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The Chronic Kidney Disease – Mineral Bone Disorder (CKD-MBD): Advances in Pathophysiology

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Abstract

The causes of excess cardiovascular mortality associated with chronic kidney disease (CKD) have been attributed in part to the CKD-mineral bone disorder syndrome (CKD-MBD), wherein, novel cardiovascular risk factors have been identified. New advances in the causes of the CKD-MBD are discussed in this review. They demonstrate that repair and disease processes in the kidneys release factors to the circulation that cause the systemic complications of CKD. The discovery of WNT inhibitors, especially Dickkopf 1 (Dkk1), produced during renal repair as participating in the pathogenesis of the vascular and skeletal components of the CKD-MBD implied that additional pathogenic factors are critical. This lead to the discovery that activin A is a second renal repair factor circulating in increased levels during CKD. Activin A derives from peritubular myofibroblasts of diseased kidneys, wherein it stimulates fibrosis, and decreases tubular klotho expression. Activin A binds to the type 2 activin A receptor, ActRIIA, which is variably affected by CKD in the vasculature. In diabetic/atherosclerotic aortas, specifically in vascular smooth muscle cells (VSMC), ActRIIA signaling is inhibited and contributes to CKD induced VSMC dedifferentiation, osteogenic transition and neointimal atherosclerotic calcification. In nondiabetic/nonatherosclerotic aortas, CKD increases VSMC ActRIIA signaling, and vascular fibroblast signaling causing the latter to undergo osteogenic transition and stimulate vascular calcification. In both vascular situations, a ligand trap for ActRIIA prevented vascular calcification. In the skeleton, activin A is responsible for CKD stimulation of osteoclastogenesis and bone remodeling increasing bone turnover. These studies demonstrate that circulating renal repair and injury factors are causal of the CKD-MBD and CKD associated cardiovascular disease.

Keywords

CKD-MBD; activin; dickkhopf 1; klotho; FGF23; parathyroid hormone; renal osteodystrophy; vascular calcification

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Introduction and Epidemiology of the CKD-MBD

The kidney disease pandemic[1] is associated with high mortality rates, in part due to cardiovascular complications [2–5]. The kidney disease produced increase in cardiovascular risk extends to type 2 diabetes[6], where the presence of mild to moderate kidney disease increases atherosclerotic cardiovascular disease risk by 87% [7]. The causes of the increased cardiovascular risk associated with kidney diseases partly reside in the chronic kidney disease – mineral bone disorder (CKD-MBD) syndrome [8]. Three novel cardiovascular risk factors (hyperphosphatemia, vascular calcification, and elevated fibroblast growth factor 23 (FGF23) levels) have been discovered within the CKD-MBD [9–11], and their risk factor status confirmed in the general population [12–14]. The CKD-MBD begins early in CKD (stage 2) [15–18] consisting of vascular osteoblastic transition/calcification, an osteodystrophy, loss of klotho and increased FGF23 secretion [15], and progress into its causes have been made [18–21]. Recent studies demonstrating that factors participating in renal repair and injury and released into the circulation contribute to the pathogenesis of the CKD-MBD will be reviewed here.

Recent Advances in the Pathogenesis of the CKD-MBD

Multiple investigators and we have shown that kidney diseases reactivate developmental programs involved in nephrogenesis during disease stimulated renal repair [22–26]. Among the nephrogenic factors reactivated in renal repair, the Wnt (portmanteau of Wingless and Integrated) family (stimulated family members include Wnt4, Wnt7b, and Wnt10) is critical for tubular epithelial reconstitution [25–28]. In the control of Wnt function, canonical signaling transcriptionally induces the expression of a family of Wnt inhibitory proteins which are secreted proteins that serve to restrict the distances of Wnt stimulation as autocrine or paracrine factors [29–33]. The Wnt inhibitors are circulating factors, and the family includes the Dickkopfs (Dkk). We and others have shown that various forms of kidney disease increase renal expression of Wnt inhibitors including Dkk1, and increase their levels in the circulation [19,23].

Developmentally, Dkk1 is the only critical Wnt inhibitor in the kidney, the other family members have overlapping and redundant functions. Dkk1 functions in limiting Wnt7b stimulation of loop of Henle and collecting duct epithelial cell proliferation driving renal papillary length. Dkk1 deficiency produces excessively long renal papillae [34]. In kidney diseases, Dkk1 expression in the kidney and circulating levels are increased early in disease associated with tubular epithelial proliferation and repair [19], then decrease but remain elevated as a transcriptional target of canonical Wnts stimulating fibrosis [19,35–39].

