Universitas Odontológica
ISSN: 0120-4319
ISSN: 2027-3444
Pontificia Universidad Javeriana

Escobar Arregocés, Francina María
X-linked Hypophosphatemia and its Impact on Hard Tissues of the Oral Cavity. An Integrative Review*
Universitas Odontológica, vol. 40, 2021, January-December, pp. 1-10
Pontificia Universidad Javeriana

DOI: https://doi.org/10.11144/Javeriana.uo40.xhih

Available in: https://www.redalyc.org/articulo.oa?id=231274792009

Universitas
ODONTOLOGICA

Vol. 40
Rolling volume, January-December
2021

ISSN: 2027-3444 (online) | ISSN: 0120-4319 (print)

Artículos

# X-linked Hypophosphatemia and its Impact on Hard Tissues of the Oral Cavity. An Integrative Review*

La hipofosfatemia ligada al cromosoma X y su impacto en los tejidos duros de cavidad Oral. Una revisión Integradora

Hipofosfatemia ligada ao X e seu impacto nos tecidos duros da cavidade oral. Uma revisão integrative

*Francina María Escobar Arregocés* [a]
*Pontificia Universidad Javeriana, Bogotá, Colombia*
escobar.f@javeriana.edu.co.
ORCID: https://orcid.org/0000-0002-4069-4719

DOI: https://doi.org/10.11144/Javeriana.uo40.xhih

Received: 28 september 2020
Accepted: 05 april 2021

## Abstract:

**Background:** X-linked hypophosphatemia (XLH) is a rare genetic disease in which increased phosphate loss in the kidney leads to hypophosphatemia and prevents normal mineralization of bone and tooth hard tissues. **Purpose:** To analyze the impact that this genetic pathology has on dental and periodontal hard tissues such as dentin, cementum, and alveolar bone. **Methods:** An integrative review of literature was carried out, through PubMed and SciELO searches. The search terms were: X-linked hypophosphatemia, dental tissue, periodontium, dentin, enamel, cementum, and alveolar bone. The search was restricted to literature in Spanish and English published between 2000 and 2020. **Results:** Thirteen articles that reported the impact of hypophosphatemia on dental tissues, mainly on dentin and cementum, were included. A negative impact of hypophosphatemia on periodontal tissues was also reported, especially on alveolar bone. **Conclusions:** The findings show us that XLH alters the structure of oral cavity hard tissues, affecting the quality of life of patients. Further research on the effect and behavior of this pathology on hard tissues of the oral cavity as well as its behavior as a risk factor for the presence of dental and periodontal disease is necessary.

**Keywords:** alveolar, bone, cement, dental tissue, dentine, enamel, oral pathology, orphan diseases, pathology, periodontium, rare diseases, X-linked hypophosphatemia.

## Resumen:

**Antecedentes:** La hipofosfatemia ligada al cromosoma X (HLX) es una enfermedad genética rara en la que el aumento de la pérdida de fosfato en el riñón conduce a la hipofosfatemia y evita la mineralización normal de los huesos y tejidos duros del diente. **Objetivo:** Analizar el impacto que tiene esta patología genética sobre los tejidos duros dentales y periodontales tales como dentina, cemento y hueso alveolar. **Método:** Se realizó una revisión integradora de la literatura a partir de búsquedas en las bases de PubMed y SciELO. Los términos de búsqueda fueron hipofosfatemia ligada a X, tejido dental, periodonto, dentina, esmalte, cemento y hueso alveolar. La búsqueda se restringió a literatura en español e inglés publicada entre 2000 y 2020. **Resultados:** Se incluyeron 13 artículos que daban cuenta del impacto de la hipofosfatemia sobre los tejidos dentales, principalmente sobre la dentina y el cemento. También se informa de un impacto negativo de la hipofosfatemia sobre los tejidos periodontales especialmente sobre el hueso alveolar. **Conclusiones:** Los hallazgos de la presente revisión integradora muestran que la HLX altera la estructura de los tejidos duros de cavidad oral, lo cual afecta la calidad de vida de los pacientes. Genera la necesidad de seguir investigando sobre el efecto y el comportamiento de esta patología sobre los tejidos duros de cavidad oral, así como su comportamiento como factor de riesgo para la presencia de enfermedad dental y periodontal.

