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Review

Dental manifestations of hypophosphatasia: translational and clinical advances

Elis J. Lira dos Santos[1], Fatma F. Mohamed[1,2], Kaitrin Kramer[3,4], Brian L. Foster[1,*]

[1]Division of Biosciences, College of Dentistry, The Ohio State University, Columbus, OH, 43210, United States
[2]Department of Biologic and Materials Sciences and Prosthodontics, School of Dentistry, University of Michigan, Ann Arbor, MI, 48109, United States
[3]Cleft Palate-Craniofacial Clinic, Nationwide Children's Hospital, Columbus, OH, 43205, United States
[4]Division of Orthodontics, College of Dentistry, The Ohio State University, Columbus, OH, 43210, United States

*Corresponding author: Brian L. Foster, Division of Biosciences, College of Dentistry, The Ohio State University, 4163 Postle Hall, 305 W. 12th Avenue, Columbus, OH 43210, United States (foster.1004@osu.edu)

Abstract

Hypophosphatasia (HPP) is an inherited error in metabolism resulting from loss-of-function variants in the *ALPL* gene, which encodes tissue-nonspecific alkaline phosphatase (TNAP). TNAP plays a crucial role in biomineralization of bones and teeth, in part by reducing levels of inorganic pyrophosphate (PP_i), an inhibitor of biomineralization. HPP onset in childhood contributes to rickets, including growth plate defects and impaired growth. In adulthood, osteomalacia from HPP contributes to increased fracture risk. HPP also affects oral health. The dentoalveolar complex, that is, the tooth and supporting connective tissues of the surrounding periodontia, include 4 unique hard tissues: enamel, dentin, cementum, and alveolar bone, and all can be affected by HPP. Premature tooth loss of fully rooted teeth is pathognomonic for HPP. Patients with HPP often have complex oral health issues that require multidisciplinary dental care, potentially involving general or pediatric dentists, periodontists, prosthodontists, and orthodontists. The scientific literature to date has relatively few reports on dental care of individuals with HPP. Animal models to study HPP included global *Alpl* knockout mice, *Alpl* mutation knock-in mice, and mice with tissue-specific conditional *Alpl* ablation, allowing for new studies on pathological mechanisms and treatment effects in dental and skeletal tissues. Enzyme replacement therapy (ERT) in the form of injected, recombinant mineralized tissue-targeted TNAP has been available for nearly a decade and changed the prognosis for those with HPP. However, effects of ERT on dental tissues remain poorly defined and limitations of the current ERT have prompted exploration of gene therapy approaches to treat HPP. Preclinical gene therapy studies are promising and may contribute to improved oral health in HPP.

Keywords: dental biology, diseases and disorders of/related to bone, genetic animal models, osteomalacia and rickets, preclinical studies, matrix mineralization

Lay Summary

Hypophosphatasia (HPP) is an inherited disorder resulting from mutations in the gene for tissue-nonspecific alkaline phosphatase (TNAP). TNAP is an important protein for bones and teeth. In the skeleton, HPP can cause problems with bone growth and increases risk of fractures. HPP also affects teeth and contributes to a range of oral health problems. The most common dental effect of HPP is premature loss of teeth in children and in adults. Patients with HPP often have complex oral health issues that require multidisciplinary dental care, potentially involving general or pediatric dentists, periodontists, prosthodontists, and orthodontists. To date, there have been relatively few reports to guide dental care of individuals with HPP. Animal models to study HPP have been critical for increasing understanding of pathological mechanisms and treatment effects in dental and skeletal tissues. Enzyme replacement therapy (ERT) is a treatment that attempts to replace TNAP in those with HPP through injections of a synthetic form of the protein. ERT has changed the prognosis for those with HPP. However, effects of ERT on dental tissues remain unclear. Early studies of gene therapy approaches to treat HPP are promising and may contribute to improved oral health in HPP.

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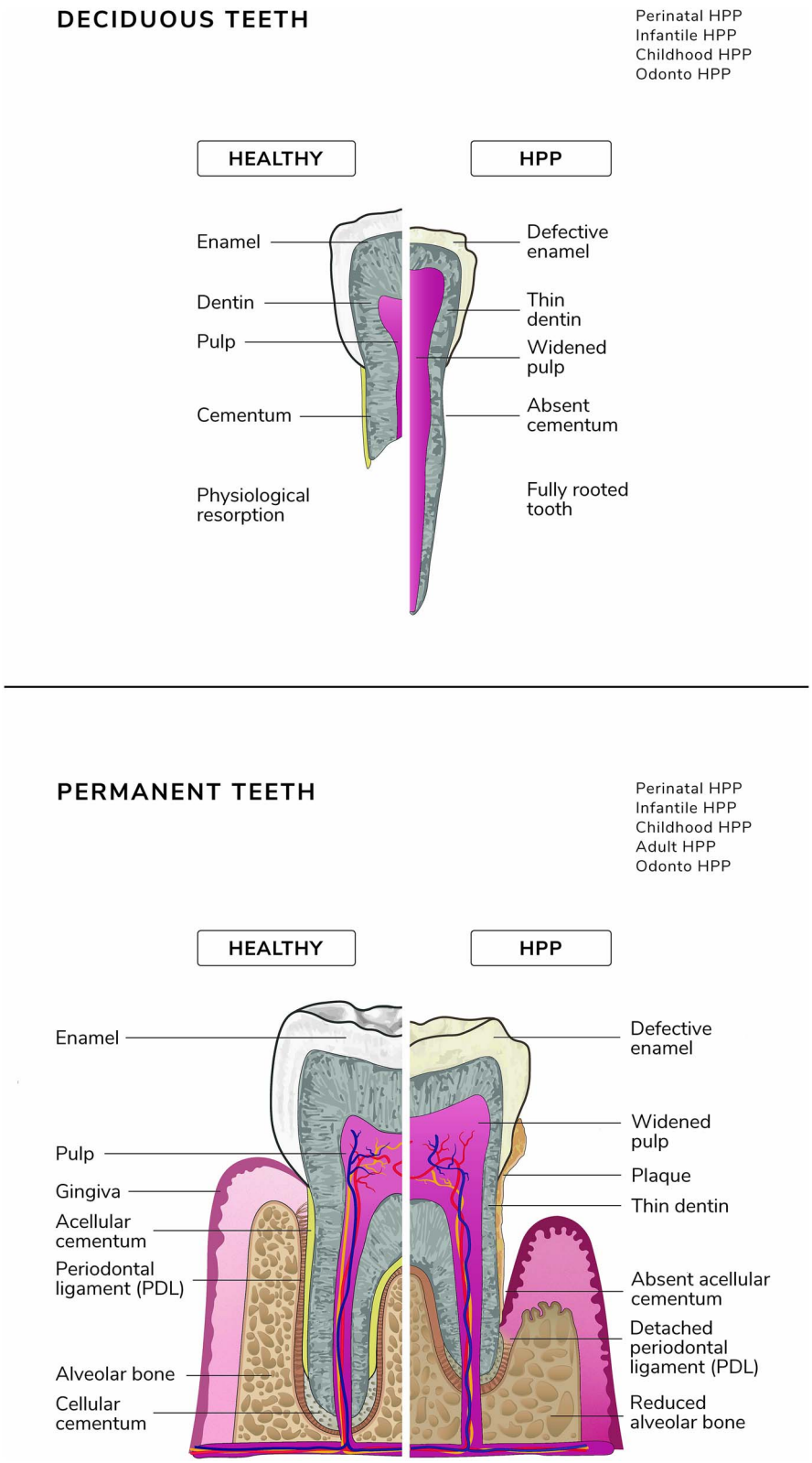
Graphical Abstract



Introduction

Hypophosphatasia (HPP) was first identified in 1948 by Dr. John Campbell Rathbun to describe a 3-wk-old boy who lost weight, showed signs of pain, and experienced seizures.[1] Radiographs revealed severe osteopenia and bone deformities and fractures. Low levels of serum alkaline phosphatase activity (ALP) were noted, with normal or elevated serum calcium and inorganic phosphate levels. This patient died at 2 mo of age. Case reports of HPP accumulated in subsequent decades, underscoring ALP deficiency as a primary diagnostic criterion.[2,3] In 1988, mutations in the *ALPL* gene were identified as the genetic basis of HPP; genetic identification of many more cases followed.[4–9] In 1996, nearly 50 yr after Rathbun's report, missense mutations were identified in *ALPL* exon 5 of the mother and exon 9 of the father of the original patient, revealing the child carried compound heterozygous defects.[10]

Over the last 2 decades, substantial progress has been made in identifying *ALPL* mutations contributing to HPP. Genotype-phenotype correlations, functional assays, in silico modeling, and animal models have provided new insights into all aspects of the disease. Research into HPP has expanded, including creation of animal models which have played an important role in the development of new treatments such as enzyme replacement therapy (ERT). These advances have improved our ability to diagnose and manage HPP, offering hope for better outcomes for affected individuals. This review focuses on dental manifestations of HPP, particularly advances in understanding pathological mechanisms, dental care, animal models used to study dental effects of HPP, and effects of ERT on dental tissues.

Introduction to HPP

Hypophosphatasia (OMIM# 146300, 241500, 241510) is an inherited error in metabolism resulting from loss-of-function variants in *ALPL*, which encodes tissue-nonspecific alkaline phosphatase (TNAP, TNSALP, or TNALP).[11,12] Natural substrates of TNAP include inorganic pyrophosphate (PP_i), pyridoxal 5′-phosphate (PLP), and phosphoethanolamine (PEA), among others. TNAP plays a crucial role in biomineralization of bones and teeth, in part by reducing local levels of PP_i, a potent inhibitor of hydroxyapatite crystal growth. Other substrates for dephosphorylation by TNAP include adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP).[13,14] Working in concert with other proteins, TNAP can generate extracellular inorganic phosphate (P_i), increasing the P_i/PP_i ratio and influencing biomineralization and purinergic signaling.

The ALPL gene is located on chromosome 1p36.1-34.[11,15,16] Pathological variants contributing to HPP have been reported in all 12 exons of *ALPL*, and as of this publication, 465 different disease-causing mutations have been documented (https://alplmutationdatabase.jku.at).[17] HPP cases result from missense mutations (79%), small deletions (10%), splicing mutations (4%), nonsense mutations (3%), small insertions (2%), and complex insertion/deletions, large deletions, and mutations in the regulatory sequence (1%).[18,19] The large proportion of missense mutations may correlate with the high level of clinical variability that characterizes HPP.

