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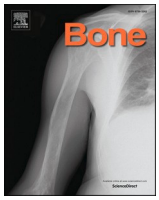

Review Article

Chronic kidney disease- mineral and bone disorder in autosomal dominant policystic kidney disease

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A B S T R A C T

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder characterized by bilateral renal cysts that detach from parental tubules, progressively leading to renal function loss. Patients with ADPKD represent a unique subset of chronic kidney disease (CKD) individuals, sharing common CKD features while also exhibiting distinct traits specific to ADPKD. This review described the unique patterns of mineral and bone disorders present in ADPKD in the early CKD stages. The principal points are: the extraosseous FGF23 production by cystic tissues in the kidneys and liver, resulting in elevated circulating FGF23 levels with possible impact on calcium and phosphate balance and cardiovascular risk in ADPKD; the higher prevalence of low bone turnover disease in ADPKD than in other forms of CKD. This is likely due to disruptions in signals mediated by the Polycystin-1 and Polycystin-2 heterodimers, which are expressed on the primary cilia of osteocytes and osteoblasts, leading to impaired bone anabolism. Given these insights, a comprehensive approach is essential for monitoring and managing mineral and bone disorders in ADPKD patients. Early intervention and targeted therapies could mitigate the progression of mineral and bone disorders and possibly improve patient outcomes.

1. Introduction

1.1. ADPKD: Pathophysiological mechanisms

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder typified by bilateral renal cysts that detach from parental tubules and gradually lead to loss of renal function [1]. In about 98 % of cases, the germline mutation involves the PKD1 and PKD2 genes, which encode the interacting proteins polycystin-1 (PC-1) and polycystin-2 (PC-2), respectively. These mutations lead to alterations in multiple signaling pathways, including altered cell cycle proliferation and misregulation of the Ca2+ signaling mechanism [2]. GANAB, DNAJB11, HNF1β, and PKHD1 represent the remaining genes involved in ADPKD phenotypic-like cases and contribute to the regulation of polycystin genes, among others. [3]. Cysts arise when the non-mutated allele acquires somatic mutations or when the proteins which interact with or regulate polycystin proteins are affected. Currently, it is accepted that polycystins regulate crucial calcium signaling pathways and renal cysts form when the level of functional polycystin proteins get below a critical threshold [4]. It has been demonstrated that different signaling pathways are affected by either being upregulated (cAMP signaling) or downregulated (Ca2+ signaling) in cystic cells following mutations to PC-1 and/or PC-2 [5].

1.2. Calcium signaling and cilia dysfunction in ADPKD

The reduction in intracellular Ca2+ level results in elevated cAMP levels that lead to aberrant cell proliferation. Despite numerous studies, the role of disrupted calcium signaling is still a matter of debate [5,6]. Calcium is involved in cellular signal transduction via the release of Ca2+ from the endoplasmic reticulum (ER) via the inositol triphosphate receptor (IP3R) [7,8]. The release of Ca2+ ions from the ER, stimulated by IP3, leads to depletion of ER Ca2+. Stromal interaction molecule1 (STIM1) are stimulated by the reduction in Ca2+ level and increase Ca2+ into the cell via a store-operated Ca2+ entry (SOCE) mechanism [9]. The sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump facilitates the reuptake of Ca^{2+} into the ER. Even if the underlying mechanisms involved in misregulation of Ca2+ signaling in ADPKD

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mechanism are still unclear, it is well accepted that reduced intracellular Ca2+ results in elevated cAMP levels which in turn stimulates aberrant cell proliferation [10]. Murali K Yanda et al. [11] demonstrated that enhanced Ca2+ signaling and alterations in proteins association with the mitochondrial Ca2+ uptake complex are associated with malfunction of PC1. Particularly, mitochondrial Ca2+ uniporter (MCU) and voltage-dependent anion channels 1 & 3 (VDAC) were down-regulated in different mouse and cell models of ADPKD along with the Ca2 + −dependent enzyme, pyruvate dehydrogenase phosphatase (PDHX). The release of Ca2+ from the ER, and Ca2+ uptake by the mitochondria were upregulated in PC1 (polycystin)-null cells. Inhibition of mitochondrial Ca^{2+} uptake with the specific inhibitor Ru360 resulted in reduced cyst growth and changes in apoptosis and cell proliferation. Moreover, VX-809, a modulator of the processing and trafficking of CFTR, reduces cyst growth in ADPKD by reversing the cystic phenotype from secretory to absorptive [12].

Patients with ADPKD represent a unique subset of individuals with chronic kidney disease (CKD) that exhibit distinct features secondary to alterations in cellular activity present in multiple organs. In this review, we highlight the characteristics of mineral and bone disorders in patients with ADPKD in particular in the early stages of CKD.