**Palabras clave:** cemento, dentina, enfermedades huérfanas, enfermedades raras, esmalte, hipofosfatemia ligada a X, hueso alveolar, patología, patología oral, periodonto, tejido dental.

## Resumo:

**Antecedentes:** A hipofosfatemia ligada ao X (HLX) é uma doença genética rara na qual o aumento da perda de fosfato no rim leva à hipofosfatemia e evita a mineralização normal dos tecidos duros dos ossos e dentes. **Objetivo:** Analisar o impacto desta patologia genética nos tecidos duros dentais e periodontais, como dentina, cemento e osso alveolar. **Métodos:** Foi realizada uma revisão integrativa da literatura, por meio das buscas na PubMed e SciELO. Os termos de pesquisa foram: hipofosfatemia ligada ao X, tecido dentário, periodonto, dentina, esmalte, cemento e osso alveolar. A busca foi restrita à literatura em espanhol e inglês publicada entre 2000 e 2020. **Resultados:** Treze artigos que relataram o impacto da hipofosfatemia nos tecidos dentários, principalmente na dentina e no cemento, foram incluídos. Um impacto negativo da hipofosfatemia nos tecidos periodontais também foi relatado, especialmente no osso alveolar. **Conclusões:** Os achados nos mostram que o HLX altera a estrutura dos tecidos duros da cavidade

## Author notes

**Author's note:** [a] Correspondence:escobar.f@javeriana.edu.co. francinaescobar@yahoo.es

oral, afetando a qualidade de vida dos pacientes. São necessários mais estudos sobre o efeito e o comportamento dessa patologia nos tecidos duros da cavidade oral, bem como seu comportamento como fator de risco para a presença de doenças dentais e periodontais.
**Palavras-chave:** cement, dentina, doenças órfãs, doenças raras, esmalte, hipofosfatemia ligada ao X, osso alveolar, patologia, patologia oral, periodonto, tecido dentário.

# INTRODUCTION

X-linked hypophosphatemia (XLH) is a skeletal genetic disease in which increased loss of phosphate in the kidney leads to hypophosphatemia and prevents normal mineralization of bones and tooth hard tissues. It is a rare disease caused by mutations in the *PHEX* (phosphate regulating endopeptidase analog, X-linked) gene. The gene encodes an endopeptidase that is expressed primarily on the surface of osteoblasts, osteocytes, odontoblasts, and cementoblasts. The disease follows an X-linked mode of transmission with dominant expression and represents the first cause of hypophosphatemic rickets (1,2,3,4).

The problem derived from this congenital pathology is that, typically, patients show low levels of serum phosphate secondary to an increase in phosphaturia, elevated alkaline phosphatase, normal levels of parathyroid hormone (PTH), and low urinary calcium. X-rays show the typical features of rickets without significant bone resorption, unlike rickets secondary to vitamin D deficiency. The growth plates of long bones have a hollow appearance, with greater thickness and irregularities (1).

Phosphate loss has been linked to two causes. First, the loss of phosphate may be secondary to increased signaling of fibroblast growth factor 23 (FGF23), which is a circulating factor secreted by osteoblasts, odontoblasts, and osteocytes. In the renal proximal tubule, FGF23 inhibits the transport of sodium phosphate through the NPT2a and NPT2c ion channels, and prevents the production of 1,25-diOH-vitamin D. As a consequence, it decreases the renal and digestive absorption of phosphate. Phosphate loss secondary to elevated FGF23 primarily results in X-linked hypophosphatemic rickets (XLHR), due to loss-of-function mutations in *PHEX*. Hypophosphatemia due to excess FGF23 and a direct effect of the absence of functional *PHEX* on the mineralization of the extracellular matrix (ECM) of the bone or tooth, generates mineralization defects that involve bones and teeth (5,6). Second, phosphate loss may be due to a primary renal tubular defect, that is, hereditary hypophosphatemic rickets with hypercalciuria (HHRH) due to molecular defects of the NPT2c sodium phosphate channel. All of these conditions share a decreased ability to transport phosphate from the glomerular filtration to the bloodstream (5,7).

The reduction in phosphate circulating levels disturbs the mineralization of bones and teeth, resulting in various clinical signs and symptoms. Those manifestations include bone tissue pain, bone deformities and fractures, growth failure, spontaneous pulpitis, abscesses, and hearing loss in both children and adults. Infection of the dental pulp tissue could be considered a secondary effect as a result of microcracks in the enamel and poor mineralization of the dentin, which facilitates microbial invasion (2).