Systemic and skeletal effects of HPP are well described in other reviews.[11,12,20–25] Low serum ALP activity is the key biochemical indicator of HPP. Elevated levels of serum PLP and increased urinary PEA levels can also indicate HPP.[20,26,27] The clinical severity of HPP varies greatly between individuals. This has prompted creation of a spectrum of clinical subtypes to describe the onset, severity, and prognosis.[12,20,21,28] *Perinatal* and *infantile* forms of HPP are the most severe and can be life threatening. Manifestations include short, bowed long bones, rickets, wide fontanelles and sutures, respiratory complications, craniosynostosis, and vitamin B-dependent seizures (summarized in Table 1). In the *childhood* form of HPP, manifestations emerge after 6 mo and can include rickets, impaired growth, skeletal deformities, and craniosynostosis (Table 1). In the *adult* onset form of HPP, individuals may have osteomalacia, chronic pain, stress fractures, pseudofractures, chondrocalcinosis, and loss of mobility. Retrospectively, a history of mild rickets and premature tooth loss is sometimes revealed (Table 1). Musculoskeletal pain, muscle weakness, and fatigue are increasingly recognized as part of the spectrum of manifestations.[24,25,29–32] *Odontohypophosphatasia* (odonto HPP) primarily affects dental tissues, as described in the next section (Table 1). The fact that only dental tissues are affected in this subtype, and the observation that dental effects are observed across the spectrum of HPP, suggests these tissues have a special sensitivity to HPP, particularly cementum, which is required for tooth attachment.[22,28] While sex differences have been identified in HPP prevalence in a small number of studies,[33–36] it has been attributed to diagnosis biases and severity of disease has not been noted to differ in males vs females.[25,37]

Inheritance of HPP is complicated because both autosomal recessive (AR) and autosomal dominant (AD) patterns occur, depending on the nature of the mutation(s). More severe forms of HPP (perinatal and infantile) typically arise from an AR pattern of inheritance wherein the affected individual carries loss-of-function variants in both *ALPL* alleles. Often these are different pathological variants contributing to compound heterozygosity. Less severe forms of HPP (childhood, adult-onset, and odonto HPP) arise from an AR or AD pattern of inheritance. In the AD inheritance pattern, dominant negative effects have been found as a result of some *ALPL* variants.[19,38–42]

Reported prevalence of HPP varies widely depending on population and HPP clinical type, and estimates have undergone revision in recent decades with additional genetic testing driven in part by availability of ERT. Prevalence of HPP in Europe was estimated at 1:300 000 for severe cases and 1:6370 for mild/moderate cases.[43] Incidence of severe forms has been estimated at 1:100 000 in the general population in North America.[44] Some populations present higher HPP prevalence, for example, 1 in 25 are carriers in the Manitoba Mennonite population, resulting in 1:2500 affected infants at birth.[45] In Japan, prevalence of the most common HPP-associated allele has been estimated at 1:900 000.[46] Importantly, there is a growing consensus that moderate and mild forms of HPP are underdiagnosed. A laboratory-based survey of a population in northern Germany, which used criteria of low ALP and high PLP, found about 1:200 individuals who could be diagnosed with moderate HPP.[47] An *in silico* and functional analysis employing low ALP and heterozygosity of an *ALPL* variant as criteria for diagnosis in a population of 424 European individuals estimated moderate HPP prevalence at 1:2430 and mild HPP prevalence at 1:508.[38] This prompted a new genetic-based nosology for HPP including a

Table 1. Dental manifestations and interventions corresponding to clinical subtypes of HPP.

Clinical subtype	Inheritance pattern	Age of onset	Systemic manifestations	Medical interventions	Dental manifestations	Dental interventions
Perinatal HPP	AR	*In utero* or at birth	Fetal death; rickets; hypomineralization; chest deformity; skeletal deformity; fractures; seizures	Asfotase alfa (Strensiq); vitamin B6; breathing and feeding support; physical and occupational therapy	Teeth are unerupted at diagnosis but significant defects will manifest later in life	Later in life, multidisciplinary care involving periodontist, prosthodontist, and/or orthodontist
Infantile HPP	AR	First 6 mo of life	Rickets; fractures; respiratory deficiency; poor weight gain; failure-to-thrive; seizures; craniosynostosis; nephrocalcinosis; hypercalcemia; hypercalciuria	Asfotase alfa (Strensiq); Vitamin B6; breathing and feeding support; physical and occupational therapy; orthopedic interventions; pain management	Teeth are unerupted at diagnosis but significant defects will manifest later in life	Later in life, multidisciplinary care involving periodontist, prosthodontist, and/or orthodontist
Childhood HPP	AD or AR	After 6 mo old	Rickets; skeletal deformity; recurrent fractures; hypomineralization; short stature; muscle weakness; nephrocalcinosis; chronic pain	Asfotase alfa (Strensiq); vitamin B6; breathing and feeding support; physical and occupational therapy; orthopedic interventions; pain management	Premature tooth loss (deciduous); variable presentation may include effects on enamel, dentin, and periodontal attachment	Increased frequency of exams by pediatric dentist Possibly partial dentures (> 3 yr old) Later in life, multidisciplinary care involving periodontist, prosthodontist, and/or orthodontist
Adult HPP	AD or AR	After 18 yr old	Fractures and pseudofractures; osteomalacia; osteoarthropathy; chondrocalcinosis; chronic pain	Asfotase alfa (Strensiq); physical and occupational therapy; orthopedic interventions; pain management	Variable presentation may include history of premature tooth loss (deciduous); adult tooth loss; effects on enamel, dentin, periodontal attachment, alveolar bone levels	Increased frequency of dental exams and cleanings. Possibly scaling and root planning (deep cleaning) with periodontist Dental rehabilitation (implants, crowns) Multidisciplinary care involving periodontist, prosthodontist, and orthodontist
Odonto HPP	AD or AR	Varies	Absence of skeletal features	Currently, limited to none	Premature tooth loss (deciduous and permanent); effects on enamel, dentin, periodontal attachment, alveolar bone levels	Increased frequency of dental exam and cleanings. Possibly scaling and root planning (deep cleaning) with periodontist Dental rehabilitation (implants, crowns) Multidisciplinary care involving periodontist, prosthodontist, and orthodontist

Summary of inheritance pattern, age of onset, systemic manifestations and interventions, and dental manifestations and interventions are summarized for clinical subtypes of HPP. Dental features for each subtype are described at the time of onset or diagnosis, with the understanding that they may expand later in life. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; HPP, hypophosphatasia.

severe form (AR), moderate form (AR or AD with dominant-negative effects), or mild form (AD due to haploinsufficiency). It remains to be seen if this nosology will be adopted by the clinical community and how dental manifestations will fit into this system.

Dental manifestations of HPP and dental treatment of individuals with HPP

Overview

Dental defects occur across the spectrum of clinical subtypes of HPP from mild to severe and represent a substantial contribution to the disease burden (Table 1).[12,25,39,48–61] Dental involvement is very common among those with HPP, often one of the most prevalent manifestations according to reports culled from the HPP Global Registry, even exceeding prevalence of skeletal manifestations in some data.[25,60,62] Genotype-phenotype correlation is notoriously challenging for HPP;[38,42] however, case reports and anecdotal evidence have suggested increased prevalence and severity of dental defects in those with infantile and childhood HPP.[48,52,57,61] The Global HPP Registry supports this; for example, 78.8% of adults with pediatric-onset HPP have dental involvement vs 42.6% of those with adult-onset HPP.[24] These results from patient- and doctor-reported surveys are a good start; though more detailed dental histories, qualitative assessments of clinical photos and dental radiographs, and quantitative analyses of dental structures, could provide more precise and

insightful data on correlation of dental defects with genetic, biochemical, musculoskeletal, and other manifestations of HPP.

Four distinct mineralized tissues comprise the dentoalveolar complex, meaning the tooth and surrounding connective tissues. The tooth is composed of enamel (a highly mineralized tissue covering the crown), dentin (a tough mineralized tissue which composes the bulk of the tooth), and the enclosed dental pulp (housing cells, nerves, and vascular supply). Periodontal tissues surround, connect, and invest the tooth. These include the gingiva (oral epithelium that provides a barrier protecting underlying tissues), cementum (a thin, mineralized tissue covering root dentin), periodontal ligament (PDL) (a soft connective tissue between the tooth root and bone), and alveolar bone (part of the jawbone surrounding teeth and required for their retention). The acellular form of cementum covers the majority of the root and is the type most affected by HPP. Humans have 2 sets of teeth: the deciduous and permanent dentitions. Deciduous teeth begin forming in utero and erupt into the oral cavity in the first few years of life. These teeth are exfoliated and replaced by the permanent dentition between 6 and 12 yr of age. The permanent dentition must last a lifetime.

Effects of HPP dentoalveolar tissues span gross observations, radiographic findings, and histological defects (summarized in Figure 1 and Table 1, with representative images in Figure 2).[48,51,53–57,63] Clinical observations can include enamel hypoplasia and discoloration (possibly contributing to increased caries prevalence), delayed tooth eruption, tooth mobility, and malocclusion (misalignment of upper and lower teeth due to incorrect positions along the dental arches) (Figure 1 and Figure 2A-F). Premature loss of fully rooted deciduous teeth is pathognomonic for HPP, and loss of permanent teeth in adulthood can also occur. Here, the term "fully rooted" indicates substantial remaining root structure (Figure 2F); teeth are lost due to defective PDL-cementum attachment. Radiographic findings include thin dentin, wide pulp chambers, short or deformed tooth roots, and reduced alveolar bone levels around roots (Figure 1 and Figure 2G-K). Histological findings may include dentin mineralization defects, wide predentin, and particularly reduced or absent cementum on root surfaces (Figure 2L-Q). Mechanisms of these manifestations are discussed below.

Dental defects and their treatment

There are limited numbers of publications on dental management of patients with HPP. Based on complex and variable clinical manifestations, patients with HPP will benefit from multidisciplinary care, potentially involving general or pediatric dentists, periodontists, orthodontists, and prosthodontists.

