FGF23 Drives Progressive Bone Loss During CKD: Longitudinal Endocrine, MicroCT, and Histomorphometry Evidence

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Introduction

- Chronic kidney disease (CKD) affects over 10% of the global population and is associated with early bone loss, fragility, and elevated fracture risk. Disruption of bone–kidney endocrine signaling, including excess fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and phosphate imbalance, contributes to CKD–mineral and bone disorder (CKD-MBD).
- While FGF23 is traditionally viewed as a systemic phosphate-regulating hormone, emerging evidence suggests that it may act locally within bone to impair osteoblast differentiation and mineralization.
- Previous research demonstrated that genetic overexpression of dentin matrix protein 1 (DMP1), an osteocyte-derived regulator of mineralization and FGF23, prevents bone loss and osteocyte alterations in mice with advanced CKD.
- However, the temporal relationship between FGF23 elevation, CKD progression, and onset of bone loss—and whether FGF23 acts locally within bone to impair osteoblast differentiation—remains unknown.

Aim

To define how endocrine changes, particularly FGF23 elevation, correlate with skeletal deterioration during CKD progression, and to determine whether DMP1 overexpression delays or prevents FGF23-associated bone loss.

Method

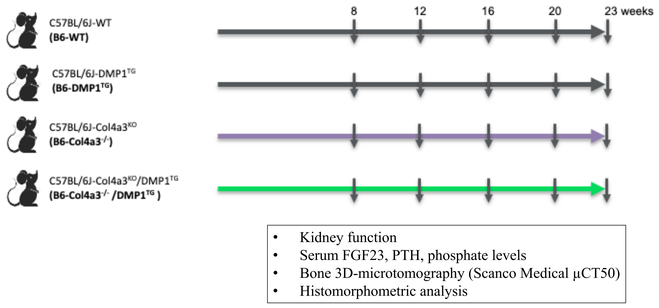

Figure 1: Serum, urine, and femur samples were collected from C57BL/6J (B6) wild-type (WT) mice, B6 collagen type IV alpha 3 chain knockout (Col4a3$^{-/-}$) mice, B6-WT mice with global DMP1 overexpression (B6-DMP1^{TG}), and B6- Col4a3$^{-/-}$ mice with global DMP1 overexpression (B6-COl4a3$^{-/-}$ /DMP1^{TG}) sacrificed from 8 to 23 weeks of age at 4-week intervals to assess kidney function, mineral metabolism, bone microarchitecture, and bone histology.

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Mineral Metabolism Alterations in CKD

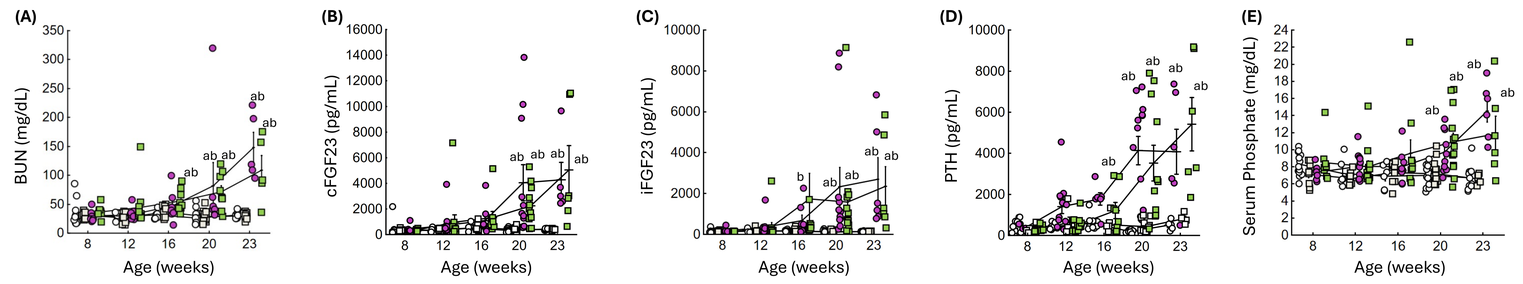

Figure 2: Kidney Function and Markers of Mineral Metabolism. Levels of **(A)** Blood Urea Nitrogen (BUN), **(B)** total fibroblast growth factor 23 (cFGF23), **(C)** intact FGF23 **(D)** Parathyroid Hormone, and **(E)** serum phosphate. N ≥ 5, P < 0.05 vs age-matched [a]B6-WT, [b]B6-DMP1TG, [c]B6-Col4a3$^{-/-}$