Since this is a rare disease, there is not much bibliography currently available, so it was pertinent to take a preliminary look at the existing evidence. For this reason, the purpose was to analyze this genetic pathology and its impact on the oral hard dental and periodontal tissues such as enamel, dentin, cementum, and alveolar bone. This, in the future, will allow increasing the number of observational and experimental clinical studies to clarify the impact on the oral cavity of this disease as well as its possible treatment alternatives. Therefore, the research question was: What impact does XLH have on the dental and periodontal hard tissues of the oral cavity?

## MATERIALS AND METHODS

An integrative literature review (8) was conducted, summarizing theoretical or empirical literature to provide a comprehensive understanding of XLH, particularly its impact on oral cavity hard tissues. In this integrative review, a search was carried out in the PubMed and SciELO databases. The search terms were *X-linked hypophosphatemia, dental tissue, periodontium, dentin, enamel, cementum*, and *alveolar bone* using AND, OR and NOT Boolean connectors. The search was limited to literature in Spanish and English published between 2000 and 2020.

## RESULTS

13 articles were selected and included in the present review, which are presented in Table 1.

TABLE 1
Articles included in the review and their main characteristics

| Author/Year | Purpose | Type of Study/Design | Main Findings |
|---|---|---|---|
| Biosse *et al.* (2017) (2) | To examine the periodontal status of patients with XLH according to treatment received for hypophosphatemia. | Observational descriptive | Patients with hypophosphatemia have strong acellular cementum hypoplasia. Patients with early treatment with vitamin D and phosphate showed less periodontal attachment loss. |
| Rabbani *et al.* (2012) (9) | To assess dental problems in patients with XLH rickets. | Cross-sectional | XLH patients show dental abnormalities such as tooth decay and delayed teething. |
| Salmon *et al.* (2014) (10) | To analyze the extracellular phosphoglycoprotein matrix and osteopontin in XLH patients. | Observational descriptive | The localization of the extracellular phosphoglycoprotein matrix and osteopontin in the dentin of XLH patients is altered. |
| Fisher & Fedarko (2003) (11) | To analyze the genes expressed in bones and teeth and that encode the current members of the SIBLING family of proteins and the factors that can alter them. | Observational descriptive | Dentin alterations related to XLH, a peptide, ASARM, derived from the extracellular phosphoglycoprotein matrix, inhibits extracellular matrix mineralization and odontoblast differentiation, while increasing the expression of extracellular phosphoglycoprotein matrix and alkaline phosphatase non-tissue specific. |
| Baroncelli *et al.* (2006) (12) | To assess the prevalence and investigate the pathogenic mechanisms of dental and periodontal lesions in children with XLH. | Observational descriptive | Patients with XLH presented abnormalities such as hypoplasia and diachronic enamel alterations, spontaneous fistulas as a consequence of periapical abscesses that occurred in the absence of dental caries. |
| Souza *et al.* (2013) (13) | To report a case of vitamin D resistant rickets and describe dental and treatment findings. | Case report | Abnormal dental morphology with thin globular dentin and enlarged pulp horns. Invasion of the pulp by microorganisms and toxins is unavoidable in these patients. |
| Boukpessi *et al.* (2017) (14) | To analyze osteopontin and dental and bone pathology of XLH. | Observational descriptive | Patients with XLH, with inactivating mutations of *PHEX* accumulated osteopontin in the sites of defective bone mineralization near the osteocytes, the so-called periosteocitic (lacunar) "halos" characteristic of XLH. |
| Coyac *et al.* (2018) (15) | To assess the local role of the PHEX gene. | Observational analytic | Hypophosphatemia alone does not fully explain the pathological phenotype observed in XLH. The loss of *PHEX* independently and locally affects the formation and quality of the mineral ECM, probably through the accumulation and impaired degradation of ostepontin. |
| Coyac *et al.* (2018) (16) | To examine changes in dentin composition and structure in human XLH teeth and using transmission electron microscopy in dentin from *Hyp* mice. | Observational descriptive | Alterations in mineral quality and matrix changes in dentin, cementum, and bone of subjects with *Xlu*-linked hypophosphatemia. |
| Ye *et al.* (2011) (17) | To assess the periodontal status of adult patients with hypophosphatemic rickets. | Case series | Patients with hypophosphatemic rickets are more prone to periodontal bone loss than the general population. |
| Ye *et al.* (2008) (18) | To analyze whether cementum and defective alveolar bone can explain periodontal degradation and increased susceptibility to bacterial infection in mice without *Dmp1*. | Observational descriptive in animal model | Reduced acellular cementum thickness, reduced cellular cementum, and defective alveolar bone matrix in mice without *Dmp1*. |
| Zhang *et al.* (2020) (19) | To analyze the dentoalveolar defects of the *Hyp* mouse at 42 and 90 days postnatally to comparatively define the effects of XLH on tooth formation and function. | Observational analytic in animal model | Robust accumulation of osteopontin in the cementum of *Hyp* mice, suggesting that it may contribute to local hypomineralization. *Hyp* mouse osteocytes in long bones and alveolar bone showed a drastic increase in *Fgf23* expression. |
| Connor *et al.* (2015) (20) | To study the relationship between treatment, enthesopathy, and dental disease in adult patients with XLH. | Observational transversal | As the proportion of adult life with treatment increased, the chances of having serious dental disease decreased. |