Another Wnt inhibitor whose circulating levels are increased in CKD and considered an important CKD-MBD factor is sclerostin [40–42], a critical regulator of bone mass [43–46]. Sclerostin is considered an osteocyte specific protein [47–52]. Although message levels are known to be high in the kidney, protein is not thought to be normally expressed [52]. Sclerostin protein is expressed in the developing kidney (see IHC at the sclerostin antibody ab194940, abcam website), and in discreet pockets of medullary tubules in normal mouse kidneys (Figure 1). Development of CKD increases kidney sclerostin expression as shown in

the Alport kidneys with reduced kidney function (Figure 1), and this may contribute to its increased urinary excretion in CKD [53]. It is unclear whether renal sclerostin contributes to the increased circulating levels in CKD, but osteocyte expression is increased early in CKD [20,21], and the skeleton is thought to be the source of increased circulating sclerostin in CKD [41,54–57].

Neutralization of sclerostin elevated in the circulation of Cy/+ polycystic kidney disease (PKD) rats with CKD failed to inhibit vascular calcification and did not affect cardiac hypertrophy [58]. The anti-sclerostin monoclonal antibody (mab) treatment increased trabecular bone volume of CKD rats with low PTH levels but not high PTH levels, but did not improve cortical bone porosity or biomechanical properties of long bones [58].

Neutralization of Dkk1 elevated in the circulation of atherosclerotic diabetic mice with CKD, inhibited CKD induced vascular dedifferentiation, vascular calcification, and renal osteodystrophy [19]. The osteodystrophy effect of Dkk1 mab treatment involved stimulation of bone formation and remodeling leading to an increase in trabecular bone volume, and decreased cortical porosity [19]. The different results associated with neutralization Dkk1 versus neutralization of sclerostin may be due to differing effects of the two molecules on the frizzled/LRP5/5 receptor complex such that sclerostin has a tissue and context dependent effect not necessarily Wnt inhibitory whereas Dkk1 is always inhibitory, or due to the differing experimental models. Dkk1 is known to be stimulated in diabetes [59], and this could have influenced our results with Dkk1 inhibition.

The vascular effects of Dkk1 inhibition were surprising since Wnt signaling in the vascular smooth muscle is implicated in stimulating osteoblastic transition and vascular calcification [60,61]. However, recent studies demonstrate that Dkk1 mediated inhibition of aortic Wnt7b stimulates smad mediated aortic endothelial-mesenchymal transition (EndMT) and vascular calcification [62]. EndMT is a developmental physiologic process involved in the development of the cardiac valves, the cardiac septum and the aortic root [63,64], and it may [65] or may not [66] contribute to cardiac fibrosis in various adult disease states. Since EndMT is a process driven by smad transcription factors activated by factors in the transforming growth factor beta (TGFβ) superfamily [67], we investigated whether other factors involved in attempted renal repair during kidney disease derive from the TGFβ superfamily and are increased in the circulation during CKD. Of the TGFβ superfamily members, activin A, a known renal developmental factor and circulating hormone, was the primary candidate [24,68].

Activin is increased in the circulation by CKD associated with increased expression of activin in the kidney [69]. Surprisingly, the activin type 2A receptor (ActRIIA) was reduced by CKD in the aortic vascular smooth muscle and not the endothelium of diabetic/atherosclerotic mice, and a ligand trap for the receptor increased rather than decreased aortic ActRIIA signaling in this model. The ActRIIA ligand trap blocked the stimulation of vascular smooth muscle osteoblastic transition, vascular calcification, and renal fibrosis by CKD [69]. In the kidney, the ligand trap inhibited activin signaling, decreased renal Wnt activation and circulating Dkk1 and increased renal klotho expression (Figure 2). As a result a composite vascular effect of indirectly increasing endothelial Wnt signaling through loss

of Dkk1 in the circulation, and vascular smooth muscle differentiation through increased p-Smad 2/3 produced loss of osteoblastic transition and decreased atherosclerotic calcification.

