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Bone and Kidney Crosstalk

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GRAPHICAL ABSTRACT

Andrea Del Fattore, PhD, is head of the Bone Physiopathology Group, at the Bambino Gesù Children’s Hospital, Rome. His main research topics are rare diseases (i.e. Gorham-Stout disease and Cystinosis) and the involvement of extracellular vesicles in the bone remodeling activity.

Giulia Battafarano is a PhD student at the Department of DAHFMO-Unit of Histology and Medical Embryology at the University of Rome “Sapienza”. Her research aims to understand the skeletal alterations in patients affected by kidney diseases. Particularly, she is studying the primary bone defects in Cystinosis, analyzing the effects of cystinosin deficiency on bone cells. She hopes that her study will lead to resolving the growth impairment and osteopenia observed in these patients.

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ABSTRACT
The regulation of mineral metabolism results from the interplay of four endocrine organs forming the parathyroid-intestine-bone-kidney axis. In this context, the skeleton stores minerals, calcium and phosphate, within its matrix and orchestrates the regulation of their levels, interacting with the kidney. Here we give an overview of the main pathways involved in the Crosstalk between these two organs. Moreover, we described the endocrine network characterized by bone and kidney derived-hormones, and further signals, i.e. parathyroid hormone, that target them.

INTRODUCTION
The skeleton is the largest organ in mammals and besides the mechanical support, the frame for locomotive muscle attachment, the protection of internal organs, it plays other functions such as energy, mineral metabolism, fertility and appetite regulation\cite{1,2}. Minerals, mostly calcium, phosphate and bicarbonate, are structural constituents of bones and the skeleton works as their storage, releasing them when it is needed\cite{3}. Mineral balance is maintained by coordination of many endocrine signals between kidney, bone and other organs, such as parathyroid glands and intestine.

Mineral Metabolism: Calcium and Phosphate.
- Calcium
Calcium is involved in several biological functions such as cell signaling, neural transmission, muscle function, blood coagulation, membrane and cytoskeletal regulation, secretion and biomineralization\cite{4}. Calcium levels are finely regulated in intracellular and extracellular compartments. Total body calcium content is approximately 1 kg and 99% resides in the skeleton, whereas the extraskeletal component accounts for only 1\%\cite{5}. Even with great variability, about 1 g of calcium is introduced by diet and half is absorbed by the gastrointestinal tract, mainly by duodenum, in a vitamin D dependent manner\cite{6}. About 10 g of calcium per day are filtered by glomeruli in the kidneys and up to 99% is reabsorbed by two mechanisms: paracellular passive reabsorption and transcellular active process mediated by CaSR (Calcium Sensing Receptor) and TRPV5 (Transient Receptor Vallinoid 5)\cite{7}. The reabsorption occurs mainly in the proximal tubules where it is largely driven by diffusion through the paracellular shunt\cite{8,9}; about 10% of filtered load is actively reabsorbed by distal tubule\cite{10}. Only 50-250 mg of calcium are excreted in urine during a day\cite{11}. Hormonal regulation of tubular calcium reabsorption and urinary excretion contribute to the maintenance of calcemic physiological range.

The most relevant hormones that control the calcium homeostasis are Parathyroid hormone (PTH) and Vitamin D\cite{11}. - Phosphate
The skeleton is also the reservoir of phosphate. Indeed most of the phosphorous builds, with calcium, skeletal hydroxyapatite, whereas the extra skeletal phosphate accounts for \~{}15\%, constituting phosphoproteins, phospholipids and nucleic acids\cite{12}. The phosphate balance is maintained by FGF23 (Fibroblast Growth Factor 23), PTH and Vitamin D\cite{13,14}. The dietary introduced phosphate is absorbed in the small intestine with both calcium dependent and independent mechanisms. The main process is through passive absorption that depends on amount of phosphorus in the gut\cite{15}. However, there is also an active sodium-dependent mechanism, mediated by NaPi2b (Sodium-dependent phosphate transport protein 2B), and stimulated by 1,25(OH)$_2$ Vitamin D\cite{16,17}. As for calcium, the kidney contributes to the regulation of phosphate levels in the blood by its reabsorption in convoluted and in proximal tubules\cite{11}. Phosphate reabsorption by the proximal tubular cells involves the uptake
across the brush border membrane mediated by NaPi2a (Sodium-dependent phosphate transport protein 2A) and NaPi2c (Sodium-dependent phosphate transport protein 2C) that collectively account for the reabsorption of ~80% of filtered phosphate. In this context, FGF23 is the main emerging phosphatonin that protects cells and tissues from high levels of phosphorus. Indeed, increased oral phosphate intake results in increased FGF23 secretion and systemic circulation, while in dietary phosphate restriction lower serum levels of FGF23 are observed. To regulate phosphate homeostasis, FGF23 establishes a complex interaction with PTH and Vitamin D by which FGF23 suppresses PTH secretion and 1,25(OH)2 Vitamin D synthesis.