## Hypophosphatemia and its Relationship with Dental Tissues

Hypophosphatemia has been associated with hypomineralization of dental tissues. Ali Rabbani *et al.* (9) in 2012 carried out a study with 19 patients with an average age of 10 (± 4.23) years. All cases of suspected hypophosphatemic rickets were enrolled in this study. The diagnosis of hypophosphatemic rickets was made on the basis of clinical and radiological findings of rickets in patients with low serum phosphate, normal or low serum calcium (<8.2 mg/dL), normal levels of 25 (OH) 2.-vit D (<15 pg/mL), and normal or slightly elevated PTH with high level of serum alkaline phosphatase (> 55 pg/mL). The most frequent dental problems were dental caries and delayed tooth eruption in 9 (47.7 %) patients. Enamel hypoplasia was found in 8 (42.1 %) patients, and 3 (15.8 %) patients had taurodontism; all in the latter groups were male. Both

dental abscesses and gingivitis were found in 2 (10.5 %) patients. Six (54.5 %) female patients and 3 (37.5 %) male patients had dental caries. The prevalence of dental caries was significantly higher in the case group ($p = 0.04$) than it was in the healthy control group (10.5 %). They conclude that hypophosphatemic rickets is a disease that can present different clinical characteristics, such as alteration in the hard tissues of the tooth, and in which dental caries is one of the most prevalent (9).

Dentin is one of the dental tissues most affected by this pathology. Human dentin mineralization is a continuous process that occurs by growth and fusion of calcospherites. This process appears to be controlled by non-collagenous proteins, particularly by a family of phosphorylated proteins called as small integrin-binding ligand N-linked glycoproteins (SIBLINGs). Some non-phosphorylated proteins such as osteocalcin, osteonectin, and proteoglycans are also involved in this process (10,11).

Patients with hypophosphatemia have been reported to show large interglobular spaces in circumpulpal dentin. With regard to XLH-related dentin alterations, a peptide, ASARM, derived from matrix extracellular phosphoglycoprotein (MEPE) has been observed to inhibit ECM mineralization and odontoblast differentiation, while increasing matrix expression extracellular phosphoglycoprotein and tissue nonspecific alkaline phosphatase (TNAP) (10,11).

Salmon *et al*. (10), in an analysis of dental germs, indicated that alkaline phosphatase activation, MEPE localization and osteopontin (OPN) in odontoblasts and in dentin of patients with XLH is abnormal and shows an accumulation of MEPE in non-mineralized interglobular spaces. Interestingly, the pulp-dentin complex in teeth of patients with XLH is poorly organized and shows impaired odontoblast polarization and arrangement. This observation is consistent with an inhibition of odontoblast differentiation, possibly resulting from increased expression of MEPE in patients with XLH. Mutations in the *PHEX* gene lead to an accumulation of protein fragments that contribute to mineralization defects observed in pathological bone and dentin. OPN accumulates in the dental dentin of patients with XLH, especially in abnormal calcospherites.