In the skeleton, the ActRIIA ligand trap blocked CKD stimulation of osteoclastogenesis, bone resorption and remodeling (Figure 3) despite not affecting the high PTH levels [70]. This suggests that Activin A stimulation of osteoclast p-Smad 2 is required for the effects of CKD. How the role of activin A interacts with the effects of PTH and sclerostin in CKD remains to be determined.

Pathogenic Mechanisms in the Components of the CKD-MBD

vascular dedifferentiation/calcification

There are two forms of vascular calcification stimulated by CKD – intimal and medial calcification. CKD stimulated intimal calcification takes the form of atherosclerotic plaque neointimal calcification produced by osteoblastic transition of cells in the neointima whose origin have been linked to smooth muscle cells and circulating mesenchymal cells [71,72]. Likewise, medial calcification has been linked to vascular smooth muscle cells undergoing chondroosseous transition [72–74]. Although elevations in plasma DKK1, sclerostin, bone morphogenetic protein-9 (BMP-9)[75] and activin have been found in human kidney diseases [69,76] (Williams M and Hruska K, unpublished observations), and linked in preclinical studies to CKD stimulated vascular calcification and vascular osteoblastic transition [19,69,75], these studies are preliminary and need confirmation and characterization.

Loss of Renal Klotho

FGF23 signaling through FGF receptors typically requires the co-receptor function of membrane-bound αklotho. High levels of αklotho expression are restricted to a few tissues and define the primary targets of FGF23 action as the proximal and distal renal tubules, the parathyroid glands and the brain [77,78]. Klotho also circulates as a physiologically active hormone after either being cleaved at the cell surface by ADAM-10 and -17 in the renal tubules. Alternative splicing of the *klotho* gene transcript produces a secreted protein with only one klotho domain of unknown function. Insulin stimulates the cleavage and release of the extracellular domain of klotho by ADAM10 and ADAM17 [79]. Cleaved klotho directly regulates calcium and phosphorus excretion in the kidney and participates in systemic mineral homeostasis by regulating 1-alpha hydroxylase activity, PTH and FGF23 secretion [80,81]. Klotho expression is significantly reduced by kidney injuries such as acute kidney injury, glomerulonephritis, calcineurin inhibitor use and chronic allograft injury [82]. We have shown that the reduction of klotho is in part related to activin and ActRIIA signaling [69]. The resulting klotho deficiency limits its regulation of FGF23 production and leaves hyperphosphatemia as the principal regulator of FGF23 secretion in CKD. Furthermore, the loss of membrane-bound klotho expression limits FGF23-stimulated signal transduction through FGF receptor/klotho complexes. One result is the loss of negative feedback to FGF23 secretion and the continual production of FGF23 and secretion by the osteocyte. In late CKD, the very high levels of FGF23 permit anomalous FGF receptor activation independent of Klotho and result in unique FGF23-stimulated pathologies such as cardiac myocyte hypertrophy [83,84]. In addition, recent mechanistic studies have directly

linked klotho deficiency with cardiovascular disease including vascular calcification, vascular stiffness, and uremic vasculopathy [18,85].

Hyperphosphatemia

As renal injury decreases the number of functioning nephrons, phosphate excretion is maintained by reducing the tubular reabsorption of filtered phosphate in the remaining nephrons under the influence of FGF23 and PTH [86]. The effects of FGF23 on phosphate excretion are limited by proximal tubular klotho deficiency in CKD, and PTH becomes a major adaptive mechanism maintaining phosphate homeostasis. In stage 4–5 CKD (GFR < 30% of normal), this adaptation is no longer adequate and hyperphosphatemia develops despite high PTH and FGF23 levels [86].

CKD contributes to hyperphosphatemia and vascular calcification through inhibition of skeletal function. Bone resorption increases phosphate release to the plasma and decreases phosphate deposition resulting in increased serum phosphorus levels [87]. Hyperphosphatemia stimulates osteoblastic transition in the vasculature and directly contributes to extraskeletal mineralization through an elevated calcium-phosphorus product [88].

Hyperphosphatemia exerts other important effects in the CKD-MBD axis. In the kidney, hyperphosphatemia suppresses 1-alpha-hydroxylase activity that further contributes to calcitriol deficiency [89]. In the parathyroid gland, hyperphosphatemia directly stimulates parathyroid cells independent of calcium and calcitriol levels, producing nodular hyperplasia and increasing PTH secretion [90]. In the skeleton, phosphorus stimulates FGF23 secretion from osteocytes [91,92].