2. Bone Mineral disorders in chronic kidney disease

2.1. CKD-MBD pathogenesis

Mineral metabolism abnormalities are an early and intrinsic feature of chronic kidney disease, characterized by phosphate retention, declining calcitriol synthesis, decreased calcium, and secondary hyperparathyroidism (SHPT). These alterations not only impair bone turnover and mineralization—resulting in renal osteodystrophy with an elevated risk of fractures—but also contribute to vascular calcification and increased cardiovascular risk [13–15]. This outlines a complex condition known as chronic kidney disease–mineral and bone disorder (CKD-MBD), whose pathogenesis remains incompletely understood [16].

2.2. FGF23, klotho, and phosphate axis

In 2000, fibroblast growth factor 23 (FGF23) was identified as a phosphaturic hormone produced by osteocytes and osteoblasts, aberrantly high levels of which cause autosomal dominant hypophosphatemic rickets (ADHR)' [17] due to the resulting phosphaturia, hypophosphatemia and reduced calcitriol. FGF23 acts on the kidney, via its receptor complex with the co-receptor Klotho, to inhibit NaPi cotransporters and renal 1α-hydroxylase, leading to enhanced phosphaturia and suppression of calcitriol synthesis. In CKD, circulating FGF23 levels increase early, often preceding detectable changes in serum phosphate or PTH levels [18–20]. One proposed mechanism for this early rise is the reduction in tubular Klotho expression, which may induce resistance to FGF23 at its target site, thereby stimulating a compensatory increase in its secretion. However, some evidence suggests that FGF23 elevation precedes the decline in Klotho [21], indicating that additional mechanisms are likely involved. Recent experimental models support the hypothesis that a declining number of

