REVIEW

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Bone and heart health in chronic kidney disease: role of dentin matrix protein 1

Aline Martin

Purpose of review
Chronic kidney disease (CKD) is a condition associated with bone disease and fibroblast growth factor 23 (FGF23) excess that contributes to cardiovascular mortality. Dentin matrix protein 1 (DMP1) is an established regulator of bone mineralization and FGF23 production in osteocytes. To date, DMP1 function has mainly been studied in the context of hereditary hypophosphatemic rickets diseases. This review describes the role of DMP1 as a potential strong candidate to prevent bone disorders, FGF23 elevation and associated cardiac outcomes in CKD.

Recent findings
Patients and mice with CKD show impaired osteocyte maturation and impaired regulation of DMP1 and FGF23 in bone. New data suggest that impaired DMP1 production contributes to CKD-associated bone and mineral metabolism disorders and we show that DMP1 repletion improves osteocyte alterations, bone mineralization and partially prevents FGF23 elevation. As a result, mice with CKD show attenuated left ventricular hypertrophy and improved survival.

Summary
There is an urgent need for new therapeutic strategies to improve bone quality and to lower FGF23 levels in CKD. By preventing osteocyte apoptosis and inhibiting *Fgf23* transcription, DMP1 supplementation may represent an ideal approach to improve CKD-associated bone and cardiac outcomes.

Keywords
chronic kidney disease, dentin matrix protein 1, fibroblast growth factor 23, left ventricular hypertrophy, osteocyte

INTRODUCTION

Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) suffer from significant alterations in mineral and bone metabolism, including loss of bone mass, increased susceptibility to fractures and increased production of fibroblast growth factor 23 (FGF23) [1–4]. Elevated circulating FGF23 contributes to cardiovascular disease and mortality [5–8]. Identifying new molecular mechanisms that contribute to reduced bone mass and FGF23 excess is a critical step toward developing improved therapeutic approaches for patients with CKD. Dentin matrix protein 1 (DMP1) is an extracellular matrix (ECM) protein produced by osteocytes that stimulates mineralization and inhibits Fgf23 transcription in bone, and therefore represents an excellent candidate to improve bone and cardiac outcomes in CKD. However, current knowledge on DMP1 function was mainly obtained from studies of hereditary hypophosphatemic rickets disorders [9–11], and only few studies have assessed the role of DMP1 in CKD or ESRD [12,13]. Recent new experimental results propose a protective role of DMP1 in CKD-induced alterations in osteocytes, FGF23 production and heart hypertrophy, which we review in this article.

DENTIN MATRIX PROTEIN 1 REGULATION, FUNCTION AND PATHOPHYSIOLOGY

DMP1 is an ECM protein that belongs to the small integrin binding ligand N-linked glycoprotein (SIBLING) family. DMP1 is mainly expressed in

Division of Nephrology and Hypertension, Center for Translational Metabolism and Health and Feinberg Cardiovascular and Renal Research Institute, Northwestern University, Chicago, Illinois, USA

Correspondence to Dr Aline Martin, Northwestern University Feinberg School of Medicine, 320 East Superior Street, Chicago, IL 60611, USA. Tel: +1 312 503 4160; e-mail: aline.martin@northwestern.edu

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KEY POINTS

- Elevated levels of FGF23 are associated with adverse clinical outcomes in patients with CKD.
- Reduced levels of the C-terminal DMP1 peptide in bone may contribute to osteocyte apoptosis and increased *Fgf23* transcription in CKD.
- C-terminal DMP1 repletion is a potential new therapeutic strategy to improve bone quality, lower FGF23 levels, and prevent cardiac hypertrophy and early death in CKD that requires further testing.