Osteodystrophy

With progressive loss of renal function, cancellous bone volume may be increased along with a loss of cortical bone, but this is in part due to deposition of woven immature collagen fibrils instead of lamellar mature fibrils. Thus, bone strength suffers despite an apparent increase in mass detected by dual energy x-ray absorptiometry (DXA) [93]. Patients with advanced CKD could have a loss or gain in bone volume depending on overall bone balance. When the bone balance is positive, osteosclerosis may be observed when osteoblasts are active in depositing new bone composed primarily of immature woven collagen. However, this scenario is rare in the 21st century due to improved therapy of secondary hyperparathyroidism. When the bone balance is negative both cortical and cancellous bone loss occurs, resulting in osteopenia or osteoporosis detected by DXA. The prevalence of osteoporosis in CKD patients exceeds that of the general population and is a major public health concern in CKD [94]. With high-turnover renal osteodystrophy, and osteitis fibrosa, bone resorption rates are in excess of bone formation and osteopenia progressing to osteoporosis may result [95]. With low-turnover renal osteodystrophy, both bone formation and resorption rates may be reduced although resorption is still in relative excess and loss of bone mass occurs [96]. Therefore in CKD, osteoporosis may be observed with either high-turnover or low-turnover renal osteodystrophy. The impact of this phenomenon extends far beyond bone health in CKD, as excessive bone resorption rates contribute to hyperphosphatemia with stimulation of heterotopic mineralization including vascular

calcification [88]. This disrupted systems biology links kidney, skeletal, and parathyroid dysfunction to cardiovascular risk and mortality through the CKD-MBD.

FGF23

FGF23 is the original phosphatonin (hormone regulating phosphate excretion) discovered in studies of autosomal dominant hypophosphatemic rickets and oncogenic osteomalacia [97]. FGF23 is produced by osteocytes and osteoblasts, and it represents direct bone-kidney and bone–parathyroid connections in the multiorgan systems biology involved in the CKD-MBD [98]. Circulating FGF23 levels rise after mild renal injury and progressively increase several fold during the course of CKD due to increased osteocyte secretion as well as decreased catabolism by the injured kidney. FGF23 levels rise prior to changes in calcium, phosphorus, or PTH levels and are now recognized as one of the earliest detectable biomarkers of the CKD-MBD [16,99].

FGF23 levels have been associated with cardiovascular risk in CKD, and kidney transplant loss and mortality [100,101]. In humans and animal models, Faul et al demonstrated that FGF23 is not only a biomarker associated with cardiovascular risk in CKD, but is also a direct pathogenic factor causing left ventricular hypertrophy (LVH) through activation of the calcineurin-NFAT pathway in cardiac myocytes [83,84].

Recently, the pathogenic nature of circulating FGF23 has become more intriguing. Andrukhova et al showed that FGF23 directly regulates the abundance of the thiazide-sensitive sodium-chloride transporter (NCC) in the distal convoluted tubule, leading to increased distal sodium reabsorption, effective circulating volume expansion, hypertension, and cardiac hypertrophy, effects that were abrogated by a thiazide diuretic [102]. Interestingly, these FGF23-mediated effects on cardiovascular pathophysiology were augmented in animal models ingesting a low sodium diet (which stimulates aldosterone secretion), raising the possibility of an interaction between FGF23 and the renin-angiotensin-aldosterone axis in CKD-stimulated cardiovascular disease. Furthermore, Humalda et al demonstrated that humans with higher baseline FGF23 levels had a reduced antiproteinuric response to dietary sodium restriction and ACE inhibitor therapy, which has been associated with heighted cardiovascular and end-stage renal disease (ESRD) risk in CKD [103]. Andrukhova et al also demonstrated that FGF23 promotes calcium reabsorption through stimulation of the apical calcium entry channel, TRPV5, in the distal tubule [104]. Because the calcium entry channel is also regulated by klotho [105], the Andrukhova et al findings [102,104] raise the issue of the mechanism of klotho's actions. Are they direct through glucuronidase activity and FGF23 independent, or as the FGF23 co-receptor and FGF23 dependent?