Parathyroid hormone: endocrine signal outside of bone and kidney.

The parathyroid gland evolved to operate as calciostat responding to serum calcium levels alteration with PTH secretion. Parathyroid hormone is secreted as 84-amino acids protein. It is synthetized as a propeptide containing a presequence of 25 amino acids and a prosequence of 6 amino acids. Presequence and prosequence are then cleaved off in the endoplasmic reticulum and the full-length PTH of 84 amino acids is stored in vesicles. PTH is released in response to reduced concentration of extracellular calcium and it acts to restore calcium levels. Parathyroid glands sense extracellular calcium concentration through the CaSR on their cell membrane. The interaction of calcium to the extracellular domain of the CaSR results in stimulation of phospholipase C-β (PLCβ) activity via Gα11. PLCβ catalyses the formation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). The accumulation of IP3 induces the release of calcium into the cytosol from intracellular stores, whereas DAG activates the MAPK (Mitogen-Activated Protein Kinase) cascade. In contrast with other cells that release their product in response to increased calcium levels, these events lead to reduced PTH secretion from the parathyroid chief cells.

PTH has a very short circulating half-life and it is primarily metabolized in the liver into amino- and carboxy-terminal fragments leading to several forms of PTH in the circulation. However, the amino terminus (known as 1-34 PTH) is the only one that can bind to the PTH receptor carrying out the biological effect on target organs. The carboxy terminus is cleared by filtration in glomeruli and it accumulates during renal failure.

Tissue response to PTH are mediated by parathyroid hormone receptor type 1 (PTHR1) belonging to G-protein coupled receptor family. When PTH binds its receptor, several downstream pathways are activated in a tissue specific manner, involving Protein Kinase A (PKA) and Protein Kinase C (PKC) activation, cyclic AMP (cAMP) signaling and MAPK pathways.

Biological effect of PTH

PTH acts directly on kidney inducing its 1,25(OH)2 Vitamin D production and calcium reabsorption mainly in the distal convoluted tubule. In addition to serum calcium, PTH regulates phosphate levels, inhibiting phosphate reabsorption by proximal tubules and causing hypophosphatemia. Indeed PTH reduces NaPi2a and NaPi2c expression in the apical membrane of proximal tubular cells. Even if a direct effect on intestinal calcium and phosphate absorption is not clear, PTH promotes their absorption through vitamin D released from kidney. PTH-mediated effects on bone seem to be dose-dependent. Indeed, chronic elevation of PTH as in hyperparathyroidism induces osteoclast resorption, whereas intermittent administration of 1-34 PTH has anabolic functions, stimulating osteoblast activity. Furthermore, since PTHR1 localizes in osteoblasts, osteocytes and stromal cells, but not in bone marrow hematopoietic cells or...
osteoclasts, the stimulation of bone resorption is likely indirect and mediated by osteoblasts production of osteoclastogenic factors\(^{39}\).