General and pediatric dentists are often the first to diagnose HPP given the clinical presentation of early loss of deciduous teeth. They also help to assist the patient in navigating and coordinating their complex dental needs in addition to routine care. One of the clinical hallmarks of HPP is premature loss of one or more fully rooted deciduous teeth, typically before the age of 5 yr old. This can happen spontaneously or can result from minor traumas that would not normally cause tooth avulsion. Given the initial oral presentation, dentists play a key role in diagnosis.[53,64] Additional studies have shown loss of permanent teeth and tooth mobility in patients with HPP.[21,65] Loss of TNAP affects the cementum more severely than other dental tissues. Teeth have been reported to exfoliate with dental plaque accumulation along the root.[52,54] This results from lack of periodontal attachment, allowing bacterial invasion deep into periodontal tissues. Subgingival plaque accumulation potentially contributes to an inflammatory environment causing additional bone loss and periodontal disease.[66,67]

Anterior teeth are most frequently reported to exfoliate prematurely in children with HPP; however, prevalence by tooth type is not well understood. Incisors may be more prone to exfoliation because of their smaller, conical-shaped roots, whereas canines may be lost less frequently because of their relatively larger roots, and molars may fall out least frequently because of multiple roots that are more difficult to displace from surrounding bone. Many reports that examine teeth affected by HPP have described only incisors.[65,68–73] However, Van den Bos and colleagues observed 19 deciduous incisors and 12 deciduous canines from 7 individuals with HPP and reported uniform absence of cementum across tooth types and no apparent dentin defects.[57] Luder also described a canine tooth affected by HPP where acellular cementum was absent but dentin was normal.[54] Wei and coauthors examined one deciduous canine and found absence of cementum.[74] Kramer et al. analyzed 8 deciduous teeth, including incisors, canines, and molars, from a child with odonto HPP, finding cementum present on some canines, which were nonetheless lost prematurely.[52] Wolfel and colleagues found dentin and cementum hypomineralization in 11 deciduous teeth from a female with HPP, but results were not segregated by tooth type.[75] This points to more complex concepts of cementum defects other than simply cementum aplasia; possibly cementum can be hypomineralized, lack PDL insertions, and/or be dysfunctional in other aspects.

Periodontists, as dental specialists who focus on the function of tooth root cementum, PDL, and alveolar bone in health and disease, play a key role in monitoring presence of inflammation, bone loss, and managing oral hygiene. Early loss of deciduous teeth occurs due to cementum developmental defects which compromise tooth attachment.[73,76] HPP also impairs alveolar bone mineralization and reduced alveolar bone may arise from both direct effects on bone and indirect effects from compromised periodontal attachment. Compromised cementum and bone can increase the risk of gingival recession and the formation of periodontal pockets, spaces that form between tooth root surfaces and gingival tissues which can contribute to accumulation of bacteria, increased inflammation, and development of periodontitis, an inflammatory and destructive condition which compromises the periodontal tissues. Similar to the general population, cumulative loss of periodontal attachment from HPP leads to greater periodontal destruction. Overall, HPP illustrates the critical importance of periodontal attachment and the consequences when one or more components of this system are defective.

Periodontal manifestations and treatment were described for a 15-yr-old boy with HPP in Japan.[67] The boy exhibited premature exfoliation of deciduous teeth and permanent dentition was beset by alveolar bone loss and mobility. Severely affected teeth were extracted, and remaining teeth were treated by periodontal surgical treatment, scaling and root planning with open flap. This procedure is a form of "deep cleaning" that involves gently lifting the gum to access

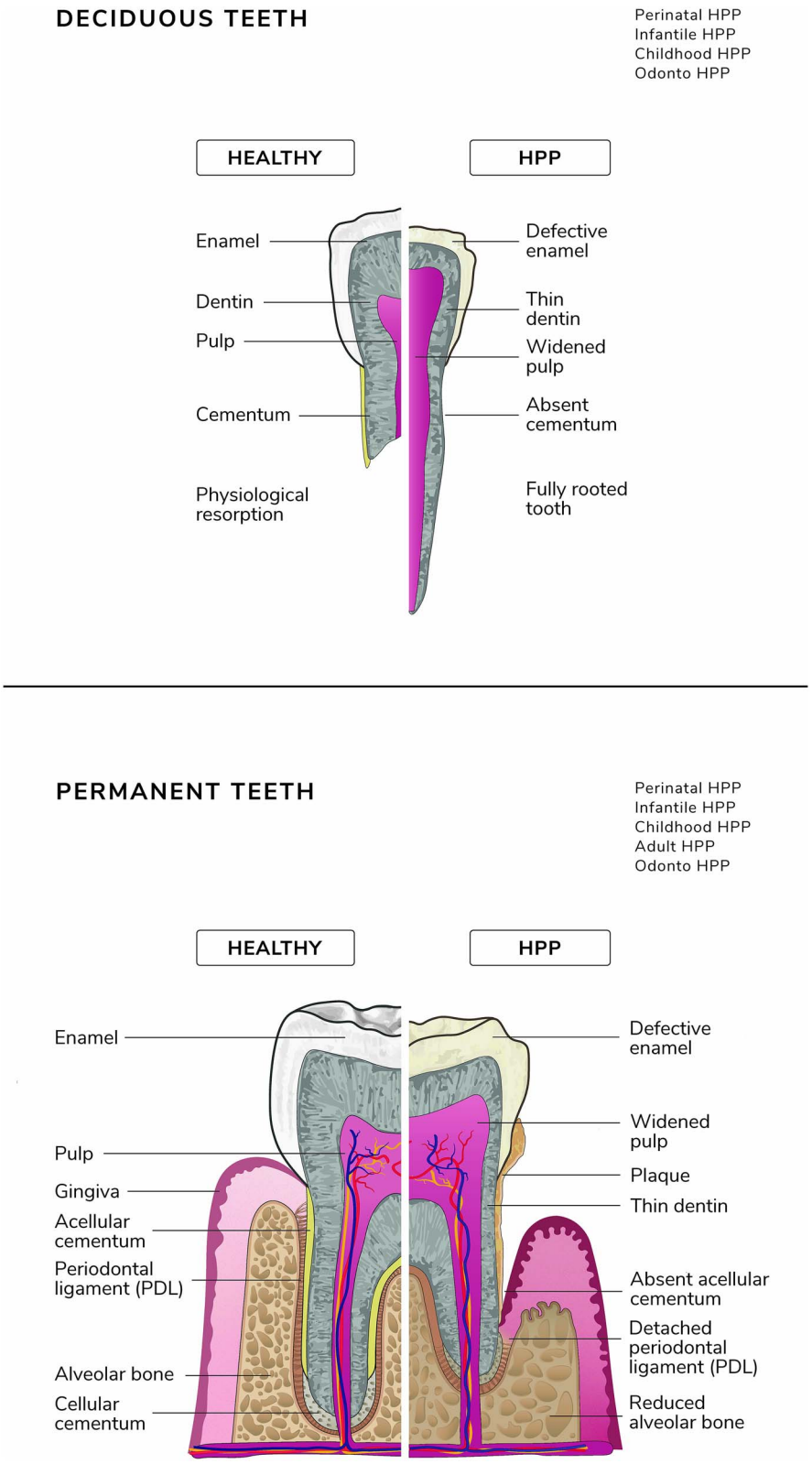


Figure 1. Dental impact of HPP. These schematics of deciduous and permanent teeth contrast health (left side) and potential effects of HPP (right side), linking effects to clinical subtypes of HPP. Dental effects of HPP are variable in severity and so affected individuals may show many or few of these effects. In HPP, deciduous teeth can exhibit enamel defects, thin dentin, enlarged pulp chambers, and reduced or absent acellular cementum. Normally, exfoliating deciduous teeth shows substantial physiological root resorption. Premature loss of "fully rooted" deciduous teeth is an important diagnostic clue for HPP. In HPP, permanent teeth can exhibit enamel defects, thin dentin, enlarged pulp chambers, short roots, reduced or absent acellular cementum, PDL detachment, and reduced alveolar bone. Many HPP subtypes share common dental effects. It should be noted that perinatal and infantile HPP do not exhibit dental features at diagnosis because during the first 6 mo of life, teeth are usually not erupted. Dental effects may become apparent later in childhood.