Vitamin D deficiency

In early CKD, the physiologic actions of FGF23 secretion from the osteocyte include inhibition of 1-alpha-hydroxylase and stimulation of 24-hydroxylase in proximal renal tubules, thereby decreasing calcitriol production and producing 25-hydroxyvitamin D deficiency [106]. As CKD advances, the decrease in functioning nephron mass combined with hyperphosphatemia and increased FGF23 levels results in calcitriol (1,25-hydroxyvitamin D) deficiency as well [107]. Calcitriol deficiency decreases intestinal calcium absorption

leading to hypocalcemia and diminishes tissue levels of vitamin D receptors, which in the parathyroid gland results in resistance to calcitriol-mediated regulation and stimulation of PTH secretion leading to secondary hyperparathyroidism [108].

Hyperparathyroidism

PTH regulates secretion of FGF23 and is required for the early stimulation of FGF23 secretion [109], which is the earliest detected abnormality of the CKD-MBD [99]. Thus, there is a regulation of PTH secretion early in CKD that remains to be clarified. As CKD progresses, components of the CKD-MBD result in increased production of PTH and nodular hyperplasia of the parathyroid glands. Sustained elevation in PTH levels, while adaptive to maintain osteoblast surfaces, are associated with an abnormal phenotype of osteoblast function and osteocyte stimulation with relatively less type 1 collagen and more RANKL ligand production than anabolic osteoblasts [110]. New studies discussed above indicate that other factors such as FGF23 and activin may impact osteoblast function besides PTH, and produce the mineralization disorder of CKD changing the material properties of bone. The outcome is a high turnover renal osteodystrophy, excess bone resorption, skeletal frailty and elevated fracture risk [111].

Cardiovascular disease

The CKD-MBD is a contributing factor to vascular stiffness and calcification that increases the systolic blood pressure, pulse wave velocity, and left ventricular mass, all of which are surrogates for cardiovascular risk in the general population and in those with CKD [112]. Structural and functional abnormalities of the vasculature are seen in early CKD, including vascular stiffness and endothelial dysfunction that progress to vascular calcification, a common phenomenon in the aging general population that is accelerated in CKD to the highest level seen in clinical medicine. Vascular calcification further intensifies vascular stiffness and promotes the development of LVH, all processes that contribute to cardiovascular risk and excess cardiac mortality in native and transplant CKD.

In animal models with mild renal insufficiency (equivalent to human stage 2 CKD), we have demonstrated that expression of proteins involved in the contractile apparatus of aortic smooth muscle cells are decreased, reflecting a dedifferentiated state of the vasculature in early CKD [19]. Within the developmental program of mesenchymal stem cells and early vascular progenitors, dedifferentiated vascular smooth muscle cells are susceptible to osteoblastic transition, which contributes to vascular calcification in CKD. Osteoblastic transition of vascular smooth muscle cells produces CKD-stimulated calcification of atherosclerotic plaques as well as the tunica media, resulting in either neointimal or medial vascular calcification [113].

Emerging Concepts in the Systems Biology of the CKD-MBD

The Wnt pathway and reactivation developmental pathways during renal repair mechanisms in kidney diseases

Kidney injuries produce circulating signals that directly affect the vasculature, the myocardium and the skeleton. These signals are derived from reactivation of developmental

programs of nephrogenesis in an attempt at kidney repair, which are typically silent in the normal adult kidney [19]. The classic example is the reactivation of the Wnt pathway that controls tubular epithelial proliferation and polarity during nephrogenesis and is a driving force in renal fibrosis [26]. Activation of the canonical Wnt pathway increases expression of downstream transcriptional targets, including Wnt inhibitors that function in a negative feedback loop to autoregulate Wnt activation. These Wnt inhibitors include Dickkopf-1 (Dkk1), soluble frizzled related proteins, Wnt-modulator in surface ectoderm (Wise), and sclerostin among others. While Wnts are strictly autocrine/paracrine factors, the Wnt inhibitors also function as circulating systemic factors [114]. The role of Wnt in renal development largely precedes the invasion of the microcirculation forming the glomerulus and the peritubular capillaries. Therefore, while the Wnt inhibitors did not evolve as circulating factors produced by the normal kidney, during kidney injury and repair they are released into the systemic circulation and may inhibit the physiologic roles of Wnt in extrarenal tissues [19].