Dental abnormalities that occur due to XLH affect both primary and permanent dentitions and are caused by impaired dentin mineralization. This results in a dental pulp with a large chamber, presence of globular dentin and large tubules, which connect the dental pulp to the dentin-enamel junction, providing a direct channel for bacteria and pulp irritants, which could be the route through which spontaneous dental abscesses occur. Front teeth can be affected more quickly and severely than molars. Other dental abnormalities include delayed tooth eruption, possible enamel hypoplasia, and short roots (12,13).

Boukpessi *et al*. (14) analyzed seven young patients with XLH and reported they accumulated OPN, which was also localized in the pericanalicular matrix that extends beyond the osteocyte lacunae, as well as in the hypomineralized dentin matrix. OPN, a potent mineralization inhibitor, is a member of an acidic, phosphorylated ECM protein family that binds to calcium and are known to regulate dental and skeletal mineralization.

Coyac *et al*. (15) evaluated the local role of the *PHEX* gene in a 3D MEC mineralization model. Collagen-dense hydrogels were seeded with human dental pulp cells from patients with characterized *PHEX* gene mutations or with healthy controls, and cultured for up to 24 days using osteogenic medium with standard phosphate concentration. Calcium quantification, tomography, and histology with von Kossa stain for minerals showed significantly less mineralization in seeded cultures of cells from patients with XLH. Although atypical mineralization was observed along the collagen fibrils by electron microscopy in both groups, Raman microspectrometry indicated that cells from XLH patients harboring the *PHEX* mutation produced less mineralized tissues. These tissues had a deteriorated mineral quality, with less carbonate substitution and lower crystallinity. In cultures of patients with XLH, immunoblot revealed higher amounts of OPN, dentin matrix protein 1 (DMP1) and MEPE than controls. Fragments of these proteins that were not found in the controls were also present, suggesting a role for the mutation of the *PHEX* gene in the degradation of the SIBLING protein.

Likewise, Coyac *et al*. (16) examined changes in dentin composition and structure using Raman spectroscopy in human teeth with XLH and transmission electron microscopy in the dentin of *Hyp* mice (XLH mouse model). The dentin of patients with XLH showed changes in the quality of the apatite mineral, with higher carbonate substitution and lower crystallinity compared to the dentin of control teeth of the same age. Furthermore, ultrastructural analysis by transmission electron microscopy revealed a significant disorganization of dentin peri and intertubular structure, with odontoblast processes residing within a non-mineralized matrix sheath in the *Hyp* mouse. Taken together, these results indicate that, as for cementum and bone, there are mineral quality alterations and matrix changes in the dentin of subjects with XLH that reflect a high sensitivity to serum phosphate levels and possibly other local changes in the dentin matrix.

## Hypophosphatemia and its Relationship with the Periodontium: Cementum and Alveolar Bone

The tooth attachment apparatus is the fundamental element of the periodontium, which is based mainly on two mineralized tissues, alveolar bone and root cement, which are attached by the periodontal ligament. Cement is part of the tooth but, from a functional point of view, it is considered part of the attachment apparatus or periodontium. Structural defects in these tissues caused by genetic diseases have been shown to result in loss of periodontal attachment and eventually loose and lost teeth. This is the case in patients with hypophosphatemia (2).

Attachment loss in hypophosphatemia arises from cementum aplasia or hypoplasia that prevents normal attachment of periodontal ligament fibers. XLH could also cause periodontal attachment loss. Evidence indicates that adults with XLH present increased prevalence and severity of periodontitis, bone loss, deep periodontal pockets, and advanced periodontal attachment loss. Preliminary data suggest that patients with hypophosphatemic rickets are more prone to periodontal bone loss than the general population and may require more careful examination by specialists (2,17).

Ye *et al.* (18) analyzed whether cementum and defective alveolar bone can explain periodontal degradation and increased susceptibility to bacterial infection in *Dmp1*-deficient mice. In different murine models with hypophosphatemic rickets they found reduced thickness of acellular cementum, reduced cellular cementum, and defective alveolar bone matrix. The authors note that, unlike humans, mice do not naturally develop periodontal disease until extreme old age, usually over one year and mainly in the maxilla. Despite the above, it was observed that *Dmp1*-deficient mice develop an early-onset periodontal defect.