differentiated cells of mineralized tissues, including osteocytes and odontoblasts, where it is secreted as an intact 106-kDa propeptide that is activated by proteolytic cleavage by bone morphogenetic protein 1 generating 37-kDa N-terminal and 57-kDa C-terminal peptides. The N-terminal 37-kDa DMP1 peptide is a proteoglycan that has not been extensively studied and shows a possible role in osteogenesis and maintenance of blood–brain barrier integrity [14,15]. In contrast, the role of the C-terminal 57-kDa DMP1 (cDMP1) peptide is well established. cDMP1 is considered as the active DMP1 peptide responsible for the classical functions of DMP1 to promote bone and dentin mineralization, and to inhibit FGF23 expression in osteocytes. Although DMP1 is an integral component of the mineralized ECM mainly detected in the bone and tooth, it is also present in the circulation in a complex with complement factor *H* [16,17]. Whether circulating DMP1 levels have a physiological significance is largely unclear, partly due to the lack of standardized assays to assess circulating full length and cleaved DMP1 peptides concentrations.

Inactivating mutations of DMP1 in humans and mice result in autosomal recessive hypophosphatemic rickets (ARHR) [9,11]. ARHR is a rare hereditary disorder in which DMP1 deficiency drives primary overproduction of FGF23 by osteocytes resulting in increased circulating intact FGF23 levels. Elevation of FGF23 in ARHR consequently inhibits renal phosphate reabsorption, resulting in renal phosphate wasting and hypophosphatemia that contribute to impaired bone mineralization and growth defects evidenced by osteomalacia and rickets [9–11]. In addition to FGF23-induced hypophosphatemia, the lack of DMP1 in the bone matrix also directly contributes to the skeletal disorders observed in ARHR. Indeed, DMP1 nucleates the formation of hydroxyapatite by binding to calcium ions [18], resulting in increased matrix mineralization. As a result, genetic deletion of FGF23 in DMP1 null mice, while preventing hypophosphatemia, only partially rescues the skeletal abnormalities [10].

Mouse genetic studies played an essential role in advancing the understanding of DMP1 function. DMP1 rescue studies established the importance of the posttranslational cleavage of DMP1 and the role of DMP1 C-terminal peptide. Indeed, expression of a full length 106-kDa DMP1 transgene or the smaller 57-kDa cDMP1 peptide in bone of DMP1 null mice fully and equally corrected bone and mineral metabolism alterations [19,20]. In contrast, expression of a cleavage-resistant full length 106-kDa DMP1 transgene [21] or constitutive nuclear expression of DMP1 [22] did not improve the DMP1 null phenotype. This indicates that DMP1 functions as an ECM protein and that cleavage of DMP1 is required for its activation. In addition, this also demonstrates that cDMP1 is the active peptide that mediates DMP1 effects on mineralization and FGF23 regulation.

Currently, there are no known diseases of DMP1 excess, and overexpression of DMP1 in mice results in a very mild baseline bone and mineral metabolism phenotype compared with wild-type controls [20,21].

FIBROBLAST GROWTH FACTOR 23 AND DENTIN MATRIX PROTEIN 1 CONCENTRATIONS IN CHRONIC KIDNEY DISEASE

In CKD, intact FGF23 levels rise early and exponentially with the progressive decline in kidney function [3,4]. Although early FGF23 elevations in CKD may represent an adaptive mechanism to maintain normal serum phosphate by increasing phosphaturia and reducing calcitriol levels [1,23,24], supraphysiological FGF23 levels ultimately become maladaptive. Indeed, elevated FGF23 in CKD is independently associated with cardiovascular disease and all-cause mortality [5–8], and is thought to contribute mechanistically to development of left ventricular hypertrophy (LVH), which is an important precursor of heart failure in patients with CKD [25–29].

The causes for FGF23 elevation in CKD are multifactorial and include the contributions of inflammation [30], iron deficiency [31], hyperphosphatemia [32] and secondary hyperparathyroidism [33]. Despite the major role of DMP1 in bone mineralization and FGF23 regulation, to date only few studies investigated the contribution of DMP1 to CKD-associated bone and mineral metabolism disorders [12,34,35▪▪,36▪]. Reports of DMP1 expression measured by immunohistochemistry, in different CKD settings yielded contradictory results and will require further investigation. Indeed, DMP1 expression was reported to be reduced in adult patients