Dmp1 Delays Bone Loss in CKD

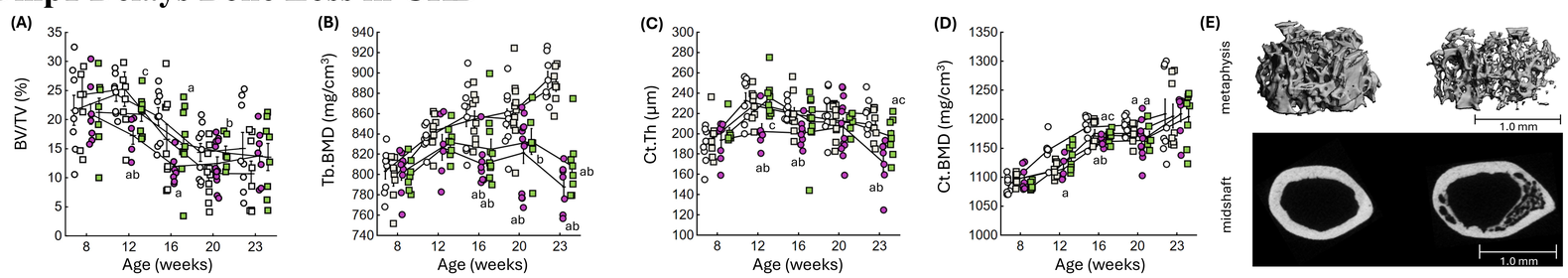

Figure 3: Bone Microarchitecture. 3D microtomography analysis of the femur diaphysis at midshaft showing **(A)** bone volume over tissue volume, **(B)** trabecular bone mineral density, (C) cortical thickness, **(D)** cortical bone mineral density, and **(E)** femur secondary spongiosa trabecular bone (top) and 2D cortical diaphysis (bottom). N ≥ 5, P < 0.05 vs age-matched [a]B6-WT, [b]B6-DMP1TG, [c]B6-Col4a3$^{-/-}$

Impaired Osteoblast Activity and Reduced Mineralization Occurs Early in CKD

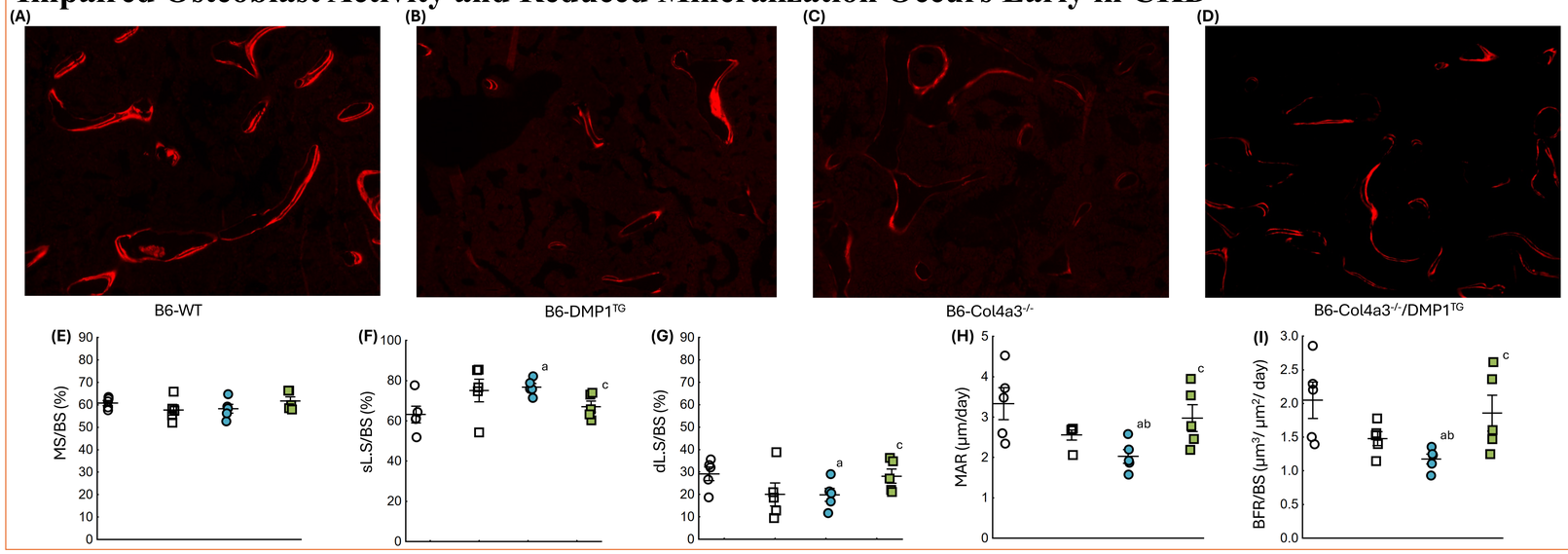

Figure 4: Bone Histomorphometry. (A-D) Representative double alizarin red fluorescent labels of femoral secondary spongiosa trabecular bone at 12 weeks of age in [a]B6-WT, B6-DMP1TG, B6-Col4a3$^{-/-}$, B6-Col4a3$^{-/-}$-DMP1TG mice. Dynamic histo-morphometric quantitative analysis showing **(E)** mineralizing surface per bone surface, **(F)** single-labeled surface per bone surface, **(G)** double-labeled surface per bone surface, **(H)** mineral apposition rate, and **(I)** bone formation rate per bone surface.
N ≥ 5, P < 0.05 vs age-matched [a]B6-WT, [b]B6-DMP1TG, [c]B6-Col4a3$^{-/-}$

Conclusion

- Dmp1 overexpression partially delays and resolves trabecular and cortical bone loss from CKD independent of kidney function decline, implying a direct protective effect of Dmp1 on skeletal integrity in CKD.
- CKD markedly suppresses osteoblast activity and mineral apposition, but Dmp1 overexpression restores these bone formation indices, indicating Dmp1 rescues osteoblastic mineralization capacity despite CKD.