We and others have recently shown this “unintended” systemic inhibition of Wnt activity and production of activin A stimulated by kidney disease to have major consequences in the skeleton and vasculature. In animal models of early CKD, incomplete recovery from acute kidney injury led to increased expression of Wnt inhibitors (e.g., Dkk1, sclerostin) and activin in the injured kidney and increased levels in the systemic circulation [19,69]. The skeleton was affected through both changes in remodeling (decreased bone formation rates) and increased bone resorption and in secretory properties of the osteocytes (increased FGF23 secretion). The cardiovascular system was affected through loss of vascular contractile machinery and dedifferentiation of vascular smooth muscle cells, stimulation of osteoblastic transition and vascular calcification, and promotion of cardiac hypertrophy [19,69]. Neutralization of circulating Dkk1 using a monoclonal antibody or a ligand trap for ActRIIA resulted in increased bone formation rates and bone volume, improved vascular function, and decreased osteoblastic transition and vascular calcification [19,69].

Conclusion and Future Directions

The CKD-MBD defines a disruption in the systems biology between the injured kidney, skeleton, and cardiovascular system that has a profoundly negative impact on survival in CKD. Recent translational discoveries have introduced a new paradigm where kidney injury directly leads to skeletal and cardiovascular injury through the production of pathogenic circulating factors during attempted renal repair, including molecules that inhibit the canonical Wnt pathway and activin, both processes that have been implicated in chronic allograft injury as well as cardiovascular disease. Future studies must clarify whether incomplete recovery from acute kidney injury is sufficient to stimulate these disturbances in the kidney-skeletal-cardiovascular axis that contribute to decreased patient and allograft survival. This would identify the early CKD-MBD as an important therapeutic target for improving long-term outcomes in CKD.

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Highlights

This review discusses novel aspects of CKD-MBD pathogenesis

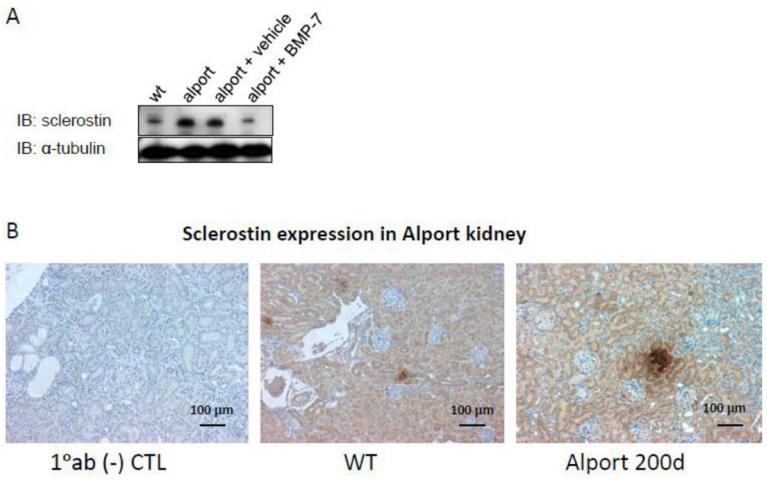

Figure 1.

Renal Expression of Sclerostin. A, Westerns of kidney homogenates. Sclerostin is expressed in 200 day old normal mouse kidneys. Sclerostin expression is increased in 200 day old Col4a5 deficient mice with severe kidney failure (GFR 15% of normal). Treatment of Col4a5 deficient Alport syndrome mice with BMP-7 decreased sclerostin expression. B, Immunohistochemistry of renal sclerostin. Renal cortical sections from kidneys of normal 200 day old C57BL6J mice show patches of tubular sclerostin expression. Tubular sclerostin expression was increased in 200 day old Col4a5 Alport mice.