**Vitamin D: kidney-derived hormone that acts on bone**

Vitamin D is a fat-soluble secosteroid that acts as a hormone interacting with a specific cytosolic receptor; it is involved in the regulation of nearly 3% of the human genome\(^{30}\). Vitamin D was first identified for its central role in calcium and phosphate metabolism. Indeed, it regulates mineral homeostasis and skeletal health by modulating intestinal absorption of calcium and phosphate, renal calcium reabsorption and coordinating with parathyroid functions. Regarding the direct effects on bone cells, van Driel and van Leeuwen described the complex interaction between vitamin D and osteoblasts\(^{31}\). Indeed, osteoblasts express Vitamin D receptor. However the effects of vitamin D on osteoblasts remains unclear because both osteoblasts-specific deletion and overexpression of VDR (Vitamin-D-Receptor) lead to increased bone mass\(^{32-34}\). Moreover, Vitamin D promotes bone resorption stimulating osteoclast differentiation and activity. Even if osteoclasts and their precursors express VDR\(^{35,36}\), vitamin D regulates osteoclast formation and function via osteoblast production of osteoclastogenic M-CSF (Macrophage Colony-Stimulating Factor) and RANKL (Receptor activator of nuclear factor kappa-B ligand)\(^{37}\). Interestingly osteoclast precursors from VDR knock-out mice can be induced by Vitamin D to differentiate in the presence of wild-type osteoblasts\(^{38}\). Moreover, further studies revealed non-classical actions of Vitamin D since its deficiency has been correlated with other conditions including autoimmune, cardiovascular, renal and neurodegenerative diseases, depression and cancer\(^{39}\).

The biologically active molecule of Vitamin D is the 1,25(OH)\(_2\) Vitamin D (also known as calcitriol) obtained by metabolic conversion of its precursors: Vitamin D\(_2\) and Vitamin D\(_3\) (often mentioned as ergocalciferol and cholecalciferol, respectively). The major source of Vitamin D3 in humans is via the skin that synthesizes it from 7 dehydrocholesterol through sunlight-exposure. Vitamin D2 and D3 are also introduced through the diet from vegetable and animal foods, respectively\(^{40}\). These precursors are then transported to the liver where they are hydroxylated by Vitamin D 25-hydroxilase encoded by the CYP2R1 gene, to generate 25-hydroxyvitamin D [25(OH) Vitamin D]; this is the most abundant circulating form of vitamin D\(^{41,42}\). Because of their lyophilic nature, all the circulating metabolites of Vitamin D are carried bound to Vitamin D-Binding-Protein (DBP). 25(OH) Vitamin D-DBP complex is filtered through the glomerulus and internalized by proximal tubular cells via megalin-mediated endocytosis. Herein, 25(OH) Vitamin D is released from DBP and it is either converted by 25-hydroxyvitamin D-1α-hydroxylase to the 1,25-dihydroxyvitamin D [1,25(OH)\(_2\) Vitamin D] or it can be recycled into the circulation\(^{43}\). Normal serum levels of 25(OH) Vitamin D are also maintained ensuring extra renal calcitriol synthesis\(^{44}\). Indeed, 1α-hydroxylase is also expressed in other tissues, such as bone\(^{45}\).

Serum phosphorus, calcium, FGF-23 and other factors can affect the renal production of 1,25(OH)\(_2\) Vitamin D. The pleiotropic actions of 1,25(OH)\(_2\) Vitamin D are mediated by its binding to the VDR\(^{44}\). VDR is a nuclear receptor belonging to the subfamily 1 and its binding to Vitamin D ligand leads to genomic and non-genomic response on target cells. To mediate genomic effects, the VDR-ligand complex forms a heterodimer with the retinoid X receptor (RXR) in the cytoplasm. This complex then translocates to the nucleus where it binds to vitamin D responsive elements (VDRE) in the promoter of VDR-responsive genes. Here, VDR-RXR recruits basal transcriptional factors, co-activators

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and co-repressors to induce/repress the transcription of target genes by RNA Pol II.

In addition, the VDR also contains an alternative 1,25(OH)2 Vitamin D-binding A-pocket that, after the binding to its ligand, can induce rapid non-genomic responses at the membrane level, independently from the VDR-RXR signaling. Furthermore, some form of vitamin D can also act on the retinoic acid-related orphan receptors (RORs)\(^{47, 48}\).

1,25(OH)2Vitamin D renal synthesis and catabolism are tightly coordinated with the Calcium/PTH axis and the Phosphate/FGF23 axis.

**Calcium/Vitamin D/PTH axis**

In hypocalcemia, PTH secretion is rapidly enhanced to restore calcium balance. High levels of serum PTH induce both calcium release from bone, activating its resorption, and 1αhydroxylase expression and activity in the kidney. In turn, calcitriol synthesis is stimulated and intestinal calcium absorption is induced in the small intestine by enhancing expression of transient receptor potential cation channel (TRPV6) and Calcium-Binding-Protein (CaBP). Moreover 1,25(OH)2Vitamin D enhances calcium reabsorption by kidney\(^{42}\). Upon calcium levels normalization, calcium and calcitriols inhibit PTH secretion and renal 1αhydroxylase in a negative feedback\(^{44}\).

