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TITLE: Dentoalveolar Defects in the *Hyp* Mouse Model of X-linked Hypophosphatemia

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ABSTRACT BODY:

Objectives: Mutations in *PHEX* cause X-linked hypophosphatemia (XLH), a form of hypophosphatemic rickets. *Hyp* (*Phex* mutant) mice recapitulate the XLH phenotype. Dental problems are prevalent in individuals with XLH, however dentoalveolar defects remain incompletely understood. We aimed to examine *Hyp* mouse dentoalveolar defects to define effects of XLH on dentin, cementum, and bone, and provide insights into biomineralization processes of these tissues.
Methods: Dentoalveolar tissues from *Hyp* and wild-type (WT) mice at 42 and 90 days postnatal (dpn) were analyzed by histology, radiography, scanning electron microscopy (SEM), high resolution microcomputed tomography (micro-CT), static and dynamic mechanical analysis, *in situ* hybridization, and immunohistochemistry.
Results: *Phex* mRNA was expressed by odontoblasts (dentin), osteocytes (bone), and cementocytes (cellular cementum). Dentin defects in *Hyp* molars were indicated histologically by wide predentin, thin dentin, and extensive interglobular dentin, as confirmed by micro-CT findings of reduced dentin volume and density ($p<0.01$ to 0.0001). Acellular cementum was thin and showed PDL detachment, and mechanical testing indicated reduced static and dynamic stiffness (>60%; $p<0.01$-0.001) in *Hyp* vs. WT periodontia. *Hyp* mandibles demonstrated expanded bone with accumulation of osteoid, and micro-CT confirmed 24% decreased bone volume fraction (BV/TV; $p<0.001$) and 25% decreased alveolar bone density ($p<0.0001$). Cellular cementum area significantly increased in *Hyp* vs. WT molars by 90 dpn ($p<0.01$). Hypomineralized cementoid increased 50-fold in *Hyp* vs. WT mice ($p<0.001$), and comprised 30-40% of total cellular cementum area. Histology and SEM revealed hypomineralized “halos” surrounding *Hyp* cementocyte/osteocyte lacunae. Altered *Spp1* and *Dmp1* mRNA expression was observed in both cementocytes and osteocytes, along with abnormal BSP, OPN, and DMP1 protein distribution in *Hyp* bone and cementum.
Conclusions: Novel findings were identified in *Hyp* mouse developmental defects, including cementocyte defects paralleling those found in osteocytes. This study provides insights into XLH and fundamental processes of cementum, bone, and dentin biology.

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KEYWORDS: Dentin, Enamel, Cementum, Bone, Mineralization.

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