Zhang *et al*. (19) analyzed *Hyp* mice (*Phex* mutants) in which the XLH phenotype is mimicked. They studied dentoalveolar defects of the *Hyp* mouse at 42 and 90 days after birth to comparatively define the effects of XLH on tooth formation and function. *Phex* mRNA was expressed by odontoblasts (dentin), osteocytes (bone), and cementocytes (cementum) in normal mice (WT). The study showed that, compared to WT, 42-day-old *Hyp* mice had shorter, arched long bones, small skulls, and radiolucent jaws, whose molars showed thin dentin and expanded pulp space. Enamel density was normal, although enamel volume was significantly reduced in *Hyp* mice. Compared to normal mice, *Hyp* molars showed greatly reduced dentin/cementum volumes and densities at both ages (30 % to 40 %, $p < 0.001$). Cellular cementum in *Hyp* mice at 42 and 90 days of birth appeared to have large ECM regions of hypomineralized cementum, or cementoid, and showed a lack of periodontal ligament attachment. Pulp and PDL volumes increased, and densities decreased in molars of *Hyp* mice when compared to WT mice (19).

Mechanical periodontal properties were found dramatically altered in *Hyp* mice when compared to WT. *Hyp* mice presented an expanded alveolar bone with osteoid accumulation, and microtomography showed a decrease in the volume fraction and alveolar bone density. The cellular cementum area increased significantly more in *Hyp* than in the molars of WT mice due to the accumulation of cementoid. Hypomineralized

"halos" surrounding the cementum and osteocyte lacunae of *Hyp* mice were shown on scanning electron microscopy and nanoindentation. Computed microtomography confirmed larger cement/osteocyte lacunae as well as a reduction in perilacunar mineral density. Long bone and alveolar bone osteocytes in *Hyp* mice overexpressed fibroblast growth factor 23. That study reported for the first time a quantitative analysis of *Hyp* mouse dentoalveolar phenotype that included all mineralized tissues (19).

### Hypophosphatemia Treatment on Dental and Periodontal Hard Tissues

Treatment effect of hypophosphatemia on oral cavity hard tissues is also being studied. In this regard, Biosse Duplan *et al*. (2) examined the periodontal status of 34 adults with XLH and grouped them according to treatment they received for hypophosphatemia. They reported the frequency of periodontitis and the severity of this pathology increased in adults with XLH, and the severity varied according to the treatment for hypophosphatemia. Patients who received early and continuous vitamin D and phosphate supplementation during childhood had less periodontal attachment loss than patients with late or incomplete supplementation. Continued treatment of hypophosphatemia throughout adulthood further improved periodontal health. When analyzing the extracted teeth in patients with late or incomplete supplements, greater acellular cementum hypoplasia was found than in healthy controls of the same age. These results show that XLH not only alters bone and dentin formation, but also alters cementum, which has been associated with periodontal attachment loss.

Connor *et al*. (20) analyzed conventional therapy (calcitriol or high doses of vitamin D and phosphate) and its effects on dental disease in adults with XLH. When analyzing the relationship between the proportion of adult life with treatment, as well as other predictors, and the number of enthesopathy sites, after adjusting for age, the proportion of adult life with treatment was not a significant predictor of the number of enthesopathy sites (global p adjusted for age = 0.96). This finding remained after adjusting for confounding factors (multivariate adjusted global p = 0.90). The researchers reported that age, BMI, and sex were important predictors of the number of enthesopathy sites (pain at tendon insertion). Age and BMI were positively associated with the number of enthesopathy sites (p <0.0010 for each covariate). Female sex was negatively associated with the number of enthesopathy sites (p = 0.0080). Those who did not receive treatment during adult life were more likely to experience severe dental disease than those who were treated. They also found that age was a significant predictor of the severity of dental disease, since with a 1-year increase in age, the odds of having severe dental disease increased by 10 % (OR 1.1 [CI 95 % 1.0-1.2]). People treated for less than 80 % of childhood were more likely to experience severe dental disease compared to people treated for 80 % or more of childhood (OR 7.2 [95 % CI 0.71-73] ). The severity of the mutation was positively associated with the severity of dental disease, as those with severe mutations were more likely to experience severe dental disease compared to those who did not have such severe mutations (OR 3.9 [95 % CI 0 , 63-25]). However, these relationships did not show statistical significance.

## DISCUSSION

In light of what has been found in the scientific literature collected and analyzed, it is evident that there is little research that accounts for the impact of XLH on dental and periodontal tissues. The evidence reported is low-level and focuses mainly on descriptive studies, case reports, and case series.