undergoing dialysis with bone fractures [35▪▪] and in adult Col4a3 null mice, an established mouse model of progressive CKD [36▪]. Consistent with immunohistochemistry detection, bone DMP1 mRNA expression was also reduced by 40% in Col4a3 null mice with advanced CKD [36▪], suggesting that DMP1 reduction may contribute to FGF23 elevation, at least in adults with advanced CKD. In contrast, DMP1 expression was increased in bone biopsies from pediatric and young adult patients with CKD [12]. In each of these studies, DMP1 detection was performed using antibodies from different companies [12,35▪▪,36▪]. Each detected separate epitopes of DMP1 within the 57-kDa region that indistinctively led to detection of both full length and cDMP1 peptides by immunohistochemistry, which excludes the detection method as a possible reason for the apparent discrepancies in DMP1 expression. Significantly, a subsequent study in pediatric CKD patients showed that doxercalciferol therapy further increased DMP1 expression, and Western blotting detection showed that only the full length DMP1 peptides increased, whereas cDMP1 peptides were mainly decreased [34]. Therefore, possible alterations in posttranslational cleavage of DMP1 may reconcile an apparent DMP1 excess and cDMP1 deficiency in pediatric CKD. The mechanisms driving cDMP1 deficiency in CKD are currently unknown. Future studies will be needed to understand the differences in DMP1 status observed between pediatric and adult CKD and to compare for instance, the levels of DMP1 mRNA expression, of full length and cDMP1 peptides, and the impact of CKD-induced alterations in bone turnover on DMP1 expression and posttranslational cleavage.

OSTEOCYTE ALTERATIONS IN CHRONIC KIDNEY DISEASE

There are only few studies focusing on osteocyte in adult patients with CKD, and two recent reports showed that osteoblast and osteocyte activity was impaired in pediatric patients and in adult mice with CKD, leading to impaired bone mineralization [36▪,37▪▪]. In both studies, primary osteoblasts isolated from bone biopsies retained impaired matrix mineralization properties when cultured *in vitro*, suggesting possible intrinsic defects in osteoblast and osteocyte maturation in CKD. In addition, we showed significant alterations in osteocyte morphology and connectivity in cortical bone of the Col4a3 null mouse [36▪]. Similar osteocyte alterations were reported in DMP1 null mice with osteomalacia [38], suggesting that bone mineralization and osteocyte morphology defects observed in mice with advanced CKD may be caused, in part, by reduced DMP1 expression.

In Col4a3 null mice with advanced CKD, the osteocyte defects coincided with increased osteocyte apoptosis assessed by TUNEL assay [36▪], suggesting that osteocyte apoptosis may be an underlying mechanism of osteocyte dysfunction. The degree of hyperphosphatemia, inflammation and oxidative stress, which are prominent clinical features of CKD, are known contributors of osteocyte apoptosis. One function of DMP1 is to exert antiapoptotic effects in osteocytes. Indeed, DMP1 deletion enhanced phosphate-induced osteocyte apoptosis in hyperphosphatemic Klotho deficient mice [39]. In addition, we showed that cDMP1 overexpression in cultured osteoblasts also prevents apoptosis induced by the proinflammatory cytokine TNFα or hydrogen peroxide [36▪]. Together, these data support a direct role of DMP1 to protect osteocytes from phosphate-induced, inflammation-induced and oxidative stress-induced apoptosis. As a result, both genetic and pharmacologic DMP1 supplementation in Col4a3 null mice with advanced CKD, prevented osteocyte apoptosis, corrected the bone mineralization defect and corrected the osteocyte morphology and connectivity, emphasizing the beneficial role of DMP1 in CKD-associated alterations in bone and osteocytes [36▪].

Unlike adult Col4a3 null mice with advanced CKD, impaired osteocyte maturation in pediatric patients with CKD resulted in an increased amount of early differentiated osteocytes that occurred despite reduced osteocyte apoptosis [37▪▪], suggesting that the mechanisms driving osteocyte defects in CKD may be context dependent and influenced by cause, sex and age. Regardless, the direct relationship between altered osteocyte maturation, apoptosis, altered bone remodeling and mineralization, and increased FGF23 production in CKD has not been fully established and requires further investigation.

