques micro-inflammation of the atherosclerotic plaque. Predominantly in medium-sized arteries aggregates of calcium sedimentations patchy and focal in distribution,	Arteriosclerosis deeper layer of the arterial wall Linear sedimentations on elastic lamellae. Diffuse contiguous fashion. extracellular matrix deposition fibroelastic intimal thickening hydroxyapatite and whitlockite deposition
Associated clinical symptoms	Plaques rupture Myocardial Infraction, or Cerebrovascular accident	Vascular stiffness: Heart failure, Left ventricular hypertrophy Cardiac Valve Calcification, Monckeberg's sclerosis
Risk factors	Lipid, macrophages, inflammation HCVD, DM, Oxidative stress	Elastin degradation, hyperphosphatemia, Hypercalcemia Dialysis vintage Decreased inhibitors of calcification
Plain radiography	Spotty calcification	Linear tram-track calcification

Table 1: Two Types of Vascular Calcification

Atherosclerosis is patchy and focal in its distribution but arteriosclerosis affects the media tunica. On plain radiographs, atherosclerosis and arteriosclerosis can usually be distinguished as spotty calcifications versus linear tram-track calcifications [41].

Pathophysiology of VC

Hyperphosphatemia, a common problem in CKD, can enhance the sodium-dependentphosphate transporter PIT-1 and contribute to increased calcification [42]. This calcification is not simply the result of calcium and phosphorus precipitation from the circulation [43]. It can induce calcification by up-regulating mRNA expression for osteogenic factors including BMP 2, Cbfα1/Runx2, Msx2, and osteocalcin [44]. Osteoblasts and VSMCs have a common mesenchymal origin. Core binding factor-1 (Cbfα1) is thought to trigger mesenchymal cell-to-osteoblast transformation [45] via causing the expression of major bone matrix components such as osteocalcin, type I collagen, and osteopontin (OPN). Hyperphosphatemia also

leads the activation of the Wnt/β-catenin signaling pathway by the translocation of β-catenin into the smooth muscle cell nucleus, increasing the expression of direct target genes such as cyclin D1, axin 2, and VCAN/versican [44]. Both BMP and Wnt signaling proteins regulate bone mass by promoting osteogenesis by stimulating Runx2 gene expression [44] but the molecular interactions between these pathways in osteogenesis and bone formation are not completely defined [46]. Therefore, hyperphosphatemia can induce the formation of bone matrix vesicles, which containapatite and calcifying collagen fibrils on the surface of VSMCs [47]. Furthermore, these vesicles almost certainly act as early nucleation sites for calcification in the vascular wall [44].

In addition, there are still many factors impacting VC, which is a precise complex process. Recently, a mounting evidence suggests that VC process is similar to mineralization in bone [48]. Many experts pointed out the transformation of VSMCs to an osteogenic/chondrogenic phenotype that promotes the release of the vesicular structures. The calcification is initiated by these osteoblast-phenotype cells then lay down an extracellular matrix of collagen and non-collagenous proteins to make matrix vesicles or apoptotic bodies, which contain hydroxyapatite [49]. The calcification process includes active and passive processes. The active process is the mineralization in these structures is stimulated by osteoblastic proteins. In contrast, the passive process involves mineral precipitation from the extra-cellular fluid surrounding the VSMCs in the vascular walls [50]. Both the up regulation of these promoters (such as: hyperphosphatemia, osteopontin, osteonectin, alkaline phosphatase, type I collagen, and bone morphogenic protein (BMP)-2) [51-53]and the down regulation of these inhibitors (such as:fetuin A, matrix gla protein, and pyrophosphate) [54-56] will enhance VC. In CKD patients, hyperphosphatemia is a major important contributor to VC [57].

Linkage Between Bone Turnover and VC in CKD

Patients with CKD may present with dysregulation of RAKN/RANKL/OPG system resulted in either high or low bone turnover disorders. Both high and low bone turnover disorders may induce vascular calcification. The calcified vessel (phenotypic osteoblast/osteocyte in calcifying vasculature) may secrete FGF23 and Wnt inhibitors such as sclerostin, DKK-1 and secreted frizzled-related protein to prevent further VC. However, all of them may fight back the inhibition of bone formation resulting in fragile bone.