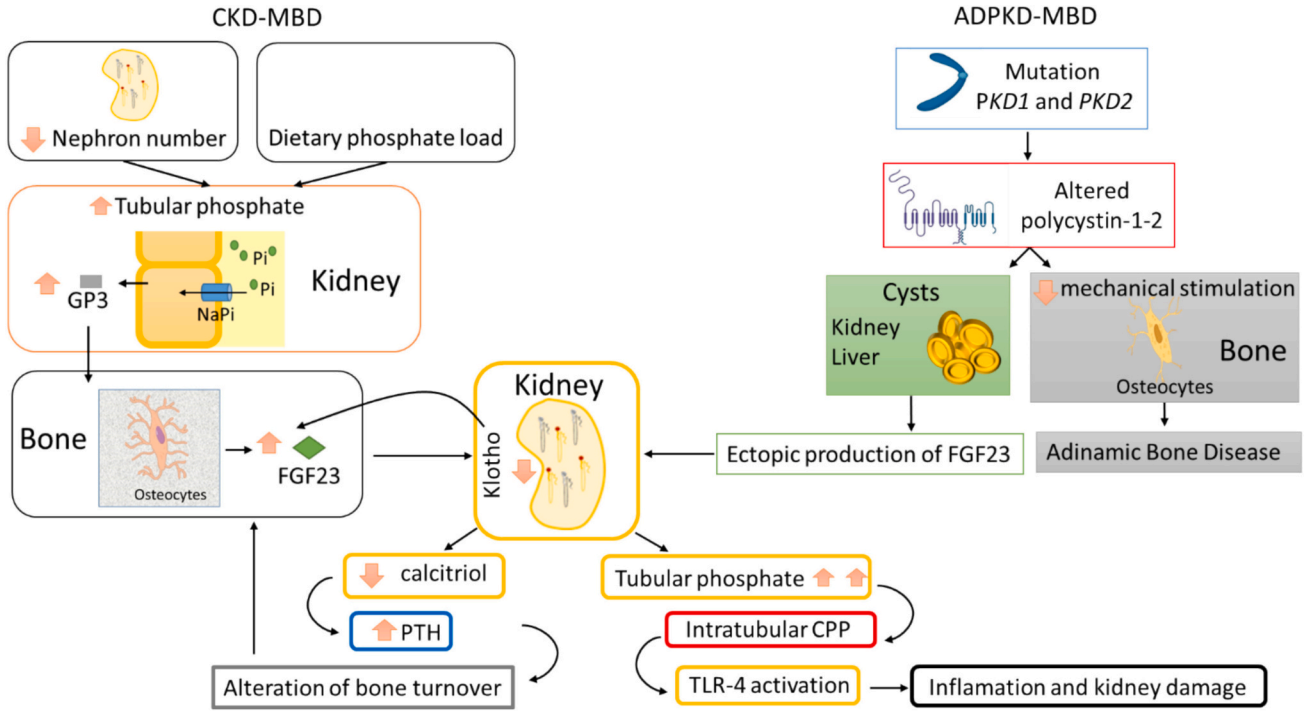

Fig. 1. Comparison between CKD-MBD and ADPKD-MBD.
In CKD, one of the key mechanisms driving the development of mineral and bone disorder (CKD-MBD) is the reduction in nephron number, which increases the phosphate load per nephron. This leads to elevated intratubular phosphate concentrations, stimulating the proximal tubular synthesis of glycerol-3-phosphate (G3P), a factor that enhances FGF23 production by bone. FGF23 acts on the kidney by suppressing calcitriol synthesis, increasing PTH levels, and altering bone turnover. It also promotes phosphaturia, which may further raise intratubular phosphate levels. Excessive phosphate can lead to the formation of calcium-phosphate particles (CPPs), which activate inflammatory pathways via toll-like receptor 4 (TLR4), reduce renal Klotho expression, and contribute to the progression of kidney damage. In ADPKD, mutations in *PKD1* and *PKD2* lead to dysfunctional polycystin-1 and -2, resulting in the formation of renal and hepatic cysts. These cysts serve as ectopic sources of FGF23. FGF23 acts on the kidney through the same pathways described above. At the skeletal level, defective polycystin-mediated mechanosensation may impair osteocyte function, contributing to reduced bone turnover.
Abbreviations: CKD-MBD: Chronic Kidney Disease - Mineral and Bone Disorders; ADPKD-MBD: Autosomal Dominant Polycystic Kidney Disease - Mineral and Bone Disorders; G3P: Glycerol-3-phosphate; NaPi: Sodium-phosphate cotransporter; FGF23: Fibroblast growth factor 23; PTH: Parathyroid hormone; CPP: Calciprotein particle; TLR4: Toll-like receptor 4.

functioning nephrons increases phosphate load per nephron, which in turn stimulates proximal tubular synthesis of glycerol-3-phosphate (G3P), a mediator shown to enhance FGF23 production in bone [22,23]. These findings point to a kidney–bone signaling axis in which tubular phosphate handling regulates osteocytic FGF23 synthesis. In this context, bone acts as an endocrine organ, adjusting its secretory profile in response to early CKD-related disturbances in phosphate and calcium homeostasis, with downstream effects on bone turnover and mineralization (Fig. 1).

2.3. Bone turnover in CKD

The coupling between the persistent process of bone resorption and bone formation is essential for bone health. Osteoclasts are responsible for resorption and osteoblasts are involved in formation. Osteocytes are also involved in the regulation of bone turnover. Two main systems, the RANK-RANK-L-OPG axis and the Wnt-Sclerostin pathway are essential for the regulation of remodeling activity. Activation of the receptor activator of NF-κB (RANK), expressed by osteoclast and its precursors, promotes the differentiation of monocytes into mature bone-resorbing osteoclasts. Receptor activator of NF-κB ligand (RANK-L) is secreted by osteoblasts and pre-osteoblasts. Osteoblasts are also the main source of osteoprotegerin (OPG). OPG, a high-affinity ligand RANK-L, acts as soluble inhibitor of RANK-L thus reducing osteoclasts differentiation. Osteocytes secrete both RANK-L and sclerostin. Wnt (Wingless type mouse mammary tumor virus integration site) signaling is a critical pathway regulating bone anabolism by promoting osteoblast differentiation and activity. Sclerostin is a potent inhibitor of bone formation, acting through binding to the LRP5/6 co-receptors and suppression of Wnt/β-catenin signaling. Alterations in these pathways are implicated in both CKD-associated bone disease and the specific bone phenotype of ADPKD [24]. Uncoupling between resorption and formation due to alteration in physiological pathways or systemic mineral metabolic disturbances leads to pathological bone conditions in turnover, volume and mineralization [25].

The term “renal osteodystrophy” (ROD) refers to various bone lesions: low turn-over lesions with defective mineralization (osteomalacia), low turn-over with normal mineralization (adynamic bone disease), and high-turnover bone usually related to secondary hyperparathyroidism (when severe osteitis fibrosa, evidenced by the presence of marrow fibrosis). Additionally, mild or mixed forms of ROD can be observed.

According to KDIGO, the TMV classification describes bone disease in terms of turnover, mineralization, and volume, providing a structured framework for histological diagnosis in CKD [26].

In CKD, secondary hyperparathyroidism, phosphate retention, and reduced calcitriol contribute to the dysregulation of the RANK–RANKL–OPG system. Elevated PTH and phosphate levels stimulate RANKL expression and suppress OPG, promoting osteoclastogenesis and bone resorption, which underlies the high-turnover bone phenotype. Simultaneously, sclerostin levels tend to rise with declining kidney function, possibly due to reduced renal clearance and increased osteocytic expression. This leads to inhibition of Wnt signaling and suppression of bone formation, potentially contributing to the development of the low-turnover phenotype often observed in early-stage CKD [27]. Together, these mechanisms contribute to the heterogeneous skeletal abnormalities seen in renal osteodystrophy. Biomarkers indicative of bone cell activity, such as alkaline phosphatase, tartrate-resistant acid phosphatase, bone collagen-derived peptides, and PTH, could help identify bone disease [28]. Recently, the concept of “CKD-associated osteoporosis” has been introduced to better capture the overlap between classical osteoporosis and bone abnormalities in CKD. This terminology, proposed in recent KDIGO recommendations, reflects the growing recognition of fracture risk and skeletal fragility in this population, beyond traditional definitions of renal osteodystrophy [29].

Some evidence suggests that in ADPKD, there are unique aspects that differentiate the development of mineral metabolism alterations.