From the point of view of biological plausibility, there is literature explaining how hypophosphatemia can impact and alter the structure of dental hard tissues (10,11,12,13,14,15,16). An emerging explanation is that structural change produced by hypophosphatemia, mainly in the dentin, could secondarily prompt dental caries because it allows the entry of cryogenic bacteria.

When analyzing the impact of hypophosphatemia on periodontal hard tissues, attachment loss in hypophosphatemia seems to be mainly related to aplasia or hypoplasia of the cementum, which could prevent normal attachment of ligament fibers and favor faster progression of periodontal disease. The biomechanical capacity of the periodontal support is also altered, which is an interesting point for future analysis, given the relevant role of the periodontium in the distribution and damping of occlusal loads (17,18,19).

The treatment of hypophosphatemia seems to have a positive impact on the hard tissues of the oral cavity, noting that those patients who receive early and continuous treatment of their systemic condition (hypophosphatemia) with Vitamin D and phosphate could present better dental and periodontal conditions. It is worth mentioning that the level of evidence is also low, and no well-conducted randomized controlled clinical trials were found that conclusively show the effect of hypophosphatemia treatment on dental and periodontal tissues.

## CONCLUSIONS AND RECOMMENDATIONS

Patients with XLH have structural changes in enamel and dentin. Studies show that the genetic mutation does not cause cavities, but the structural changes it generates could favor its appearance.

Likewise, structural changes in the cementum and alveolar bone could favor the progression of periodontal disease.

The findings presented in this literature review show the need to continue investigating the effect that XLH has on hard tissues of the oral cavity. Similarly, future studies should focus on the behavior of this pathology as a risk factor for the presence of dental and periodontal disease.

This literature review provides a preliminary basis for the analysis of the relationship of hypophosphatemia with the hard tissues of the oral cavity. Within the limits of the integrative review research design it is possible to envision the need for studies with a higher level of evidence.

It is recommended to conduct analytical observational clinical studies focused on early diagnosis and control of risk factors, as well as rigorous and well-designed controlled clinical trials reporting on treatment effectiveness in patients with XLH, in such a way that it can contribute to the improvement of oral tissues and their quality of life.

### REFERENCES

1. Emma F, Cappa M, Antoniazzi F, Bianchi ML, Chiodini I, Eller Vainicher C, Di Iorgi N, Maghnie M, Cassio A, Balsamo A, Baronio F, de Sanctis L, Tessaris D, Baroncelli GI, Mora S, Brandi ML, Weber G, D'Ausilio A, Lanati EP. X-linked hypophosphatemic rickets: an Italian experts' opinion survey. Ital J Pediatr. 2019 May 31; 45(1): 67. https://doi.org/10.1186/s13052-019-0654-6
2. Biosse Duplan M, Coyac BR, Bardet C, Zadikian C, Rothenbuhler A, Kamenicky P, Briot K, Linglart A, Chaussain C. Phosphate and Vitamin D Prevent Periodontitis in X-Linked Hypophosphatemia. J Dent Res. 2017 Apr; 96(4): 388-395. https://doi.org/10.1177/0022034516677528
3. Haffner D, Waldegger S. Trastornos del metabolismo del fósforo. En: Geary DF, Schaefer F, editores. Enfermedad renal pediátrica. Berlín Heidelberg: Springer-Verlag; 2016. p. 953-972
4. Wang H, Yoshiko Y, Yamamoto R, Minamizaki T, Kozai K, Tanne K, Aubin JE, Maeda N. Overexpression of fibroblast growth factor 23 suppresses osteoblast differentiation and matrix mineralization in vitro. J Bone Miner Res. 2008 Jun; 23(6): 939-948. https://doi.org/10.1359/jbmr.080220
5. Linglart A, Biosse-Duplan M, Briot K, Chaussain C, Esterle L, Guillaume-Czitrom S, Kamenicky P, Nevoux J, Prié D, Rothenbuhler A, Wicart P, Harvengt P. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014 Mar 14; 3(1): 13-30. https://doi.org/10.1530/EC-13-0103