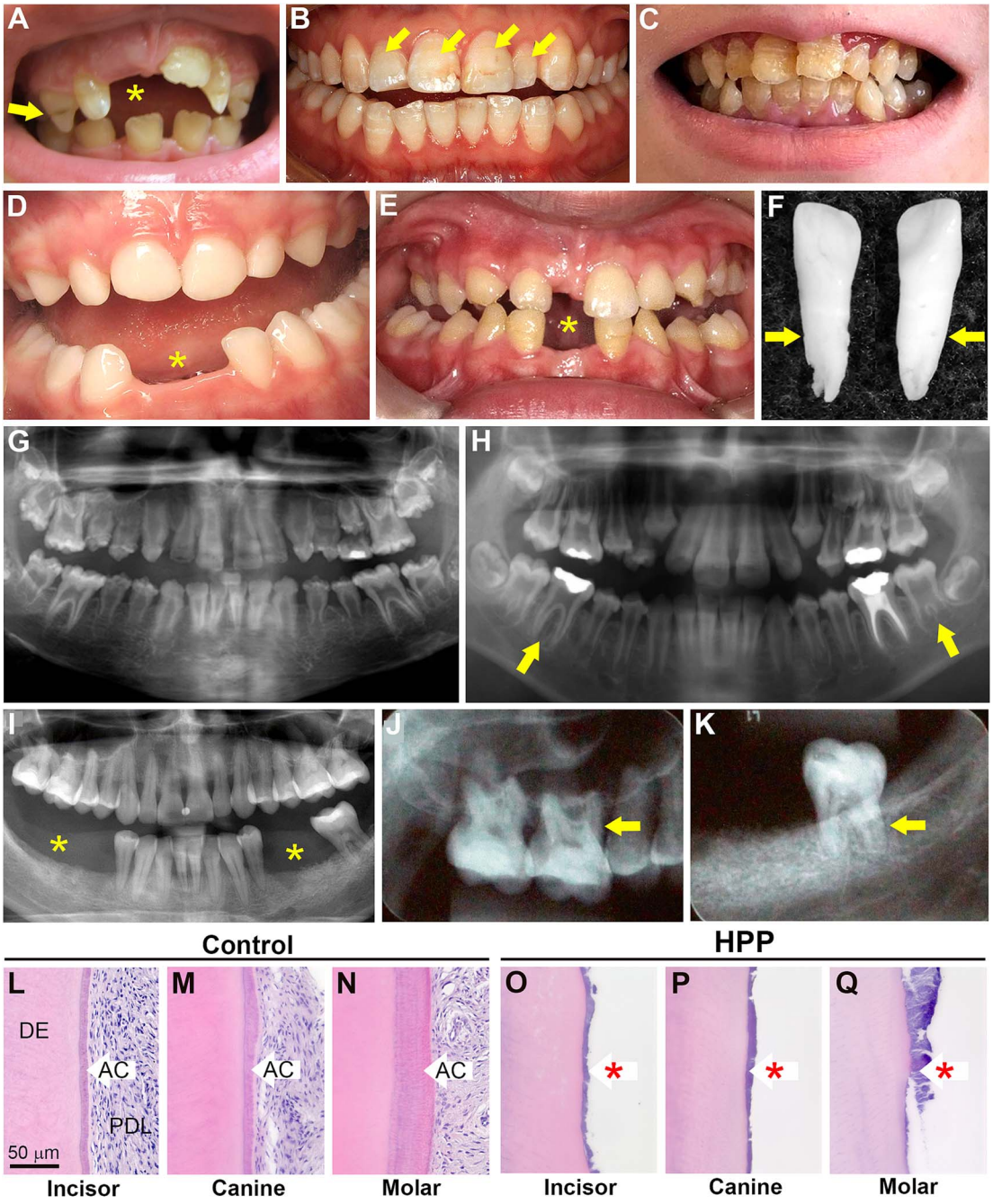


Figure 2. Dental manifestations of hypophosphatasia. Dental defects associated with HPP are variable across the spectrum of patients, organized by clinical or gross observations (A-F), radiographic observations (G-K), and histologic observations (L-Q). (A) Linear enamel hypoplasia of the deciduous maxillary canines (eg, at the arrow) and delay in the eruption of the maxillary right central incisor (star), in a 7-yr-old with infantile HPP. (B) Pale spots indicative of mild enamel hypoplasia (arrows) in a 27-yr-old patient with odonto HPP. (C) Severe enamel discoloration and hypoplasia manifested as horizontal bands and irregular crown appearance and texture in a boy with severe childhood HPP. (D) Premature loss of 3 deciduous lower incisors (star) before 3 yr of age in a youth with childhood HPP. (E) Loss of permanent maxillary and mandibular incisors (star) in a 14-yr-old boy with childhood HPP. (F) Deciduous incisors spontaneously exfoliated from a child with HPP retain substantial root structure (arrows), an abnormal finding. (G) Panoramic radiograph of a child with odonto HPP at 10 yr of age showing generalized enlarged pulp chambers and abnormality of crown and root shapes. (H) Panoramic radiograph of a child with infantile HPP at 12 yr of age showing enlarged pulp chambers and abnormality of crown and root shapes. Second molars dramatically increased pulp chamber size (taurodontism) than the first molars (arrows). (I-K) Dental radiographs of a 36-yr-old woman with adult HPP showing loss of numerous posterior mandibular teeth (stars), reduced alveolar bone height, and short roots (arrows). (L-Q) Histology of deciduous incisors, canines, and molars showing presence of acellular cementum (AC) on root dentin (DE) surface in healthy control tooth, and absence of AC in the tooth from a youth with childhood HPP. Teeth from the child with HPP shows the presence of dental plaque (stars), an abnormal finding. Images in (A), (D), and (H) reproduced under creative commons 2.0 license from Reibel et al., *Orphanet J Rare Dis* 21;4:6, 2009. Image in (B) reproduced under creative commons 4.0 license from Wang et al, *BMC Oral Health* 16(1):70, 2016. Image in (C) reproduced with permission from Bowden and Foster, *Adv Exp Med Biol* 1148:279-322, 2019. Image in (E) reproduced under creative commons 4.0 license from Okawa et al., *BMC Oral Health* 21(1):323, 2021. Image in (G) reproduced under creative commons CCBY license from Luder, *Front Physiol* 6:307, 2015. Image in (F) reproduced with permission from Whyte, *J Bone Miner Res* 32(4): 667-675, 2017. Images in (I-K) reproduced with permission from Martins et al., *Osteoporos Int* 31(11):2251-2257, 2020. Images in (L-Q) reproduced with permission from Kramer et al., *Bone* 143:115732, 2021.

the tooth roots and underlying bone for the removal of subgingival plaque and calculus. Remaining permanent teeth showed stabilized periodontal status. In another case report, long-term periodontal therapy was described for male identical twins with odonto HPP who suffered from premature loss of deciduous teeth, short roots, reduced alveolar bone height, and tooth mobility (Patients 1 and 2 in Figure 3A and B).[58] Both patients began losing permanent teeth as teenagers. Supportive periodontal therapy was initiated, including frequent visits every 3 mo, nonsurgical mechanical debridement of plaque, and oral hygiene instructions. Signs of worsening periodontal conditions in their 20s prompted a more proactive regime of visits every 2 mo and scaling and root planning. This approach stabilized the periodontal condition over the course of 2 yr, preparing for orthodontics and dental implants.

Orthodontists' main role is to address teeth crowding and create adequate spacing for implant placement or restorative work, as needed. Additionally, orthodontists can ensure a proper occlusion, that is, positions and alignment of upper and lower teeth. Orthodontic treatment was performed on the twin brothers with odonto HPP described in the previous section (Patients 1 and 2 in Figure 3C and D).[58] This phase of dental treatment was initiated after tooth stability was improved through periodontal therapy, and with the goal of improving occlusion, the way the upper and lower teeth come together. While orthodontic treatment has undoubtedly been performed on additional individuals affected by HPP, no detailed case reports have yet been published with which to guide clinical approaches. Those with HPP have difficulty finding specialists because of limited exposure to such complex cases, increased risk and liability if treatments are unsuccessful, and lack of publications to provide guidance on treatment planning.

Prosthodontists assist with the replacement of missing teeth through crowns, bridges, or implant prostheses. In addition to periodontal changes outlined above, enamel and dentin defects can create challenges for successful dental rehabilitation, including crowns and bridges that require adhesive bonding to the tooth. Thin, hypomineralized dentin, and short roots contribute to tooth mobility, exacerbating instability due to defects in cementum and alveolar bone. The majority of HPP-centered dental case reports describe prosthetic approaches to tooth loss.[77–81] A report from Ireland outlined placement of 7 implants to support fixed partial dentures following tooth mobility and loss.[80] The work took place over 6 yr, while the patient was in his 20s. One implant failed, likely due to insufficient bone quantity. In another report, prosthetic rehabilitation for a 16-yr-old woman with HPP was challenging due to loss of nearly all anterior teeth and severe reduction in alveolar bone height.[79] A maxillary overdenture and mandibular partial denture were prepared. Reduced bone height was also a limitation for an 18-yr-old woman with HPP who had lost numerous maxillary and mandibular permanent teeth.[78] Insufficient bone for implant retained prostheses, leading to interim removable partial dentures. A recent case report followed a 24-yr-old female who was diagnosed with HPP as a child (Patient 3 in Figure 3E).[77] She experienced early loss of all deciduous and several permanent teeth. Despite excellent oral hygiene, she was diagnosed with periodontal disease due to alveolar bone loss secondary to HPP. Full mouth prosthetic rehabilitation was planned over several steps, which required approximately 2 yr. This approach involved extraction of several teeth due to substantial mobility and use of guided bone regeneration with autogenous bone and bone graft material to prepare for implant-retained fixed partial prostheses (Figure 3E-H). Follow-up included oral hygiene instructions and regular cleanings. After 7 yr, implants were reported to be stable.

The above cases highlight the need for a multidisciplinary dental care team. Active periodontal disease must be resolved prior to restorative and orthodontic interventions. It is critical to have adequate imaging to evaluate bone levels prior to orthodontic tooth movement or implant placement. Notably, dental implants may be contraindicated in young children until jaw bone growth is completed.[82] Excellent oral hygiene is vital to successful outcomes. Patients with HPP should be seen more frequently for cleanings and dental exams. Treatment plans may extend much longer to account for more extensive rehabilitation and/or conservative approaches to treatment planning. In addition to the dental management, it is also necessary to consult with the managing endocrinologist to verify ALP levels and determine if the patient is receiving ERT (described in more detail below) prior to starting intervention. Additional research is needed to create specific guidelines for management of the changing dental needs from childhood to adulthood for patients with HPP.

As more patients start ERT at younger ages, we will gain a better understanding of dental effects and the impact on bone quality. If patients can avoid early tooth loss and periodontal disease then dental management becomes less complex. Older patients who have experienced loss of teeth at an early age, but now have increased ALP due to ERT, may be good candidates for orthodontics or dental implants. Understanding the impact of ERT on the alveolar structures and dental tissues will help guide diagnosis and treatment planning thus creating the best outcomes for patients.

Expression of TNAP in dental tissues and animal models to study mechanisms of dentoalveolar pathologies in HPP

Animal models of HPP have provided key insights into the role(s) of TNAP in dentoalveolar tissues and served as preclinical models for development of therapies.