3. CKD-MBD in ADPKD

3.1. FGF23 production and actions

Experimental evidence indicates that ADPKD possesses unique elements that induce mineral metabolism alterations, specifically elevated FGF23, which are independent in the early CKD stages by the renal disease severity or phosphate balance. Spichtig et al. demonstrated that PKD animal model exhibited higher FGF23 levels compared to non-PKD model with equivalent renal function [30]. Evaluating tissue expression of FGF23 revealed that bone tissue produced similar amounts of FGF23 in both models. However, renal tissue, particularly the cells lining renal cysts in the PKD model, produced elevated levels of FGF23, accounting for the increased circulating levels. Importantly, in this study, the increase in FGF23 did not result in other differences in mineral metabolism; the two models did not differ in calcium, phosphate, PTH, or tubular phosphate transport capacity. This apparent dissociation between elevated FGF23 and normal phosphate handling may reflect a state of partial FGF23 resistance. In some PKD animal models, early reductions in renal Klotho expression have been reported [31,32] pointing to a mechanism for this resistance. In contrast, in early-stage ADPKD patients, serum and renal Klotho levels appear relatively preserved [33,34], suggesting that other mechanisms—distinctive of ADPKD—may underlie impaired FGF23 responsiveness (Fig. 2).

Consistent with this experimental evidence, Pavik et al. studied 99 patients with ADPKD and CKD stages 1–2, finding higher FGF23 levels compared to groups with the same CKD stage without ADPKD [33]. Furthermore, unlike the control group, where not all patients had pathological FGF23 levels as expected, all ADPKD patients exhibited elevated FGF23 levels regardless of disease stage or FGF23/Klotho levels. This indicates that FGF23 production in this population does not follow the same regulatory mechanisms as in the non-ADPKD population. Similar results were observed by Gitomer et al., who compared 472 patients from the HALT-PKD study with 472 patients from the CRIC study, both with comparable GFR of 50 ml/min [35]. ADPKD patients had higher FGF23 levels compared to CKD patients. Again, in the ADPKD population, FGF23 levels were not modulated, with almost all patients displaying elevated FGF23 levels, unlike the CKD population. These findings align with experimental evidence of ectopic FGF23 production in ADPKD patients at the cystic tissue level. Consistently, liver biopsies of ADPKD patients with liver cysts demonstrated increased pericystic hepatic FGF23 production compared to non-cystic controls [36]. Furthermore, reducing cystic liver mass in these patients decreased circulating FGF23 levels.

In most clinical studies of ADPKD, including those by Pavik et al. and Gitomer et al., FGF23 was measured using assays specific for the intact, biologically active form. This confirms that the observed elevation reflects a true increase in the circulating hormone capable of interacting with renal and extrarenal targets.

The clinical relevance of elevated FGF23 levels in ADPKD on mineral metabolism and disease progression requires further evaluation. Evidence suggests reduced expression of type II sodium/phosphate cotransporters in renal tubules in ADPKD models, resulting in decreased serum phosphate levels but increased phosphate load per nephron [37]. However, these findings are largely derived from the Han: SPRD (cy/+) rat model, in which cystic changes primarily affect the proximal tubule and lead to brush border loss. Since human ADPKD typically involves more distal nephron segments, the translational relevance of these observations should be interpreted with caution. These observations are consistent with findings in ADPKD, where circulating FGF23 levels are elevated from early disease stages, while serum phosphate concentrations are often maintained within the normal range. This pattern may reflect reduced tubular responsiveness to FGF23, despite normal Klotho values reported in ADPKD patients [33,34]. In agreement with these