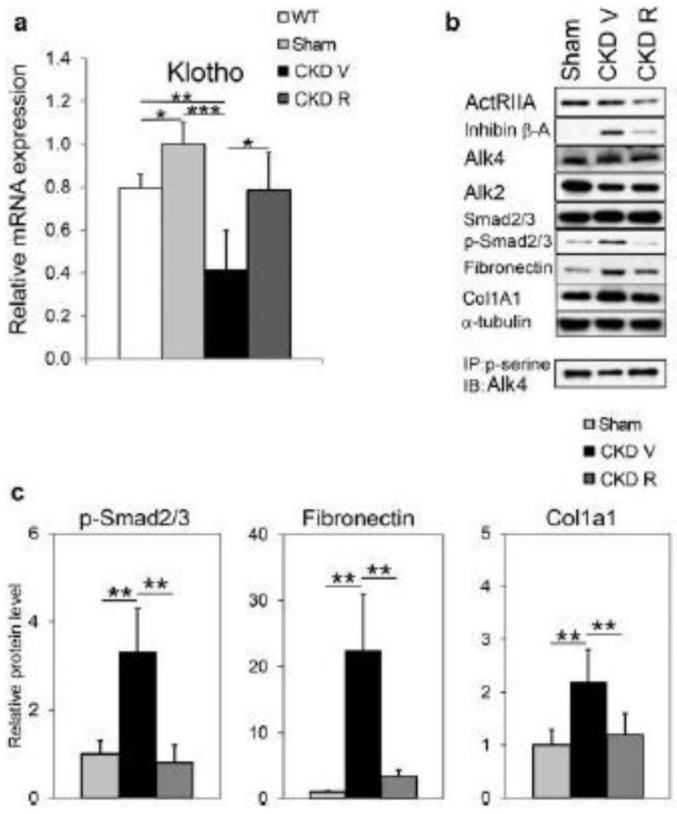

Figure 2.

Renal αklotho mRNA and activin A (inhibin β-A homodimer) signaling in renal homogenates. A, Compared to sham operated *ldlr−/−* high fat fed mice, *ldlr−/−* high fat fed CKD mice (CKD V) had reduced αklotho expression that was restored by treatment with a ligand trap for the activin receptor type IIA (ActRIIA) (CKD R). B, Inhibin β-A (activin A) expression was increased in homogenates of *ldlr−/−* high fat fed CKD kidneys and reduced by treatment with the ActRIIA ligand trap. B and C, Homogenates of *ldlr−/−* high fat fed CKD kidneys had increased levels of p-Samd2/3, the transcription factor activated by ActRIIA signaling. C, Smad2/3 transcriptional targets, fibronectin and Col1a1, were increased by CKD and decreased by treatment with the ActRIIA ligand trap. (Reproduced with permission from Agapova et al., Kid Int 89: 1231–1243, 2016).

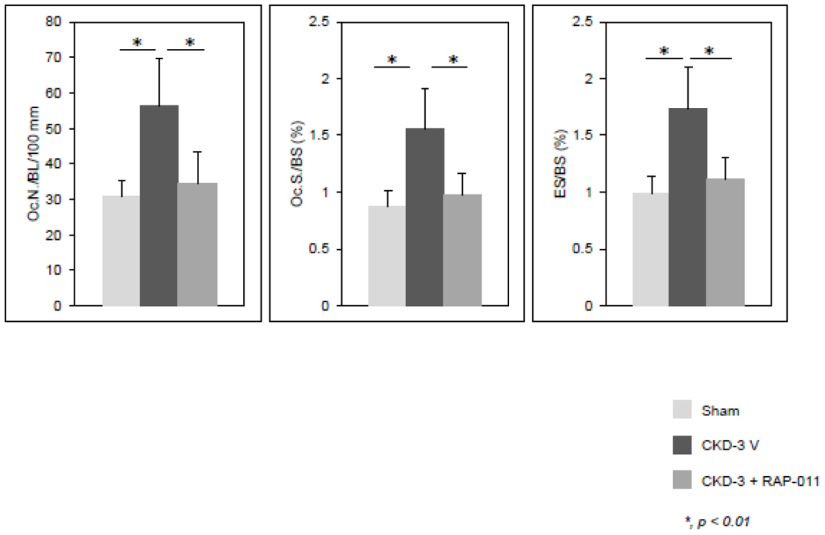

Figure 3.

Osteoclast number, surfaces, and eroded surfaces in trabecular bones of sham operated *ldlr−/−* high fat fed mice, *ldlr−/−* high fat fed CKD mice (CKD V), and *ldlr−/−* high fat fed CKD mice treated with RAP-011, an ActRIIA ligand trap, (CKD R). CKD increased and RAP-011 treatment reversed the increase in osteoclast numbers, surfaces and eroded surfaces. (Reproduced with permission from Sugatani et al., Kid Int 91: 86–95, 2107).