TNAP is expressed in dental cells and tissues

TNAP expression in dentoalveolar tissues has largely been explored in mice. The dentoalveolar complex, that is, the tooth and supporting periodontia, includes 4 unique hard tissues: enamel, dentin, cementum, and alveolar bone. Gene expression and protein localization experiments demonstrated TNAP in hard tissue cells during odontogenesis, suggesting important roles in tooth formation and mineralization.[83,84] The first evidence of increased TNAP in the oral cavity is during jawbone mineralization (Figure 4A).[22] During crown formation, TNAP is abundant in both the enamel organ and odontoblasts that make dentin (Figure 4B-E).[22,84,85] TNAP shows a specific pattern of expression in the enamel organ, localized in maturation stage ameloblasts, aligning with their role in mineralization of the enamel. Pre-ameloblasts and secretory stage ameloblasts do not express TNAP, whereas the adjacent stratum intermedium shows intense TNAP staining.[85–87] The role of TNAP in the stratum intermedium, a supportive but nonmineralizing tissue, remains unclear. During root formation, TNAP is abundant in the forming

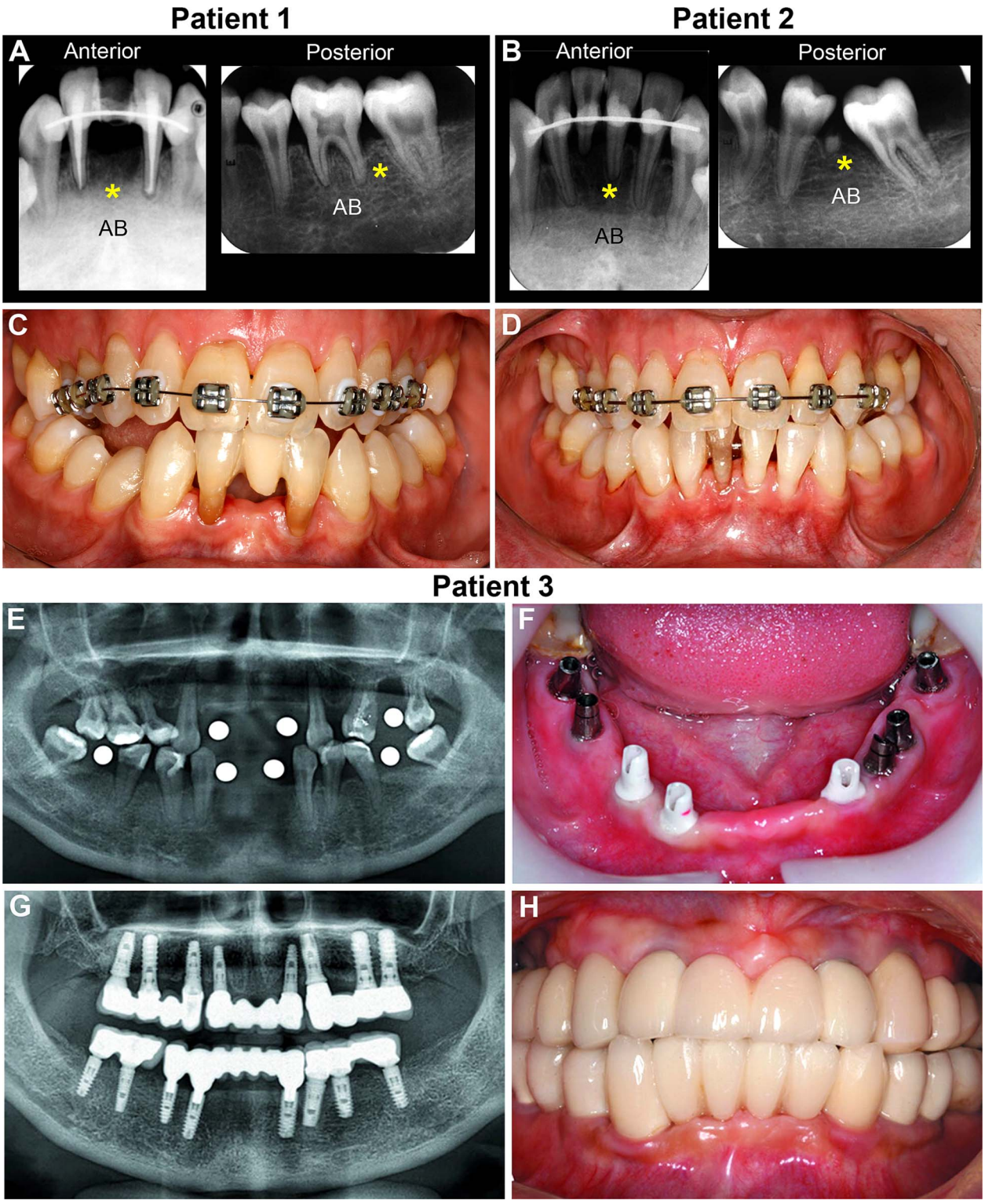


Figure 3. Dental treatment of individuals with hypophosphatasia. Patients 1 and 2 in (A-D) received periodontal and orthodontic treatment. (A, B) Periapical radiographs of anterior and posterior teeth of 20-yr-old twin male patients showing severe reduction in alveolar bone (AB) height (stars), wide pulp chambers, and short tooth roots with some abnormal shapes. (C, D) Photographs of the same patients taken after periodontal treatment and during the active phase of orthodontic treatment. Patient 3 in (E-H) received prosthodontic treatment. (E) Panoramic radiograph showing extensive tooth loss in a 24-yr-old female with HPP (edentulous regions indicated by circles). (F) Placement of abutments for dental implants following mandibular tooth extraction. (G) Alveolar bone levels appear stable at 7-yr follow-up and (H) the patient remains satisfied with the prosthetic rehabilitation. Images in (A-F) reproduced with permission from Rodrigues et al, clinical correlate: Case study of identical twins with cementum and periodontal defects resulting from odontohypophosphatasia. In: Mineralized tissues in oral and craniofacial science: Biological principles and clinical correlates, Wiley, 2012. Images in (E-H) reproduced with permission from Yang et al., *J Prosthodont* 30(9), 2021.

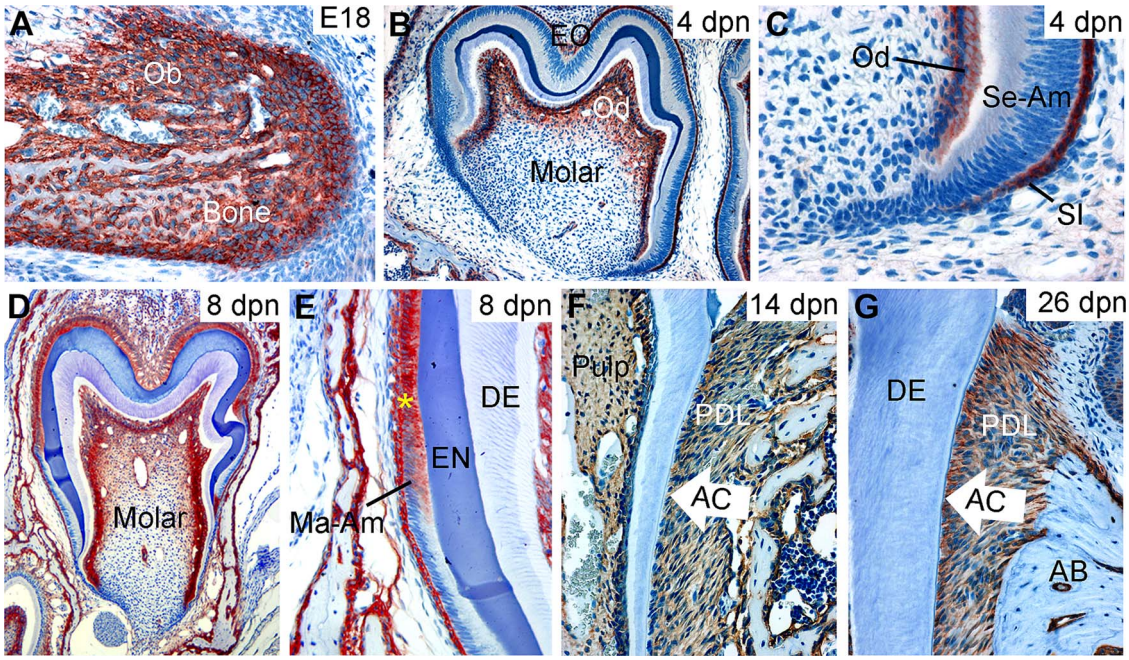


Figure 4. TNAP is expressed in dental cells and tissues. Immunohistochemistry in mouse mandibular tissues shows the expression of TNAP protein (red color). (A) Osteoblasts (Ob) of the mouse jaw bone at embryonic Day 18 (E18) strongly express TNAP. (B, C) At 4 d postnatal (dpn), odontoblasts (od) that make dentin and the enamel organ (EO) that produces enamel (EN) express TNAP, though secretory ameloblasts (Se-Am) do not. (D, E) by 8 dpn, ameloblasts transitioning to maturation stage (Ma-Am) begin expressing TNAP (yellow star). (F, G) At later ages of 14 and 26 dpn, after periodontal tissues have formed, the entire periodontal ligament (PDL) between the root surface acellular cementum (AC) and alveolar bone (AB) becomes strongly positive for TNAP. Image in (A) reused with permission from Bowden and Foster, *Adv Exp Med Biol* 1148:279-322, 2019. Images in (B) and (C) reused with permission from McKee et al., *J Dent Res* 92(8): 721-727, 2013. Images in (D) and (E) reused with permission from Yadav et al., *J Bone Miner Res* 27(8): 1722-1734, 2012. Images in (F) and (G) reused under creative commons license from Zweifler et al., *Int J Oral Sci* 7(1): 27-41, 2015.

periodontium, including cementoblasts, osteoblasts, and in the wider PDL region (Figure 4F and G).[22,88,89]

Mouse models of HPP

Several mouse models of HPP have been engineered over the past 3 decades, allowing experiments into mechanisms of HPP as well as therapies. Mice engineered to globally delete *Alpl* (Formerly *Akp2*$^{-/-}$, now *Alpl*$^{-/-}$) exhibit skeletal and dental features consistent with severe infantile HPP.[90–92] The research group of Dr. José Luis Millán developed the *Alpl*$^{-/-}$ mouse line in 1997 which has been used for the majority of studies in the ensuing decades. These *Alpl*$^{-/-}$ mice exhibit defective cranial vault and base mineralization, abnormal cranial shape, and craniosynostosis, consistent with severe, infantile HPP (Figure 5A).[93–95] Molars and incisors of *Alpl*$^{-/-}$ mice displayed defective enamel mineralization and disrupted ultrastructure (Figure 5B).[85] Histologically, *Alpl*$^{-/-}$ ameloblasts showed abnormal and disorganized morphology. In a separate study, the first molar germ of *Alpl*$^{-/-}$ mice showed a thin, uneven, enamel layer on postnatal Day 5, linked to disrupted enamel matrix proteins.[96] While it is clear that global deletion of TNAP disrupts amelogenesis, the exact function(s) of TNAP in enamel development and mineralization remain incompletely understood.