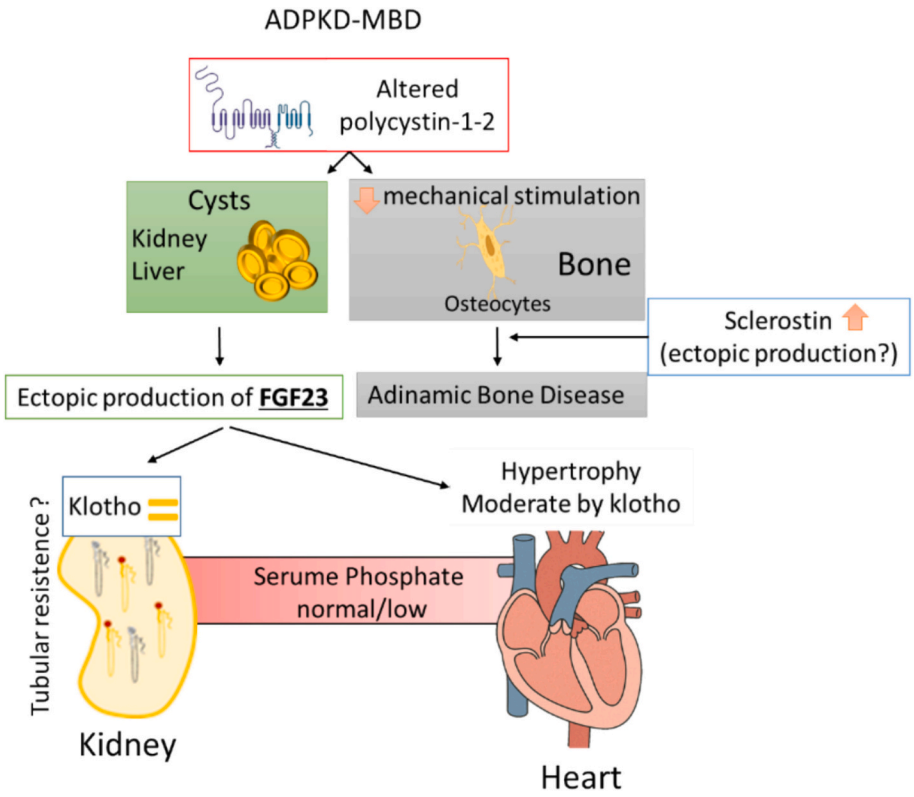

Fig. 2. ADPKD-MBD.
Polycystin dysfunction in ADPKD leads to: 1)the development of renal and hepatic cysts, which serve as ectopic sources of FGF23. Despite elevated circulating FGF23 levels and preserved renal Klotho expression, serum phosphate concentrations are often normal or only mildly reduced. This paradox may be explained by a form of tubular resistance to FGF23 that is not mediated by Klotho deficiency. Furthermore, preserved Klotho expression may mitigate the cardiotoxic effects of FGF23, particularly in the early stages of ADPKD; 2)impaired osteocytic function, resulting in reduced bone turnover. This low-turnover state may be further aggravated by increased sclerostin levels, potentially due to ectopic production.
Abbreviations: ADPKD-MBD: Autosomal Dominant Polycystic Kidney Disease - Mineral and Bone Disorders;

observations, Xue et al. demonstrated in a large ADPKD cohort that phosphaturia was regulated independently of FGF23, as its levels did not differ between patients with lower versus higher tubular phosphate reabsorption [38]. Collectively, these data suggest that ADPKD patients exhibit extraosseous FGF23 production by cystic tissues (kidney and liver), which is responsible for elevated circulating FGF23 levels irrespective of phosphate balance. The elevated FGF23 levels observed in ADPKD, despite preserved Klotho expression, do not appear to significantly affect serum phosphate or phosphaturia [34–39]. This suggests the presence of disease-specific mechanisms in the regulation of phosphate handling in ADPKD, which warrant further investigation. The contribution of ectopic FGF23 production to CKD-MBD pathogenesis therefore remains uncertain. It is important to underline that the increase intratubular phosphaturia has been detected as an important factor of kidney damage progression. The study by Shiizaki illustrates that the increased phosphate load in the S3 segment can, upon reaching critical thresholds, lead to the precipitation of intratubular calcium-phosphate particles. In a murine model, these particles were shown to activate Toll-like receptor 4, initiating intracellular NF-κB and p38 signaling pathways, which in turn induce inflammation, reduce renal Klotho expression, and contribute to CKD progression [40]. Observational data have reported an association between elevated circulating FGF23 levels and more rapid disease progression in ADPKD, although causality has not been established and FGF23 does not appear to improve prognostic prediction over established risk models [41]. Consistent with these observations, higher FGF23 levels have been associated with lower eGFR in both ADPKD and non-ADPKD CKD populations, as shown in the CRIC and HALT-PKD studies [35]. However, these findings do not establish a causal role for FGF23 in disease progression. Notably, although FGF23 levels were higher in HALT-PKD than in CRIC, the slope of the relationship between FGF23 and eGFR was similar across cohorts, suggesting that elevated FGF23 may reflect rather than drive renal function decline [35]. Similar associations between elevated FGF23 and faster CKD progression have also been reported in non-ADPKD populations [42], although these findings remain observational and the underlying mechanisms are still under investigation. It should be noted, however, that most studies evaluating FGF23 in ADPKD are observational, with heterogeneous cohorts and limited follow-up. These limitations reduce the ability to infer causality and may contribute to conflicting results regarding its role in disease progression and cardiovascular outcomes.

3.2. *Bone phenotype and turnover in ADPKD*

In ADPKD patients, also the bone disease appears to be different from that seen in patients with CKD but without ADPKD. The most frequently observed bone phenotype in ADPKD patients is low bone turnover. In a study of 99 ADPKD patients with end-stage renal disease (ESRD), circulating levels of bone alkaline phosphatase were significantly lower compared to 419 non-ADPKD patients, suggesting low osteoblastic activity. Additionally, histomorphometric parameters of bone formation in a subgroup of the same ADPKD patients ($n = 10$) showed that bone turnover was lower than non ADPKD patients ($n = 61$). No differences were observed in bone volume and mineralization between the ADPKD and non-ADPKD subgroups. Associations between ADPKD and parameters of bone formation persisted even after adjusting for classical determinants such as PTH, age, and sex. Notably, patients with ADPKD showed elevated circulating sclerostin levels, suggesting disrupted Wnt