RANK/RANKL/OPG and VC

More and more researchers now approve that VC is an actively regulated process with stimulative and suppressive factors, just like bone remodeling process [58]. It is clear that impaired bone metabolism plays an important role in the development of VC [50]. As previous mention, there are three key elements that influence the bone formation process: RANK, RANKL, and OPG. In addition, mounting evidence suggests that the RANK/RANKL/OPG triad is involved in bone metabolism, and may be important in VC [59,60]. Experts found OPG, RANKL, and RANK exists in extra osseous calcifications such as atherosclerotic calcifications and cardiac valve calcifications. Also, the varied stages of CKD present the relative different expression levels of RANK/RANKL/OPG [61,62].

Panizo et al. [63] stated that RANKL directly increased VSMC calcification by binding to RANK and stimulating BMP4 secretion by the alternative NF-kB pathway. Thus, RANK/RANKL may be crucial in stimulating VC, whereas OPG inhibits VC. OPG appears to be the molecular link between bone resorption and VC, which may help recognize the close relationship between atherosclerosis and osteoporosis in postmenopausal women [64]. Estrogen, as osteoblast stimulator and osteoclast inhibitor, influences on TGF-β, which also stimulates calcitonin production as well. The other functions of estrogen are decreasing the level of pro-inflammatory cytokines and increasing OPG gene expression in osteoblast. It is believed that the postmenopausal women with low estrogen concentration will increase bone resorption. Because the higher level of proinflammatory cytokines lessens the activity of endothelial nitric oxide synthase (eNOS) to limit the production of nitric oxide that can stimulate osteoblasts and block osteoclasts [65]. Therefore, prescribing postmenopausal women with estrogen is a benefit to reduce vascular calcification [66,67]. Shargorodsky et al. [68] identified that serum OPG level is an independent predictor of early cardiovascular events in osteoporotic postmenopausal women.

Altered bone turnover (high or low) on VC in patients with CKD

The bone and the vascular system have a multifaceted relationship. Both have similar and mutual changes in mineralization, a situation called the bone-vascular axis [69]. It was continuously indicated that the connection between bone osteoporosis and VC was because of a significant negative correlation between bone mineral density and aortic calcification [70]. However, this correlation is poorly understood and underlying association has not yet been well-characterized. Besides, CKD is usually in low bone turnover status, which reduces the ability of bone buffering mineral metabolites such as calcium and phosphate. The excess calcium and phosphate, unable to enter bone, leads the advance of promoting epromote VC in circulation [71]. Hence, low bone turnover is frequently associated with coronary artery calcium (CAC) score progression in hemodialysis patients [72].

Some studies also revealed that low bone turnover or mineralized bone mass is inversely related to the degree of coronary artery calcification and vascular stiffness [73]. Rodriguez-Garcia et al. [74] analyzed hemodialysis patients and found that calcification in the large-or medium-size- artery is associated with a higher possibility of vertebral fractures. As well, this study showed that both VC and vertebral fractures were associated with increased mortality among research samples [74].

The relationship between low bone turnover and VC remains unclear [75]. Recent publications examining low or even high bone turnover, discovered that VC is not influenced by bone turnover itself, but is related to situations where bone resorption is greater than bone formation (Figure 1). These researchers approved that VC can occur at any level of bone turnover [75]. As described before, serum phosphate may be one of the connections between bone turnover and VC. When bone turnover is low, as with a dynamic bone, the amount of interchangeable calcium and phosphate is decreased, leading to higher concentrations in blood serum associated with intake. Additionally, bone resorption is more prominent than bone formation, interfering with the buffering function of the skeleton for extra phosphate. Oppositely, when high bone turnover is present as in secondary hyperparathyroidism, a lot of phosphate is released from bone and, again, the reservoir function of the skeleton is ruined [50]. Therefore, the correcting the balance in bone turnover, either high or low, will protect against the progression of VC [72].