Defective root dentin mineralization was described in the *Alpl*$^{-/-}$ mice.[88,97,98] Defects varied from minor delays to severe disruptions in root dentinogenesis (Figure 5C and D). Delays were documented in mantle dentin mineralization; mantle dentin is the initial dentin matrix secreted and a form which depends on matrix vesicles to initiate mineralization.[52,88] The defects were correlated with disordered odontoblasts and altered expression of osteocalcin (*Bglap*/OCN) and dentin sialophosphoprotein (*Dspp*/DSP and DPP).[88,89] Further characterization of dentin in molars and incisors of *Alpl*$^{-/-}$ mice demonstrated wider mantle dentin was associated with defective mineralization of the adjacent circumpulpal dentin.[52] *Alpl*$^{-/-}$ mice also exhibit acellular cementum hypoplasia responsible for impaired periodontal attachment (Figure 5E).[83,97,99] Interestingly, the absence of acellular cementum was commonly observed in HPP teeth with mantle dentin defects, indicating a possible link between these phenotypes.[52]

Alpl$^{-/-}$ mice phenocopy many aspects of severe infantile HPP; however, they die before weaning age and their disease severity and lethality hinder analysis at advanced ages. This limitation prompted efforts to develop alternative HPP mouse models to better understand the enzyme's role in development and explore strategies for rescuing dental defects. The first mouse model of odonto HPP was engineered by knocking in a human HPP mutation (c.346G>A) into *Alpl* exon 5, resulting in an A116T substitution.[100] This variant was associated with a large kindred of individuals with primarily dental manifestations.[61] *Alpl*$^{+/A116T}$ mice exhibited 50% reduced ALP, with minimal impact on skeletal and dental mineralization. The A116T mutation showed hypomineralization of mouse alveolar bone and cellular cementum, with a trend of reduced acellular cementum. However, the defects were so unexpectedly mild as to make it difficult to pursue additional studies of interventions.

Additional mouse models of later-onset HPP with extended life spans were developed employing the Cre/loxP system to

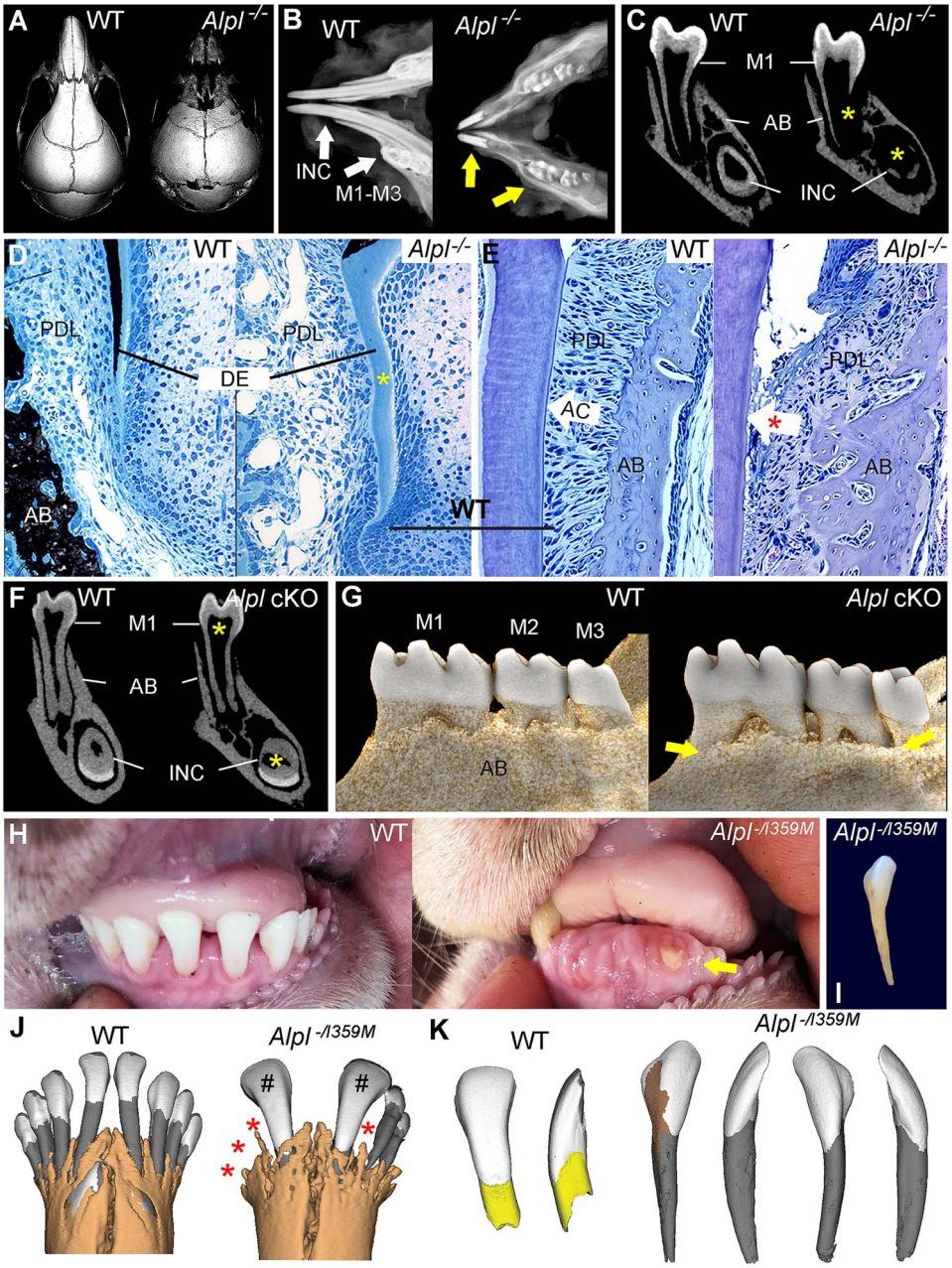


Figure 5. Animal models of hypophosphatasia. (A) Radiographs of skulls of WT and *Alpl*$^{-/-}$ mice at 15 d postnatal (dpn). *Alpl*$^{-/-}$ mouse cranial bones feature severe hypomineralization and altered craniofacial shape. (B) Radiographs of mandibles with incisors (INC) and molars (M1-M3) of WT and *Alpl*$^{-/-}$ mice at 22 dpn. *Alpl*$^{-/-}$ mouse mandibles show reduced radiopacity in molars and incisors (arrows). (C) Micro-CT of WT and *Alpl*$^{-/-}$ mouse mandibles at 14 dpn. *Alpl*$^{-/-}$ mandibular first molar (M1), incisors (INC), and alveolar bone (AB) show radiolucency (star) indicative of severe hypomineralization. (D) Von Kossa stained undecalcified tissue sections of WT and *Alpl*$^{-/-}$ mouse mandibles at 12 dpn. Compared to well mineralized molar dentin (DE) in WT (indicated by black stain), *Alpl*$^{-/-}$ mouse molar roots featured hypomineralized dentin matrix (star indicating lack of black stain). (E) H&E stained tissue sections of WT and *Alpl*$^{-/-}$ mouse mandibles at 22 dpn. Compared to the acellular cementum (AC) and periodontal attachment in WT, *Alpl*$^{-/-}$ mouse molars lack AC (star), causing detachment of the periodontal ligament (PDL) and disorganized PDL and alveolar bone. (F) Mandibles of *Col1a1*-mediated *Alpl* cKO show defective mineralization and progressive breakdown, including reduced (arrows) alveolar bone (AB). Compared to WT, *Alpl* cKO molars feature short roots with thin dentin and widened pulp chambers (star) and the lingual DE of the incisor is severely dysmorphic with delayed mineralization (star). (G) 3D reconstructions of micro-CT scans show reduced AB height (arrows) in cKO mice, indicating periodontal breakdown. (H) Intraoral photos show premature loss of deciduous incisors (arrow) in *ALPL*$^{-/I359M}$ vs WT sheep by 12 mo. (I) Prematurely lost incisor from *ALPL*$^{-/I359M}$ sheep retains substantial root length. (J) Premature tooth loss in *ALPL*$^{-/I359M}$ sheep was associated with early eruption of permanent incisors (# marks permanent central incisors). Increased distance between permanent central incisors is due to drifting resulting from premature loss of several deciduous teeth (stars) in *ALPL*$^{-/I359M}$ sheep. (K) 3D micro-CT reconstructions of deciduous incisor of *ALPL*$^{-/I359M}$ vs WT sheep show substantial root length compared to WT sheep. Micro-CT analysis identifies cementum (yellow) covering WT tooth roots, but cementum is undetectable on *ALPL*$^{-/I359M}$ sheep root surfaces (Gray indicates underlying DE). Images in (A) reproduced with permission from Liu et al., *Bone* 67:81-94, 2014. Images in (B) reproduced with permission from Yadav et al., *J Bone Miner Res* 27(8): 1722-1734, 2012. Images in (D) reproduced with permission from Foster et al., *J Bone Miner Res* 28(2): 271-282, 2013. Images in (C) and (E) reproduced with permission from Bowden and Foster, *Adv Exp Med Biol* 1148:279-322, 2019. Images in (F) and (G) reproduced with permission from Foster et al., 96(1):81-91, 2017. Images in (H-K) reproduced from Mohamed et al., *J Bone Miner Res* 37(10):2005-2017, 2022.

engineer conditional *Alpl* deletion. *Alpl*$^{fl/fl}$ mouse models, when crossed with with mice harboring Cre recombinase driven by either the *Col1a1* promoter (to target *Alpl* in osteoblasts and dental cells) or *Prx1* promoter (to target *Alpl* in limb buds, chondrocytes, osteoblasts, and craniofacial mesenchyme), phenocopied key aspects of human juvenile and adult forms. These conditional knockout (cKO) models exhibit 75% decreased ALP at 24 wk and pronounced skeletal anomalies including rachitic changes, deformations, and fractures.[101] *Col1a1* cKO of *Alpl* caused dental defects including thin dentin, absence of acellular cementum, alveolar bone hypomineralization, and periodontal breakdown (Figure 5F and G).[101]

Sheep model of HPP

HPP mouse models have significantly contributed to advancing our knowledge of disease mechanisms and therapeutic strategies. Despite showing reduced cementum and detachment of PDLs, HPP mouse models do not exhibit the hallmark of premature tooth loss, which is a key diagnostic criterion in HPP. This disparity may be attributed to differences in growth and physiology between mice and humans; mice are monophyodonts with only one set of teeth. Mouse appendicular bones are also imperfect models for human skeletal diseases, as mice lack osteonal bone remodeling and load bearing is substantially different.