signaling and impaired bone remodeling. Although FGF23 levels were initially higher in ADPKD, this association was no longer significant after adjustment for serum phosphate, which was also higher in these patients. The upregulation of sclerostin may reflect impaired osteocytic mechanosensation, possibly related to primary cilium dysfunction (see below) and could contribute to the distinct low-turnover bone phenotype observed in ADPKD [43]. Even in the setting of early CKD stages (eGFR >90 ml/min), 472 with ADPKD had lower alkaline phosphatase levels and higher circulating intact FGF23 compared to 472 non-ADPKD patients with matched eGFR. Bone biopsy analysis confirmed decreased bone formation rate, indicated by lower osteoid volume per bone volume and lower bone formation rate per bone surface [35]. Finally, upregulated expression of dentin matrix protein 1 (DMP1) and FGF23 was observed on bone samples.

These clinical data confirm that both early and late stages of ADPKD are associated with decreased bone formation (low turnover), as indicated by alkaline phosphatase levels and bone histomorphometry. However, ADPKD patients have preserved [43] or even higher cortical bone mineral density [44].

Osteocytes appear to be involved in this process, as suggested by alterations in the levels and expression of protein secreted by these cells, such as sclerostin, DMP1, and FGF23. A plausible explanation may involve the role of polycistyn-1 (PC-1) in mechano-sensing. Mechanical stimulation of the skeleton is an essential anabolic signal that leads to osteoblastic proliferation and matrix deposition, while the absence of mechanical stimulation (such as immobilization or disuse) causes bone loss [45]. Osteocytes, and potentially osteoblasts, are key mechanosensitive cells in bone that transduce mechanical load into anabolic signals, thus stimulating bone formation.

In PC-1 null mice, abnormalities in skeletal development have been observed [46]. Homozygous inactivating mutations of PC-1 are associated with delayed endochondral and intramembranous bone formation, whereas heterozygous mutations are associated with decreased bone mineral density, trabecular bone volume, cortical thickness, and reduced osteoblastic function [47]. Both heterozygous and homozygous mice show a dose-dependent decrease in the expression of Runx2 and osteoblast-related genes. Additionally, overexpression of PC-1 leads to an increase in Runx2 expression. These data are consistent with a functional role of cilia and PC-1 in anabolic signaling in osteoblasts and osteocytes.

We know that PC-1 forms heterodimers with PC-2 and co-localize in the primary cilia [47]. The primary cilium is present on nearly every cell, including bone osteoblasts and osteocytes. Osteocytes and osteoblasts express the PC1/PC2 complex. The precise mechanisms by which bone cells respond to mechanical stimulation are not fully understood, but alterations in the Wnt pathway and sclerostin may play a key role in mechanotransduction. In fact, both experimental and clinical studies have shown that bone sclerostin expression and circulating sclerostin levels are increased during skeletal disuse [48]. While circulating sclerostin levels have been reported to be elevated in patients with ADPKD [43], histomorphometric analyses have not consistently shown increased bone sclerostin expression [43,49]. This discrepancy may reflect altered renal clearance or extra-skeletal production of sclerostin and warrants further investigation to clarify its pathophysiological significance (Fig. 2).

In conclusion, it is speculated that the specific bone phenotype of ADPKD patients is strongly related to the role of primary cilia in bone anabolism. However, the clinical implications of these findinds remain elusive. In fact, although a low bone turnover phenotype is increasingly recognized in ADPKD, current evidence does not indicate an increased fracture risk. In the study by Gitomer et al., no increased fracture risk was observed in ADPKD patients compared to diabetic patients [35], similarly, Ziolkowski et al. reported a comparable fracture incidence between ADPKD and diabetic patients with ESKD, although both groups showed a higher risk than patients with IgA nephropathy [50]. This apparent paradox, low bone turnover without increased fracture risk, may reflect the preservation, or even increase, of cortical bone mineral density (BMD) observed in these patients, particularly post-transplant [43]. Most available data derive from DXA-based assessments, while advanced imaging modalities—such as HR-pQCT, microMRI, and ^{18}F-NaF PET—have not yet been systematically explored in this setting. Given their established utility in CKD for evaluating microarchitecture, cortical porosity, and turnover [51,52], the application of these techniques in ADPKD may help clarify the relationship between bone quality and fracture susceptibility in this distinct population [53]. Overall the biochemical and skeletal alterations characterizing ADPKD remain insufficiently investigated. In particular, the fracture risk and the contribution of bone disease to musculoskeletal symptoms require further research. To date, few studies have specifically assessed fracture risk in ADPKD, and most have not demonstrated a clearly increased risk. Further studies are needed to clarify fracture risk across different stages of kidney disease.

4. Vascular disease in ADPKD

The increased incidence of cardiovascular events and high cardiovascular mortality in ADPKD patients is well documented, yet the exact etiopathogenesis leading to such vascular damage remains unclear. The main cardiovascular alterations in this population include arterial hypertension, present in 80 % of patients as an initial symptom; left ventricular hypertrophy, seen even in young adults, regardless of blood pressure values (30–40 % prevalence); intracranial aneurysms, which have been reported to have a prevalence twice that of the general population in some studies [54].