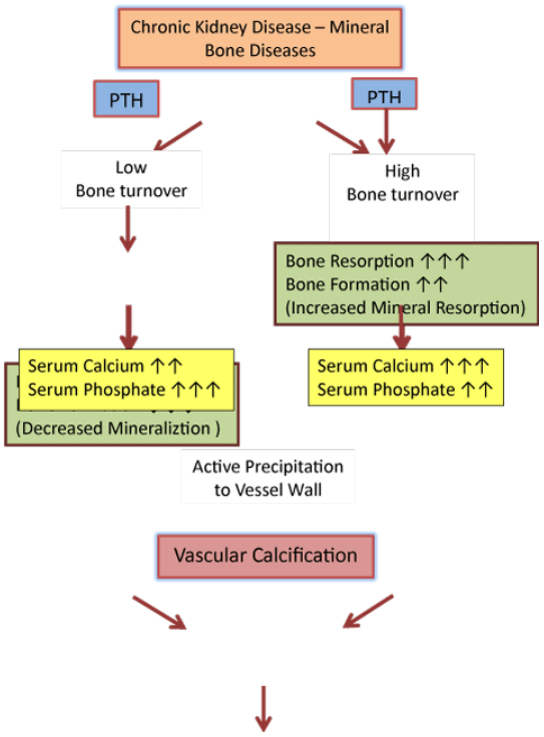

Figure 1: Bone turn and vascular calcification in CKD

Basically, bone cells in CKD were less vitality than in normal. Thus, low bone turnover is the innate character of CKD. In the presence of high serum PTH levels, high PTH will overcome the indolent bone cells and present with high turnover bone disease with a characteristic of relative higher bone resorption than bone formation. The high turnover status in SHPT will induce an increased bone demineralization which will increase release Ca and Pi from bone into circulation. In contrast, CKD patients overtreatment with Ca-salts, VDRA or aluminum may develop low turnover bone disorders and low serum PTH levels. In low bone turnover status, the decreased bone mineralization leading difficult of Ca and Pi entry into bone resulting increase of serum Ca and Pi. Both high and low turnover bone disorders have a relatively higher degree of bone resorption than bone formation which may contribute the elevation of serum Ca and Pi and aggravate vascular calcification/ossification.

Calcified vessel affect bone metabolism through Wnt signaling inhibitors VC and impaired bone metabolism are the common and important reasons of mortality and morbidity in patients with CKD or osteoporosis [2]. The Wnt signaling pathway is a complicated network of several proteins that impact normal physiologic bone formation metabolism [76]. The consequence of Wnt signaling in bone is mediated by stimulation of stem cells and proliferation of pre-osteoblasts, induction of osteoblastogenesis, inhibition of osteoblast and osteocyte apoptosis, and attenuation of osteoclastogenesis [77,78]. Thus, the physiological mechanisms of Wnt signaling lead to both formation and anti-resorption benefits at the same time [79]. The effect of Wnt signaling depends on a trans membrane receptor complex composed of the frizzled receptor and the low-density lipoprotein receptor-related protein (LRP)-5 or LRP-6 co-receptors [77,78].

Recent evidence supports the concept that there are inhibitors associated with the Wnt signaling pathway, such as sclerostin, secreted frizzled proteins 2 and 4, and DKK-1, that enhance osteoclast function and link VC and bone loss [80,81] (Figure 2). Pinzone et al. [82] pointed out that DKK-1 has two differing roles in influencing bone mass, which are increasing the osteolytic activity and decreasing osteoblast differentiation. Tumor necrosis factor alpha (TNF-α) stimulatesthe secretion of DKK1, which leads to decreased bone mass by inhibiting the prevention of mesenchymal stem cells (MSC)-derived osteoblastogenesis and lowering OPG levels. When DKK-1 increases RANKL levels and raises RANKL/OPG ratio which promotes osteoclast activity and results in bone resorption [82].