**FGF-23: Bone-derived hormone that acts on kidney**

FGF23 is an endocrine hormone produced in the bone by osteocytes and osteoblasts and targets several organs mainly through FGFR1c/αKlotho. FGF23 is the most recently discovered member of FGFs superfamily and it was identified by 3 different groups around 2000. Yamashita and colleagues identified FGF23 preferentially expressed in the ventrolateral thalamic nucleus\(^{49}\), whereas ADHR consortium associated FGF23 to ADHR (Autosomal Dominant Hypophosphatemic Rickets)\(^{50}\). At the same time Shimada et al discovered FGF23 effect on the tumor-induced osteomalacia\(^{51}\).

FGFs superfamily is constituted by 22 FGF members classified in 7 subfamilies\(^{52}\). Fifteen are paracrine-acting, 4 have an intracellular activity and do not interact with FGF receptors, and 3 have endocrine functions. The endocrine hormones are FGF19, FGF21 and FGF23; in contrast to other FGF members, their structure lacks of heparin binding domain allowing them to enter in the circulation and execute their endocrine function\(^{53}\). Eighteen FGF ligands bind to FGF tyrosine kinases receptors (FGFRs), characterized by three extracellular immunoglobulin-like domains and a long cytoplasmic C tail. The FGF-FGFR interaction leads to the activation of multiple downstream effectors such as PLCγ-PKC, JAK-STAT, PI3K-Akt-mTor and Grb2-Ras-Raf-MAPK\(^{54}\).

There are many germline and somatic mutations of FGFRs. While the somatic alterations are particularly frequent in human cancer, the germline mutations cause musculoskeletal phenotypes. Activating mutations of FGFR1 cause craniofacial dysmorphism, synostosis of skull and homerus, and dwarfism, whereas inactivating genetic alterations lead to syndactyly; activating mutations of FGFR2 induce craniodysostosis, syndactyly and digitopalmal fusion; achondroplasia and hypochondroplasia are associated with gain-of-function mutations of FGFR3. Genetic lesions of FGFR4 and FGFR5 and their effects on the human skeleton are not known\(^{55}\).

For the endocrine function of FGFs, a co-receptor is required and it is provided by Klotho\(^{56}\). Endocrine FGFs and Klotho gene families are a complex system that co-evolved with the endoskeleton\(^{55}\). Klotho family accounts for 3 members: α, β and γ. They share a similar structure but the αKlotho is the only one found in the circulation\(^{57}\). Indeed membrane-bound α Klotho can be cleaved by ADAM10 and
ADAM17 metalloproteinases resulting in the secretion of a soluble molecule. αKlotho is an obligate co-receptor for FGF23 and it was identified serendipitously when a transgenic experiment accidentally disrupted the αKlotho promoter. The αKlotho coupling with FGFR1 confers high affinity to circulating FGF23 and specificity to its target organs. Indeed, even if FGF23 receptors are largely expressed, the FGF23 downstream signaling has been detected only in those tissues characterized by high expression of αKlotho, including kidney, parathyroid glands and brain.

FGF23 directly inhibits renal phosphate reabsorption via suppressing NaPi2a activity in proximal tubular cells, leading to phosphaturia. Moreover, it inhibits 1α-hydroxylase and the PTH release from parathyroid glands. Thus, FGF23 indirectly reduces intestinal absorption of dietary phosphorus, by the reduction of circulating 1,25(OH)2 Vitamin D. Furthermore, it has been recently shown that FGF23 regulates also calcium handling through TRPV5 channel in renal distal tubules.

For its relevance in physiology, FGF23 is regulated by stimulating and inhibiting factors. Saito et al. demonstrated in vivo a positive correlation between 1,25(OH)2 Vitamin D, phosphate, PTH and FGF23 levels, whereas a negative regulation of FGF23 from PHEX (Phosphate regulating endopeptidases on the X chromosome) and DMP1 (Dentin Matrix acid Phosphoprotein 1) in bone are also known.

Quarles proposed a model to explain DMP1 and PHEX regulation of FGF23 in osteocytes. DMP1 is subjected to metalloproteinases cleavage to create an N and a C terminus; the C terminus interacts with PHEX via the ASARM (Acidic, Serine- and Aspartic acid-Rich Motif) and in turn, FGF23 promoter is inhibited. Moreover both PHEX and DMP1 regulate the mineralization of extracellular matrix, thus coordinating bone phosphate accretion with renal phosphate conservation.