REGULATION OF FIBROBLAST GROWTH FACTOR 23 BY DENTIN MATRIX PROTEIN 1

In addition to its function in osteocyte maturation, DMP1 is an established upstream inhibitor of FGF23 production. Phenotypic and transcriptomic comparisons between murine models of hereditary hypophosphatemic rickets, which display similar traits such as reduced bone mineralization and FGF23 excess, contributed to our understanding of the role of DMP1 in FGF23 regulation. The overlapping phenotypes of DMP1 null mice (homologue of ARHR) and Hyp mice [homologue of X-linked hereditary hypophosphatemic rickets (XLH) induced by PHEX mutations] led to the current

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hypothesis that a potential binding between cDMP1 and PHEX at the osteocyte membrane is a key upstream mechanism involved in the regulation of mineralization and FGF23 production. In support of this hypothesis, all SIBLING proteins, including cDMP1, contain a signature arginine–glycine–aspartate motif and an acidic serine–aspartate rich matrix extracellular phosphoglycoprotein-associated (ASARM) motif, for binding to integrins [40] and PHEX [41,42], respectively. In addition, mice with deactivating mutations in SIBLING proteins other than DMP1 do not develop rickets, osteomalacia or FGF23 excess [43–46]. Indeed, DMP1 null mice are the only phenocopies of PHEX mutant (Hyp) mice, and combined DMP1 and PHEX mutations in double mutant mice do not lead to a worsened phenotype [47]. Finally, overexpression of cDMP1 fails to rescue the bone and mineral metabolism alterations of Hyp mice, suggesting that PHEX facilitates cDMP1 function [20].

Elevations of circulating intact FGF23 levels in hereditary rickets and CKD result from increased *Fgf23* transcription in osteocytes and impaired posttranslational cleavage. The *Fgf23* promoter contains a nuclear factor of activated T-cells (NFAT) response element which controls *Fgf23* transcription in response to calcium and inflammatory stimuli [48–50]. In hereditary rickets, DMP1 and PHEX mutations result in paracrine activation of fibroblast growth factor receptor 1 (FGFR1) [47], and increased *Fgf23* transcription induced by FGFR activation is mediated by increased calcium-dependent NFAT signaling [49]. Taken together, it is possible that DMP1 regulates NFAT signaling, although this has not been tested in models of hereditary rickets. In Col4a3 null mice with advanced CKD, we have shown that DMP1 administration represents a successful method to inhibit *Fgf23* transcription [36▪]. Similar to FGFR activation, CKD results in increased bone NFAT1 signaling in mice which DMP1 supplementation specifically prevented [36▪], supporting NFAT signaling as the first direct link between DMP1 and *Fgf23* transcription in bone (Fig. 1). The specific stimuli leading to reduced cDMP1 and bone NFAT activation in CKD remain to be determined.

In addition to the regulation of *Fgf23* transcription, DMP1 rescue studies in both models of DMP1 null and Col4a3 null with CKD showed a partial reduction of circulating intact to total FGF23 ratio [20,36▪], used as a surrogate marker of FGF23 cleavage, suggesting that DMP1 exerts a coupled control over *Fgf23* transcription and posttranslational cleavage. In line with these findings, DMP1 supplementation in Col4a3 null mice with CKD partially reduced circulating intact FGF23 levels but not down to the levels observed in healthy mice [36▪]. This residual FGF23 excess may be due to extraosseous FGF23 expression, which has been reported in CKD [28,51]. Alternatively, another contributing factor is the activation of DMP1-independent regulatory mechanisms of *Fgf23* transcription and posttranslational cleavage [30], including hyperphosphatemia [52], which is further accentuated in DMP1-treated mice as a result of FGF23 reduction [36▪].