Alterations in mineral metabolism in CKD can significantly complicate cardiovascular health. Among the molecules implicated in this context, FGF23 is the most extensively studied and is thought to contribute to vascular and cardiac damage. Plasma concentrations of FGF23 are higher in ADPKD patients than in the healthy population, even with normal GFR values. It is thought that the cardiovascular action of FGF23, when not bound to its co-receptor α-Klotho, include multiple outcomes: induction of vascular calcifications, increased peripheral resistance and vascular stiffness, cardiac hypertrophy. However, the evidence supporting these hypotheses is conflicting and involves heterogeneous populations. Scialla et al. found a relationship between increased serum FGF23 and atherosclerosis development in CKD patients [55]. Conversely, Manghat et al. reported no association between serum FGF23 levels and atherosclerosis development in pre-dialysis CKD patients [56]. Ford et al. also found no relationship between serum FGF23 levels and atherosclerosis development in early-stage CKD patients [57]. In a study by Coban et al., conducted in ADPKD patients across all CKD stages, both FGF23 levels and arterial stiffness (measured by baPWV) increased with declining renal function. While a positive association between FGF23 and vascular parameters was observed, these findings are confounded by reduced eGFR and do not establish a direct pathogenic role for FGF23 in vascular calcification [58]. While this observation is valuable, it lacks comparison with adequately matched control group with other kidney diseases and similar renal function, being compared only to healthy controls. In studies involving CKD patients, elevated FGF23 levels, alongside declining renal function, have been correlated with left ventricular hypertrophy [59]. However, similar findings are not observed in ADPKD patients with preserved renal function who also have high FGF23 levels. This discrepancy may be partially explained by different regulatory mechanisms of FGF23 synthesis and action in ADPKD. As previously discussed, some evidence shows elevated FGF23 levels despite preserved Klotho expression. This relative maintenance of normal circulating Klotho concentrations may help mitigate the adverse cardiovascular effects typically associated with high FGF23 levels [33,60]. In fact, FGF23 acts through a specific myocardial receptor, FGFR4, which activates pro-hypertrophic signaling only in the presence of low Klotho expression on cardiomyocytes [61]. Moreover, a defect in calcium binding, potentially caused by polycystin

mutations, has been hypothesized to directly contribute to increased left ventricular mass [62,63]. However, these hypotheses lack experimental support. While cardiovascular disease is a leading cause of morbidity and mortality in ADPKD, the extent to which CV event rates differ from those in non-ADPKD CKD populations remains uncertain [64]. In conclusion, while the increased cardiovascular mortality in ADPKD patients cannot be directly linked to CKD-MBD, it remains conceivable that elevated FGF23, PTH, and abnormalities in intracellular calcium signaling could contribute to vascular damage, a possibility that warrants further investigation.

4.1. Potential specific therapeutic strategies

As described, the elevation of FGF23 in ADPKD patients with early-stage CKD appears to be independent of phosphorus balance. While a low-phosphorus diet remains recommended, its effects on the modulation of mineral and bone disorders (MBD) in ADPKD are uncertain. A potential therapeutic strategy could involve targeting intratubular phosphorus levels to mitigate kidney damage caused by elevated intratubular phosphorus concentrations, which are mediated by increased FGF23. In this context, Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) may offer promise. These relatively novel antidiabetic drugs improve glycemic control, reduce cardiovascular risk, and slow renal function decline by inhibiting glucose reabsorption in the proximal tubule. Emerging evidence suggests that SGLT2i may also influence bone and mineral metabolism. By inhibiting the cotransport and reabsorption of sodium and glucose, SGLT2i preserve the sodium gradient necessary for sodium-dependent phosphate transport proteins IIa (NaPi-IIa, SLC34A1) and IIc (NaPi-IIc, SLC34A3) [65].