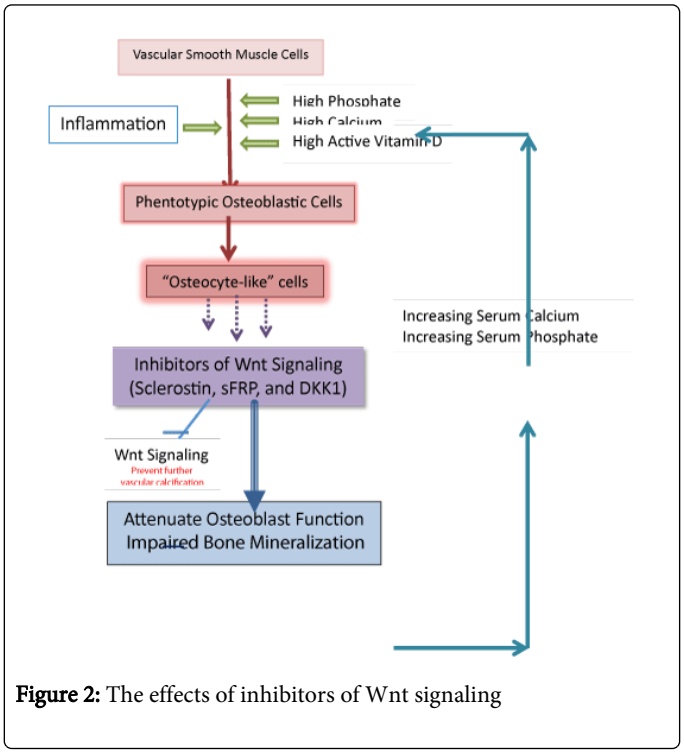

Figure 2: The effects of inhibitors of Wnt signaling

The phenotypic osteoblast/osteocyte in calcified vessels may secrete sclerostin (SOST), secreted frizzled-related protein (sFRP), and Dickkopf-related protein 1 (DKK1) which prevent the further calcified the victim vessel. The secreted SOST and sFRP will process an autocrine or paracrine effects on the inhibition of Wnt signalling on the osteogenic trans differentiation of VSMCs which will prevent further calcification of the vessel wall. As the secreted SOST and sFRP from calcified vessel may release into circulation, which may fight back inhibits Wnt signaling of osteoblast on bone. This inhibition of bone osteoblast reduced bone accretion and then turnover, which may also contribute to the elevation of serum phosphate and calcium. The increased serum phosphate and calcium further promote vascular calcification.

Sclerostin, a glycoprotein inhibitor of osteoblastogenesis, is secreted by osteocytes and travels through osteocyte canaliculi to the bone surface where it binds to LRP-5 and LRP-6 co-receptors. Consequently, sclerostin prevents frizzled proteins from colonizing on bone and blocks Wnt signaling to reduce osteoblastogenesis and bone formation [76]. Then, sclerostin may have a negative feedback role in osteoblasts signaling at the onset of osteoid mineralization [19,83]. Additionally, more recent evidence suggests that the Wnt signaling

pathway not only plays an important role in bone metabolism, but is also involved in medial artery and aortic valve calcification [84-86].

Sclerostinis an important inhibitor in alkaline phosphatase activity [87]. In vascular and aortic valve calcification cases, sclerostin has also been shown to increase expression[86].The purpose of this up regulation of sclerostin or other Wnt inhibitors in vascular calcification is a feedback loop to slow down the calcification process of vascular [86].

Because sclerostin secreted from either the osteoid or the calcified vessel may spread to the circulation, Drake et al. [88] stated that bone marrow plasma and peripheral serum sclerostin levels were strongly correlated. Thus, sclerostin may be a significant communicator between bone and vascular soft tissue calcification [89]. Some evidence suggests that ageing, diabetes, male gender, and low PTH levels are all associated with high circulating sclerostin levels [90-92]. Particularly, sclerostin levels also increase with the progression of CKD and correlate inversely with histological parameters of bone turnover, and osteoblast number and function in hemodialysis patients [19]. Sclerostin spreads from the calcified vessel and may deteriorate bone structure and retard further mineralization [86,89]. This may clarify why VC is negatively associated with bone density and positively related to fractures [74,93]. Moreover, sclerostin may be a main mineralization regulator in VC [86] and impaired bone metabolism [94]. Therefore, it plays an important role in the bone–vascular axis [50].

Conclusions

The patients with CKD-MBD usually have either low bone turnover rate or high rate, both of these two situations will promote VC. Furthermore, the bone turnover disorders and VC maycontribute the acceleration of morbidity and mortality in CKD. Many studies have suggested that VC, impaired bone turnover and increased bone fracture risk were interrelated closely. However, it ismore clear that VC is not strongly related to bone turnover, but the real cause of VC is bone resorption in excess of boneformation, which can occur at any rate of turnover.

Currently, the Wnt signaling pathway is known to play an important role in bone homeostasis and VC. Besides, the increased expression of sclerostin, sFRP, DKK1, inhibitors of Wnt signaling, is approved to retard the transformation of VSMC into osteoblasts during VC. However, the higher circulating sclerostin level will inhibit Wnt signaling in bone to result in lowering bone turnover rates and increases serum phosphate levels. High phosphate levels induce VSMC transforming to osteoblast-like cells and lead to produce sFRP. Wnt signaling also promotes VSMCs changing to osteoblasts. Those Wnt signaling inhibitors may not only reduce mineralization of the artery wall but also reduce bone mineralization. Thus, bone inhibition and VC will affect each other in harmful ways.

So, the most important methods to prevent soft tissue calcification are maintaining normal mineral metabolism and promoting bone health. In other words, to control serum phosphorus and serum calcium in the standard range through keeping up normal bone turnover rate may provide the greatest benefit to VC.

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