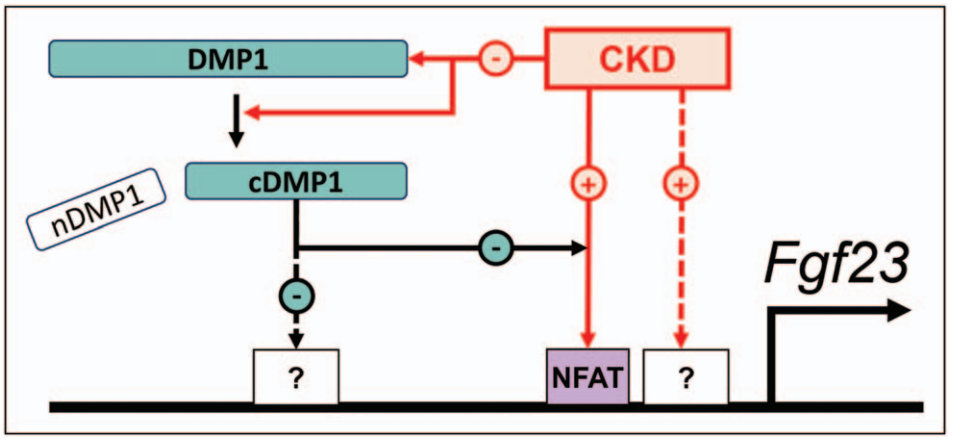

FIGURE 1. Transcriptional regulation of fibroblast growth factor 23 (FGF23) by dentin matrix protein 1 (DMP1) in chronic kidney disease (CKD). In health, intact DMP1 is cleaved to produce N-terminal and C-terminal DMP1 peptides (blue). C-terminal DMP1 (cDMP1) inhibits *Fgf23* transcription through inhibition of multiple signaling pathways, including nuclear factor of activated T-cells 1 (NFAT1). In CKD (red), the NFAT response element of *Fgf23* promoter (purple) is activated due to increased NFAT1 signaling which results in increased *Fgf23* transcription. Inhibition of DMP1 expression, or alternatively inhibition of DMP1 cleavage, also contributes to increased *Fgf23* transcription in CKD. cDMP1 supplementation specifically prevents NFAT-activated *Fgf23* transcription in CKD. Additional mutual or independent signaling targets of cDMP1 and CKD remain to be determined (dashed arrows).

DENTIN MATRIX PROTEIN 1 INVOLVEMENT IN CARDIOVASCULAR DISEASE

Elevations of circulating FGF23 levels during CKD progression are independently associated with cardiovascular mortality [5,6,8], via direct and reversible effects of FGF23 on cardiac myocytes that culminate in LVH [25–29]. Accordingly, B6 Col4a3 null mice with slow CKD progression display FGF23-induced LVH at 20 weeks of age, and die a few weeks later [53▪]. Given the significant effects of DMP1 on FGF23 production in mice with CKD, we recently investigated the effects of DMP1 repletion on the development of LVH. Genetic overexpression of DMP1 in these mice did not improve kidney function or hypertension, but partially lowered FGF23 levels, leading to delayed onset of LVH and a marked increase in lifespan [36▪]. This study demonstrates that lowering FGF23 levels in a CKD model can attenuate development of LVH and improve survival. In contrast to prior studies using conditional FGF23 deletion or FGF23 blocking antibodies leading to severe hyperphosphatemia due to complete neutralization of FGF23 effects [54,55▪], this shows that reducing FGF23 while preserving a physiological FGF23 signal prevents a drastic increase in circulating phosphate and attenuates cardiovascular outcomes. Although studies using titrated doses of anti-FGF23 antibodies will be needed to fully establish the beneficial effects of preventing FGF23 elevations in CKD, DMP1 supplementation could represent a reasonable alternative approach to improve both bone and cardiac outcomes that will need to be tested in other models of CKD.

Finally, it is still unknown whether cardiac hypertrophic effects of FGF23 are CKD-specific. The heart phenotype in models of FGF23 excess with normal kidney function is still debated, and studies show absence [56] or presence [57] of LVH in Hyp mice and abnormal cardiomyocyte contractility in DMP1 null mice [58]. Additional data also suggest that events of cardiac hypertrophy observed in pediatric patients with XLH may not necessarily correlate with FGF23 [59]. Nevertheless, lower circulating DMP1 levels are also associated with cardiovascular events in patients undergoing peritoneal dialysis [13], suggesting that DMP1 protective effect against the development of LVH in CKD may be FGF23-dependent or independent. Although the beneficial effects of DMP1 on osteocytes and at least FGF23-mediated LVH are convincing, a potential direct role of DMP1 on the heart still remains to be determined.