This action promotes phosphate reabsorption in the proximal tubule and may transiently raise serum phosphate, thereby stimulating FGF23 secretion and leading to secondary reductions in calcitriol and increases in PTH [66,67]. However, these effects appear variable and may depend on baseline phosphate handling and kidney function. While these interactions raise concerns about potential impacts on bone and mineral metabolism, current evidence remains limited and largely inferential, warranting further study. For instance, a randomized crossover trial in healthy volunteers demonstrated that canagliflozin treatment increased renal tubular phosphate reabsorption, leading to transient elevations in FGF23 and serum phosphate levels [68]. Similar findings have been reported in diabetic patients, with these effects likely linked to enhanced tubular phosphate reabsorption [69]. Moreover, by enhancing proximal phosphate reabsorption, SGLT2 inhibitors may reduce phosphate availability in the S3 segment of the tubule. It has been hypothesized that lower phosphate concentrations in this segment may decrease the formation of urinary calcium-phosphate particles, thereby attenuating the activation of pro-inflammatory pathways mediated by toll-like receptor 4 (TLR4) [40]. This mechanism may contribute to the nephroprotective and anti-inflammatory properties of SGLT2i. The potential renal and systemic protective effects of SGLT2i in ADPKD warrant further investigation. Notably, SGLT2 inhibitors are not currently recommended in ADPKD. According to the 2025 KDIGO ADPKD guidelines [70], their use is discouraged due to the diuretic effect of glucosuria, which may raise serum vasopressin levels and has shown mixed effects on cyst growth in preclinical models. Moreover, patients with ADPKD have been excluded from SGLT2 inhibitor clinical trials to date. Future studies, such as the EMPA-PKD trial [71], are essential to evaluate the safety and efficacy of SGLT2i in this population. Considering the bone phenotype of ADPKD, partly due to the role of primary cilia in bone anabolism, we can speculate that in ADPKD patients needing osteoprotective therapy due to an increased fracture risk we should carefully evaluate the pharmacological approach (osteoanabolic vs antiresorptive). It also may be reasonable perform a bone biopsy in complex clinical cases to either exclude or confirm suspicions of low bone turnover that requires osteoanabolic therapy. While osteoanabolic agents such as romosozumab may offer therapeutic potential in patients with low BMD and low or normal bone turnover, their use in CKD—and possibly in ADPKD—remains cautious due to concerns over cardiovascular safety. This is particularly relevant given the high burden of vascular calcification and cardiovascular disease in these populations [72].

Interestingly a recent article by Bargagli et al. investigates the impact of tolvaptan, a selective vasopressin V2 receptor antagonist, on bone mineral density (BMD) and mineral metabolism in patients with autosomal dominant polycystic kidney disease (ADPKD) [73]. Tolvaptan treatment was associated with an increase in femoral neck BMD, suggesting benefits for bone health in ADPKD patients. Tolvaptan's positive effect effect on bone metabolism was mediate in this cohort of ADPKD patients by the reduction in parathyroid hormone (PTH), improvement in acid-base status, increase in plasma magnesium and a positive calcium balance. Also, a direct and indirect effects on bone cells is possible, in fact vasopressin V1a and V2 receptors, targeted by tolvaptan, are expressed in osteoblasts and osteoclasts, which regulate bone remodeling. The blockade of V2 receptors may indirectly activate V1a receptors, which could influence osteoblast activity, promote bone formation, and reduce bone resorption. So MBD in ADPKD has to be treated like to in general CKD population but we have to remember that the common therapy approach can be less effective in this population and we have to look for new specific therapeutic approach.

5. Conclusions

In conclusion, patients with ADPKD display distinctive alterations in mineral metabolism, including elevated FGF23 levels independent of phosphate balance or Klotho reduction, and a tendency toward low bone turnover. Remarkably, unlike in other CKD populations, these abnormalities do not consistently translate into overt disturbances of calcium–phosphate homeostasis, tubular phosphate handling, or increased fracture and cardiovascular risk. This unique profile highlights the need to interpret biochemical and skeletal findings in ADPKD within the specific context of the disease and underscores the importance of future research to unravel the mechanisms underlying these discrepancies. Given these insights, a comprehensive approach to the monitoring of mineral and bone disorders in ADPKD, integrated with strategies to preserve renal function, may be warranted, while the potential role of targeted interventions remains to be determined (Table 1).

Table 1
Practical Clinical Implications in ADPKD-related CKD-MBD.

Clinical Consideration	Rationale/Implication
Elevated FGF23 levels in the early stages	Consider ectopic production independent of mineral metabolism disturbances
Assess bone turnover status (e.g., using PTH, bone-specific alkaline phosphatase, or sclerostin)	ADPKD patients are at risk of low bone turnover even in early CKD stages; marker-based stratification may guide therapy.
Consider bone biopsy in selected cases	Particularly in patients with unexplained bone pain, fragility fractures, or when turnover status is uncertain and impacts treatment choice.
Be cautious with anti-sclerostin agents (e.g., romosozumab)	Despite potential benefit in low-turnover bone disease, cardiovascular safety concerns remain, especially in CKD.
SGLT2 inhibitors in ADPKD	Not currently recommended due to potential vasopressin-mediated cyst growth; limited data on mineral metabolism impact.
Fracture risk assessment in transplant and advanced CKD	ADPKD patients may share fracture risks comparable to other high-risk CKD populations; targeted screening is warranted.

CRediT authorship contribution statement

S. Lai: Writing – original draft, Validation, Supervision, Conceptualization. **A.M. Perrotta:** Writing – original draft. **L. Tartaglione:** Writing – original draft. **D. Mastroluca:** Writing – original draft. **F. Tinti:** Writing – original draft. **P. Menè:** Supervision. **M. Pasquali:** Supervision. **P.M. Ferraro:** Writing – original draft. **S. Mazzaferro:** Supervision. **S. Rotondi:** Writing – original draft, Supervision, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used chatGPT in order to mproving the clarity and quality of the English language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Silverio Rotondi reports was provided by University of Rome La Sapienza. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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