Mutations of FGF23 and αKlotho can cause low FGF23 levels with hyperphosphatemia due to renal phosphate retention and high levels of 1,25(OH)2 Vitamin D, leading to familial tumoral calcinosis condition. On the other hand, gene mutations of PHEX and DMP1 result in increase of FGF23, renal phosphate wasting, low levels of 1,25(OH)2 Vitamin D and hypophosphatemia.

**Phosphate/Vitamin D/FGF23 axis**

FGF23 function in the phosphate homeostasis regulation is coordinated with Vitamin D and PTH. Indeed calcitriol increases the phosphate serum levels directly by inducing intestinal absorption and indirectly by stimulating its tubular reabsorption through the suppression of PTH. Even if calcitriol enhances NaPi2b protein expression in the gut, it was demonstrated that its upregulation occurs also in vitamin D null mice. This result confirms that other factors such as FGF23 also affect intestinal phosphate transporters.

Both high phosphate serum levels and circulating calcitriol induce FGF23 synthesis on bone. The interaction between Vitamin D, PTH and FGF23 in the phosphate homeostasis are not completely understood. Indeed, it remains to be clarified if PTH directly affects FGF23 production.

**CKD**

Mineral homeostasis is preserved by a concert of endocrine hormones above described. As in the physiological conditions, also in pathological conditions kidney and bone influence each other. Chronic kidney disease (CKD) is an international public health problem affecting 5–10% of the world's population. Chronicity is conventionally defined as renal impairment lasting for at least 3 months; to assess staging and severity of the disease estimated or measured glomerular filtration rate is...
used\(^{68}\). For adults, it is considered CKD when the glomerular filtration rate ≤ 60 ml/min/1.73 m\(^2\) because herein alteration of calcium, phosphorus, PTH and Vitamin D are detectable. For children, the glomerular filtration rate at which CKD is determined is higher (<89 ml/min/1.73 m\(^2\))\(^{69}\). Changes in mineral parameters play an essential role in CKD pathophysiology. Indeed, in CKD, kidney function declines leading to a progressive deterioration of mineral homeostasis, with increased FGF23, phosphate and PTH plasma levels, and a reduction of Klotho and 1,25(OH)\(_2\) Vitamin D\(^{35}\).

Specifically, the decrease of Vitamin D have been related to the high levels of FGF23 produced by osteocytes to compensate the phosphate retention\(^{90}\). FGF23-mediated inhibition of 1α-hydroxylase and concurrent 24-α-hydroxylase stimulation lead to calcitriol degradation and reduction. Moreover, the decrease of glomerular filtration rate and reduced megalin expression by proximal tubular epithelial cells impair 25(OH) Vitamin D uptake\(^{44}\). Thus, the decrease of kidney function with progressive decline of serum calcitriol levels leads to hypocalcemia, secondary hyperparathyroidism and its complications such as secondary osteoporosis\(^{30}\).

Since the increase in FGF23 precedes other changes of mineral metabolism in CKD, and it has been proposed as an early biomarker of acute kidney injury, it has been suggested that FGF23 could be involved in the transition from acute kidney injury to the CKD. Moreover, it was shown that FGF23 maintains a linear relationship with GFR in the transition from mild to moderate CKD, whereas in advanced stages their relationship becomes exponential\(^{70}\). In parallel, Klotho can be considered a parameter as sensitive as FGF23. Indeed the rise of FGF23 levels in CKD is associated to simultaneous Klotho reduction\(^{71}\), 72. Furthermore, FGF23 exacerbates Klotho deficiency via its suppression, thus leading to a vicious cycle of FGF23 excess and klotho deficiency that may lead to CKD-related complications such as cardiovascular disease\(^{70}\).

Kuro-o and Moe describe CKD progression as a process of adaptative response of FGF23/αKlotho endocrine axis to the progressive loss of functional nephrons. While nephron number reduces, it will be necessary for remaining nephrons to compensate in order to maintain phosphate balance. The increase of FGF23 production represents a compensatory response; this can induce further nephrons loss due to the increased phosphate excretion per nephron, thus injuring the kidney. Considering the theoretical threshold of 0.5 µg/day of phosphate excretion per nephron in healthy individuals, the loss of 50% of nephrons in CKD is sufficient to attain kidney damage. This can induce an amplifying loop in which reduced number of nephrons induces FGF23 production that, in turn, enhances phosphotoxicity and further nephrons loss\(^{55}\).