Sheep, unlike mouse models, have a diphyodont dentition (2 sets of teeth: deciduous and permanent) and osteonal bone remodeling similar to humans, making them a better model for studying the pathophysiological mechanisms underlying HPP dental and skeletal defects. CRISPR/Cas9 was used to develop a sheep model of HPP by introducing a missense mutation (c.1077C>G; p.I359M) into the *ALPL* gene.[102] This mutation was based on a human patient with childhood HPP.[52] Longitudinal analysis revealed a spectrum of musculoskeletal, craniofacial, and dental abnormalities in sheep, including premature tooth loss, hypomineralization, muscle weakness, and metaphyseal flaring of long bones.[102,103] Interestingly, compound heterozygous sheep (*ALPL*$^{-/I359M}$) exhibited the most severe defects, followed by homozygous (*ALPL*$^{I359M/I359M}$) and heterozygous (*ALPL*$^{+/I359M}$) mutants, correlating with ALP levels. Key dental findings include early defects in cementum and alveolar bone, possibly leading to poor periodontal attachment and premature tooth loss, with fully rooted teeth being shed (Figure 5H-K). Reduced crown dentin thickness and severe mantle dentin hypomineralization were observed in an HPP sheep model, along with genotype-associated cementum hypoplasia.[103] These dental manifestations in sheep closely resemble those observed in a human patient carrying the same mutation. While a previous study reported a mutation in Karelian Bear Dogs resembling HPP, dental abnormalities were not observed.[104] This makes sheep the first animal model to replicate premature deciduous tooth loss seen in HPP.[103]

Therapeutic approaches for HPP and effects on oral health

Prior to the advent of the ERT, treatment of HPP patients was largely limited to supportive care, including pain management, orthopedic surgeries for rickets and fractures, and respiratory support for severely affected infants. Early attempts to treat HPP included transfusion of ALP-rich blood and bone marrow cell transplantation; benefits were transient and lasting improvements were not achieved.[105–110] Bisphosphonates, drugs that inhibit osteoclast function, have in some cases been administered to HPP patients, usually because of misdiagnosis or misunderstanding of the etiopathology of HPP.[111–115] These drugs worsen the hypomineralization caused by HPP and are contraindicated for use in HPP patients.

Teriparatide (TPTD), a recombinant peptide based on parathyroid hormone, is an anabolic agent used to treat osteoporosis. Case reports indicate potentially positive effects on reducing osteomalacia and accelerating bone healing in those with HPP.[112–114,116] Relative success of TPTD therapy may depend on the clinical subtype and biochemistry of each individual HPP patient as the increased numbers and activity of osteoblasts will still produce defective TNAP enzyme.

Development of ERT for HPP

Based on prior unsuccessful attempts to treat HPP, a new goal was set to develop a recombinant ERT. Dr. Philippe Crine and scientists at Enobia Pharma engineered a soluble form of TNAP via removal the hydrophilic GPI anchor and adding the Fc region of human IgG, allowing column purification and increasing the protein's half-life in circulation.[98] A highly negatively charged deca-aspartate (D_{10}) tail was added in order to target delivery to mineralized tissues (Figure 6A and B). Preclinical studies of TNAP-D_{10} (Asfotase alfa) were conducted by Dr. José Luis Millán and colleagues using the *Alpl*$^{-/-}$ mouse. Starting with newborns, daily subcutaneous injections of 8.2 mg/kg TNAP-D_{10} prevented seizures, increased lifespans, and ameliorated skeletal defects and fractures (Figure 6C).[98,117]

Following preclinical studies, clinical trials for TNAP-D_{10} in infants and young children with perinatal or infantile HPP began in 2008. Over the next decade, additional clinical trials conducted by Alexion Pharmaceuticals, Inc., enrolled infants, children, juveniles, and adults. The drug substantially improved bone mineralization, leading to improvement in respiratory function and survival, resolution of rickets and skeletal deformities, and improved fracture healing in neonates and infants with severe HPP.[118–127] In 2015, Asfotase alfa Strensiq was approved in Japan, Canada, the European Union, and the United States for pediatric-onset HPP.

Asfotase alfa is delivered 3 or 6 times weekly as a subcutaneous injection. ALP levels following treatment dramatically increase as high as ~24 000 IU/L within weeks (about 50-fold higher than normal, age-adjusted ALP levels) and remain elevated at 3000-6000 IU/L after years of therapy.[124,125] Clinical trial results showed good safety profiles, with the most common adverse effects being injection-site reactions in approximately 75% of treated individuals, including edema, pain, irritation, and in rare cases, an anaphylactic response.[118,124,125] An unusual, localized lipohypertrophy reaction occurs in some patients and appears to persist for several years, even after discontinuation of ERT.[125,128,129]

Effects of ERT on dental tissues

Responses of craniofacial and dentoalveolar tissues to asfotase alfa were evaluated in the *Alpl*$^{-/-}$ mouse model. ERT prevented craniosynostosis and normalized cranial shape and mineralization (Figure 6D).[93,94,130] ERT prevented enamel

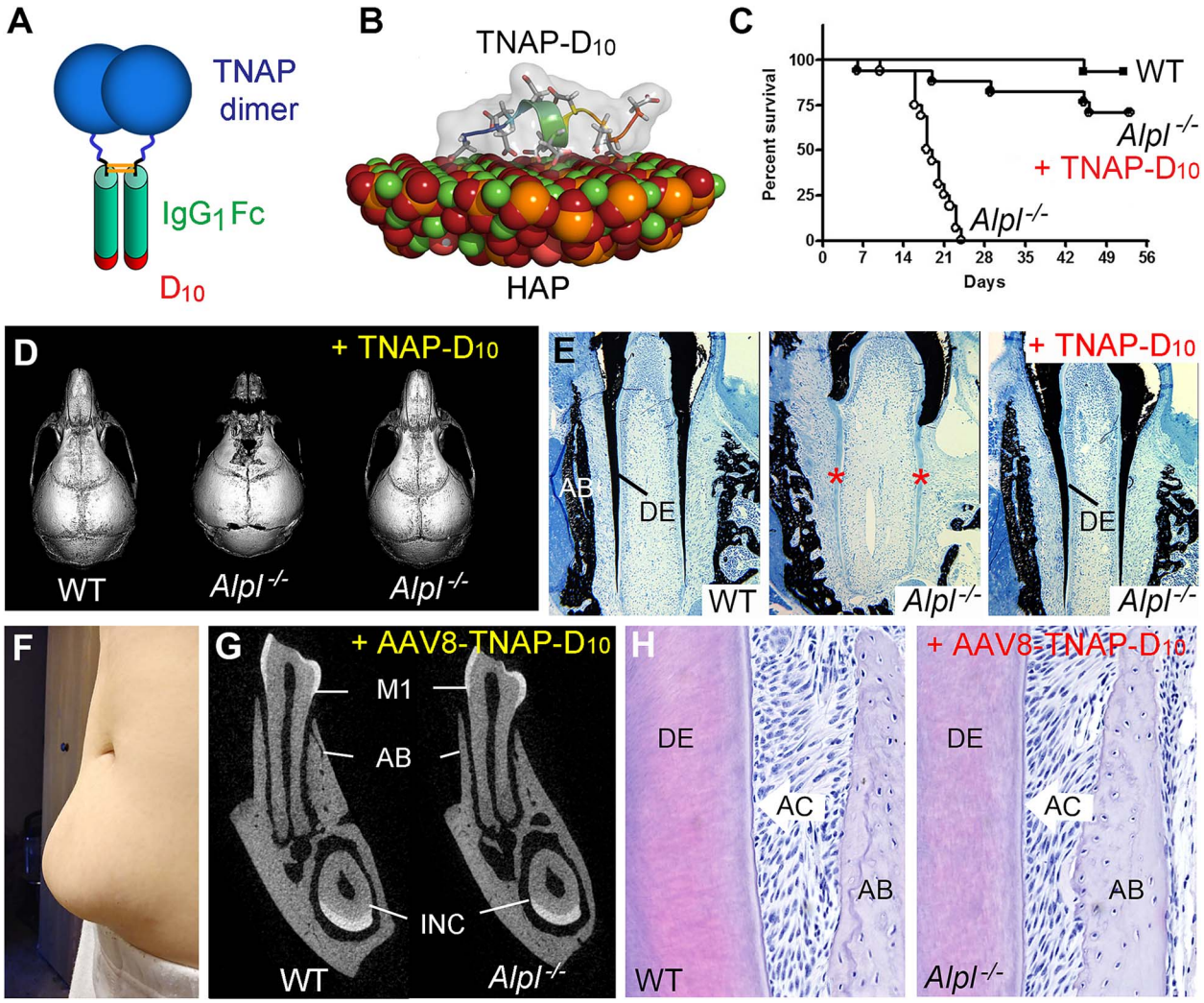


Figure 6. Effects of enzyme replacement therapy on dental tissues. (A) Schematic of recombinant Asfotase alfa enzyme showing the TNAP dimer, human IgG1 Fc domain, and D_{10} deca-aspartate tail. (B) A simulated model shows predicted interaction of the highly negatively charged D_{10} tail with the positively charged calcium plane in the hydroxyapatite (HAP) crystal. (C) Kaplan-Meier curve showing survival of wild type (WT), untreated *Alpl*$^{-/-}$, and *Alpl*$^{-/-}$ mice receiving 8.2 mg/kg TNAP ERT throughout the study. (D) Micro-CT of skulls at 15 dpn shows that ERT produces improvements in size, shape, and mineralization of craniofacial bones in *Alpl*$^{-/-}$ mice. (E) Von Kossa stained undecalcified tissue sections reveal ERT rescues dentin (DE) mineralization defects (stars) in *Alpl*$^{-/-}$ mice, as indicated by black stained appearance of mineralized tissues. (F) Lipohypertrophy at an abdominal injection site remained the same size in an adolescent after discontinuing ERT for more than a year. (G) 2D micro-CT renderings of first molars (M1) and incisors (INC) exhibit normal tooth structures in AAV8-TNAP-D_{10} treated *Alpl*$^{-/-}$ mice similar to those in WT controls at 70 dpn. (H) H&E staining shows no evident dental defects in treated *Alpl*$^{-/-}$ mice compared with WT controls. Images in (A) and (B) reproduced with permission (via republication of material within the agreed upon thresholds between STM permissions guidelines signatories) from McKee et al., *J Dent Res* 90(4):470-476, 2011. Images in (C) and (E) reproduced with permission from Millán et al., *J Bone Miner Res* 23(6):777-787, 2008. Images in (D) reproduced with permission from Liu et al., *Bone* 78:203-211, 2015. Image in (F) reproduced with permission from Bowden and Foster, *Adv Exp Med Biol* 1148:279-322, 2019. Images in (G) and (H) reproduced under creative commons CCBY license from Kinoshota et al., *J Bone Miner Res* 36(9):1835-1849, 2021.