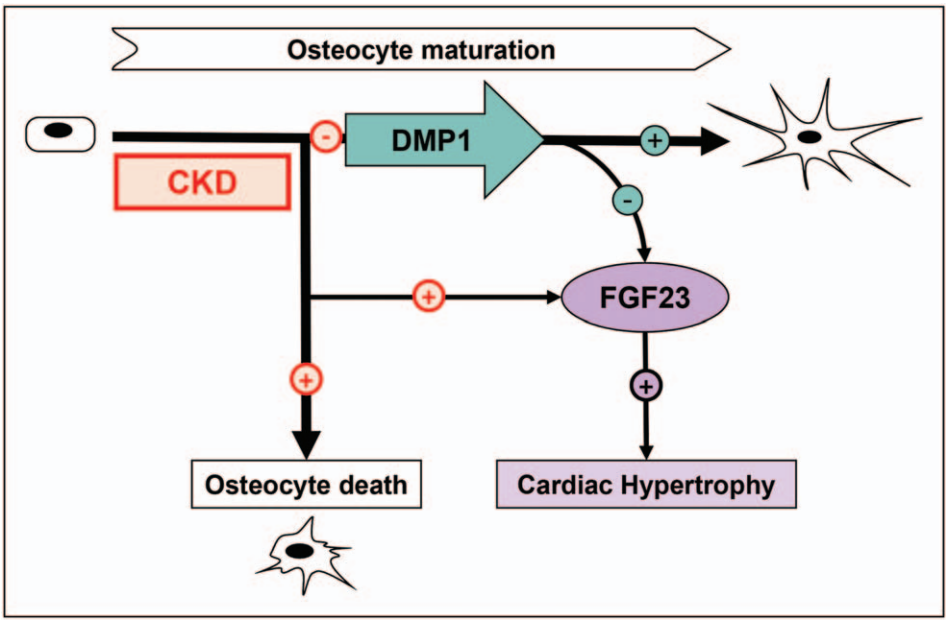

FIGURE 2. Hypothetical model of the coupled regulation of fibroblast growth factor 23 (FGF23) and osteocyte maturation by dentin matrix protein 1 (DMP1) in chronic kidney disease (CKD). In health, DMP1 promotes osteocyte differentiation and inhibits FGF23 production (blue). In CKD (red), the inhibition of DMP1 prevents osteocyte maturation resulting in early cell death and increased FGF23 production. Increased circulating FGF23 levels contribute to development of cardiac hypertrophy (purple). DMP1 supplementation in CKD restores osteocyte maturation and inhibition of FGF23 production, which prevents development of cardiac hypertrophy.

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CONCLUSION

Several studies using models of hereditary hypophosphatemic rickets with primary FGF23 excess have established DMP1 as a positive regulator of bone mineralization and a negative regulator of FGF23 production. Severe alterations in osteocyte maturation and FGF23 production occur during CKD progression, which contribute to poor cardiovascular outcomes and mortality. New recent studies indicate that DMP1 reduction may significantly contribute to CKD-associated alterations in bone and mineral metabolism and that DMP1 supplementation improves LVH and survival (Fig. 2), at least in a murine model of progressive CKD. Partial, but not complete, reduction of FGF23 levels may be key in improving outcomes at the expense of a mild increase in serum phosphate levels, whereas complete suppression of FGF23 signaling results in severe hyperphosphatemia which would negate the cardiovascular benefit of FGF23 reduction. The lack of standardized DMP1 analysis across various CKD settings and the lack of experimental data in additional models of CKD represent major limitations in advancement of DMP1 as a potential new therapeutic strategy to improve outcomes in CKD. Future studies will need to address these critical questions.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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