**CKD-MBD**

Since mineral metabolism is essential in bone tissue homeostasis, its alterations in CKD lead to bone abnormalities in patients. In the past decade, it was suggested that extra skeletal calcification that occurs in CKD may result from altered mineral and bone metabolism of CKD. Indeed, abnormal mineral metabolism, bone, and extra skeletal calcification are closely related and all together contribute to the morbidity and mortality of patients with CKD\(^{73}\). Since the traditional definition of renal osteodystrophy did not accurately encompass the broader clinical syndrome, the acronym CKD-MBD was coined in 2006. In contrast to renal osteodystrophy that considered only the alterations of bone morphology displayed by CKD patients, CKD-MBD defines “A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: Abnormalities of calcium, phosphorus,
PTH, or vitamin D metabolism; Abnormalities in bone turnover, mineralization, volume, linear growth, or strength; Vascular or other soft-tissue calcification”73. The alterations of bone morphology that occur in CKD-MBD can be assessed by hystomorphometry and are classified according to turnover, mineralization and volume (TMV system)69. This scheme provides a clinically relevant description of underlying bone pathology and helps to define pathophysiology and therapeutic approaches. TMV classification system precisely describes the pathologic abnormalities in CKD patients:

- Osteomalacia (OM) is characterized by low bone turnover with abnormal mineralization. Depending on severity and duration, the bone volume may be low to normal.
- Adynamic bone (AD) features a low bone turnover with normal mineralization and bone volume from low to normal.
- Mild Hyperparathyroid-related bone disease (mild HPT) represents abnormality with medium turnover and a bone volume depending on the duration of the disease process.
- Osteitis Fibrosa (OF), also known as advanced HPT, is characterized by abnormalities along a continuum with mild HPT, with high bone turnover.
- Mixed Uremic Osteodystrophy (MUO) is depicted as high turnover, normal bone volume and abnormal mineralization69.

CKD-MBD represents a complex disorder characterized by alterations of interconnected organs that influence each other. The complexity of this system makes difficult to understand causes and effects of these dysfunctions.

One molecular pathway emerging as crucial in CKD-MBD pathogenesis is the Wnt pathway. Several studies reported increased circulating levels of Wnt inhibitor sclerostin in individuals with impaired renal function compared with those with normal kidney function74, 75. Moreover sclerostin values progressively raise across the CKD stages and are associated with cardiovascular events in a non-dialyzed CKD population76. Although the causes of this increase are debated, they are likely due to increased sclerostin production. So far, the bone has been considered the major source of sclerostin. Sabbagh and colleagues reported that the repression of Wnt/βcatenin signaling within osteocytes and the increased bone expression of sclerostin occur early in a mouse model of CKD77. However, a new concept of Wnt pathway activation as a developmental program reactivated during renal injury is emerging78. Early stage of CKD is characterized by nephrogenesis programs reactivation in order to repair the kidney. Wnt pathway coordinates tubular epithelial proliferation and polarity during nephrogenesis. When the canonical Wnt signaling is activated, Wnt inhibitors expression increases in order to regulate the pathway in a negative loop. In contrast to Wnt glycoproteins that once secreted have autocrine/paracrine effects, during renal injury, the Wnt inhibitors also act as systemic factors entering in the circulation and targeting extrarenal tissues78.

Circulating sclerostin has been also associated with vascular disease and mortality in CKD-MBD74, 76. All together these studies suggest sclerostin implication in the cross talk between kidney, bone and vasculature and involvement in the renal-bone-vasculature disease pathogenesis. Thus, a deep knowledge of the implication of Wnt pathway may open new avenues for CKD-MBD prevention and treatment74.

Conclusion
In conclusion, bone and kidney functions are tightly related. They coordinate each other to maintain mineral homeostasis through the release of endocrine factors. Likewise, their connection results in pathologic conditions as CKD-MBD. Moreover, bone and kidney share common molecular pathway alteration that need to be better investigated in order to improve
our understanding of CKD-MBD pathogenesis and the translational implications.

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