defects in *Alpl*$^{-/-}$ mice.[85] The same regiment also dramatically reduced dentin mineralization defects and prevented cementum hypoplasia and alveolar bone defects, restoring periodontal attachment and function (Figure 6E).[88,97,98]

Preclinical experiments in *Alpl*$^{-/-}$ mice indicated tremendous potential for ERT to prevent craniofacial and dental manifestations of HPP. One caveat was that ERT was initiated at early postnatal ages, prior to onset or before maximum impact of dental manifestations. Because the skeleton is in a constant state of remodeling, introduction of TNAP-D_{10} to mice or humans with HPP would be expected to replace poorly mineralized osteoid with improved bone. In contrast, enamel, dentin, and cementum of teeth do not remodel, and dentin and cementum have limited ability for repair. Deciduous and permanent dentitions in humans are forming and mineralizing *in utero* and during early months to years after birth. Early therapeutic intervention is critical to maximally improve formation, mineralization, and function of the teeth.

No detailed prospective, randomized studies of the effects of ERT on dental tissues in patients with HPP have been conducted, making it difficult to assess the real clinical impact. However, some insights can be gained from clinical trials and case reports. In an early open-label study, ERT was administered to 10 infants and young children (aged 7.5-36 mo) with life-threatening HPP.[118] All treated patients experienced eruption of deciduous teeth, with only one female patient experiencing premature tooth loss. This patient had

already lost 9 deciduous teeth before beginning ERT treatment at 36 mo of age, and the remaining 6 exhibited mobility. After 6 mo of treatment, the remaining 6 teeth became less mobile, and 4 additional teeth erupted. Another 7-mo-old female patient in the same study showed improved tooth mineralization after 1 yr of ERT. The long-term results showed improvements in skeletal mineralization, respiratory function, growth, and cognitive and motor function.[131] Four patients (36%) experienced tooth loss.

Case studies and series offer mixed assessments regarding the effects of ERT on oral tissues. Conclusions about efficacy of ERT are often obfuscated by different subtypes and severity of HPP and age at initiation of ERT. One case report focusing on the impact of ERT on dental features described a patient with infantile HPP that initiated ERT 1 d after birth.[132] During examination at 41-mo-old, enamel and dentin were hypomineralized and permanent tooth development appeared delayed, but no prematurely lost deciduous teeth were noted. However, by 47-mo-old, this patient lost 3 incisors due to trauma. The exfoliated teeth were examined and showed hypomineralization of enamel, dentin, and cementum, and hypoplastic cementum. In a case of an infantile HPP in Japan, a 20-mo-old boy experienced early exfoliation of deciduous teeth.[133] ERT was initiated at 21-mo-old, and the patient demonstrated stable periodontal conditions of deciduous molars afterwards. In another report from Japan, an 11-yr-old boy with childhood HPP had premature loss of 2 deciduous incisors.[134] ERT appeared to positively affect mandibular bone density and periodontal stability.

Larger studies have provided more incisive insights. A nationwide survey conducted in Japan gathered dental findings from 52 HPP cases, including 16 individuals with odonto HPP and 36 with other forms of HPP.[135] Some dental manifestations appeared resistant to ERT. Two patients with childhood and infantile HPP treated with ERT experienced loss of permanent teeth. Four patients with various HPP forms showed severe periodontal disease and early exfoliation of deciduous dentition. In this study, early exfoliation of deciduous teeth and treatment with ERT were not correlated. In perhaps the most conclusive study to date, a Canadian open-label clinical trial for ERT collected data on the development and loss of deciduous and permanent teeth in a group of 11 children under the age of 5 with infantile HPP was collected.[136] The study found that children who were treated with ERT at an early age experienced significantly fewer lost deciduous teeth compared to those who started treatment at a later age.

Results from both preclinical studies and human case reports and clinical trials suggest starting ERT early and maintaining consistent treatment may ameliorate some dentoalveolar defects. However, the effects of ERT are somewhat limited in many cases, likely due to varying severity of disease and variable age at initiation of ERT. Clinicians should remain cautious and expectations should be tempered by the complexities of HPP. Earlier intervention should be considered if maintenance of the dentition is a goal of ERT.

Gene therapy approaches for treatment of HPP

Shortcomings of current ERT have driven research into alternative treatment strategies. Limitations include high frequency of administration (3 or 6 times weekly), injection site reactions and lipohypertrophy (Figure 6F), costly drug prices, and lifetime requirement. For more than a decade, gene therapy strategies to deliver RT have been tested in the *Alpl*$^{-/-}$ mouse model of severe HPP. These approaches typically employ single injections of TNAP-D_{10}-expressing viral vectors. In the first study, a lentiviral vector expressing TNAP-D_{10} was injected intravenously into newborn pups, resulting in vector integration in liver and 10-fold higher ALP levels than control mice.[137] Treatment eliminated seizures, normalized body size, improved skeletal mineralization, and extended lifespans in *Alpl*$^{-/-}$ mice.

Subsequent gene therapy approaches employed a variety of adeno-associated viral (AAV) vectors. Expression of TNAP-D_{10} under the tissue-nonspecific CAG promoter and delivered in an AAV8 vector promoted phenotypic correction of *Alpl*$^{-/-}$ pups injected shortly after birth.[138] Fetal gene therapy was successfully accomplished using transuterine intraperitoneal injection of AAV9-expressed TNAP-D_{10} in a pregnant dame carrying *Alpl*$^{-/-}$ mouse fetuses on embryonic day 15 (about 4 d before birth).[139] ALP levels were increased in pups after birth, preventing seizures, normalizing weight and growth rate, and ameliorating skeletal defects. A strategy was pursued to deliver a muscle-directed AAV8 construct expressed TNAP-D_{10} under the muscle creatine kinase (MCK) promoter.[140] Muscle-driven production of TNAP-D_{10} increased ALP levels in *Alpl*$^{-/-}$ to more than 10-fold over normal levels, extending lifespans, increasing body size, and improving skeletal mineralization. Skeletal rescue was incomplete, as indicated by reduced bone lengths, abnormal cortical and trabecular bone parameters, and hypomineralization. This was the first preclinical gene therapy study to include dentoalveolar analyses. In treated *Alpl*$^{-/-}$ mice, jawbones showed improved mineralization, though molars exhibited thin and hypomineralized root dentin and periodontal detachment suggested defective cementum.[141]

As an alternative to gene therapy approaches outlined above, Shimada and colleagues attempted *ex vivo* gene therapy using lentiviral expressed TNAP-D_{10} transduction of BM cells (BMCs), which were then transplanted into irradiated *Alpl*$^{-/-}$ mouse pups.[142] Transduced BMCs elevated ALP levels to 10-fold higher than controls, prolonged survival, and improved bone parameters. However, limitations were evident in disorganized growth plates and reduced bone lengths. There was little evidence for improvement in dentin, cementum, or periodontal attachment and function, possibly reflecting different origins of craniofacial tissue precursors and inability of the elevated ALP to reach these tissues.[143] Most recently, a refinement of this approach used a single intramuscular dose of AAV8 encoding TNAP-D_{10}.[144] This increased ALP levels 800-fold over normal, extended lifespan, and essentially normalized skeletal and dentoalveolar development in *Alpl*$^{-/-}$ mice, a dramatic result (Figure 6G and H). The same vector improved skeletal mineralization in mouse models of adult-onset HPP and osteomalacia.[145]

ERT gene therapy approaches have the potential to revolutionize therapy for those with HPP and ameliorate the disease burden for many affected individuals. While a clinical trial for ERT gene therapy is yet to begin, it is important for dental clinician-researchers to be included in this work because of their key roles in diagnosis and treatment of HPP and missed opportunities of past clinical trials.

Conclusions

Research in recent decades has yielded critical insights into HPP, including mechanisms underlying dental and periodontal

defects. However, more work is required on multiple fronts. First, additional genotype-phenotype studies of HPP in different clinical types are required to understand the sensitivity of enamel, dentin, cementum, and alveolar bone to reduced TNAP function. Second, dental researchers and clinicians should be involved in preclinical studies and clinical trials for any new treatment. Third, more case report publications on dentoalveolar manifestations and responses to ERT are necessary to increase awareness and provide guidance for dental clinicians to treat HPP patients.

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Author contributions

E.L.S.: Conceptualization, creation of original draft, review and editing, funding. F.F.M.: Conceptualization, creation of original draft, review and editing, funding. K.K.: Conceptualization, creation of original draft, review and editing. B.L.F.: Conceptualization, creation of original draft, review and editing, funding.

Elis J. Lira dos Santos (Conceptualization, Writing—original draft, Writing—review & editing), Fatma Mohamed (Conceptualization, Funding acquisition, Writing—original draft, Writing—review & editing), Kaitrin Kramer (Conceptualization, Writing—original draft, Writing—review & editing), and Brian L. Foster (Conceptualization, Funding acquisition, Writing—original draft, Writing—review & editing).

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Conflicts of interest

The authors declare that they do not have any real or perceived conflicts with the content of the manuscript.

Data availability

No new data were generated or analyzed in support of this research.

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