6. Levy-Litan V, Hershkovitz E, Avizov L, Leventhal N, Bercovich D, Chalifa-Caspi V, Manor E, Buriakovsky S, Hadad Y, Goding J, Parvari R. Autosomal-recessive hypophosphatemic rickets is associated with an inactivation mutation in the ENPP1 gene. Am J Hum Genet. 2010 Feb 12; 86(2): 273-278. https://doi.org/10.1016/j.ajhg.2010.01.010

7. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A. 2001 May 22; 98(11): 6500-6505. https://doi.org/10.1073/pnas.101545198

8. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs. 2005 Dec; 52(5): 546-553. https://doi.org/10.1111/j.1365

9. Rabbani A, Rahmani P, Ziaee V, Ghodoosi S. Dental problems in hypophosphatemic rickets, a cross sectional study. Iran J Pediatr. 2012 Dec; 22(4): 531-534.

10. Salmon B, Bardet C, Coyac BR, Baroukh B, Naji J, Rowe PS, Opsahl Vital S, Linglart A, Mckee MD, Chaussain C. Abnormal osteopontin and matrix extracellular phosphoglycoprotein localization, and odontoblast differentiation, in X-linked hypophosphatemic teeth. Connect Tissue Res. 2014 Aug;55 Suppl 1:79-82. https://doi.org/10.3109/03008207.2014.923864

11. Fisher LW, Fedarko NS. Six genes expressed in bones and teeth encode the current members of the SIBLING family of proteins. Connect Tissue Res. 2003; 44 Suppl 1: 33-40

12. Baroncelli GI, Angiolini M, Ninni E, Galli V, Saggese R, Giuca MR. Prevalence and pathogenesis of dental and periodontal lesions in children with X-linked hypophosphatemic rickets. Eur J Paediatr Dent. 2006 Jun; 7(2): 61-66.

13. Souza AP, Kobayashi TY, Lourenço Neto N, Silva SM, Machado MA, Oliveira TM. Dental manifestations of patient with vitamin D-resistant rickets. J Appl Oral Sci. 2013 Nov-Dec;21(6):601-6. https://doi.org/10.1590/1679-775720130249

14. Boukpessi T, Hoac B, Coyac BR, Leger T, Garcia C, Wicart P, Whyte MP, Glorieux FH, Linglart A, Chaussain C, McKee MD. Osteopontin and the dento-osseous pathobiology of X-linked hypophosphatemia. Bone. 2017 Feb; 95: 151-161. https://doi.org/10.1016/j.bone.2016.11.019

15. Coyac BR, Hoac B, Chafey P, Falgayrac G, Slimani L, Rowe PS, Penel G, Linglart A, McKee MD, Chaussain C, Bardet C. Defective Mineralization in X-Linked Hypophosphatemia Dental Pulp Cell Cultures. J Dent Res. 2018 Feb;97(2):184-191. https://doi.org/10.1177/0022034517728497

16. Coyac BR, Falgayrac G, Penel G, Schmitt A, Schinke T, Linglart A, McKee MD, Chaussain C, Bardet C. Impaired mineral quality in dentin in X-linked hypophosphatemia. Connect Tissue Res. 2018 Dec; 59(sup1): 91-96. https://doi.org/10.1080/03008207.2017.1417989

17. Ye L, Liu R, White N, Alon US, Cobb CM. Periodontal status of patients with hypophosphatemic rickets: a case series. J Periodontol. 2011 Nov; 82(11): 1530-1535. https://doi.org/10.1902/jop.2011.100736

18. Ye L, Zhang S, Ke H, Bonewald LF, Feng JQ. Periodontal breakdown in the Dmp1 null mouse model of hypophosphatemic rickets. J Dent Res. 2008 Jul; 87(7): 624-629. https://doi.org/10.1177/154405910808700708

19. Zhang H, Chavez MB, Kolli TN, Tan MH, Fong H, Chu EY, Li Y, Ren X, Watanabe K, Kim DG, Foster BL. Dentoalveolar Defects in the Hyp Mouse Model of X-linked Hypophosphatemia. J Dent Res. 2020 Apr; 99(4): 419-428. https://doi.org/10.1177/0022034520901719

20. Connor J, Olear EA, Insogna KL, Katz L, Baker S, Kaur R, Simpson CA, Sterpka J, Dubrow R, Zhang JH, Carpenter TO. Conventional Therapy in Adults With X-Linked Hypophosphatemia: Effects on Enthesopathy and Dental Disease. J Clin Endocrinol Metab. 2015 Oct; 100(10): 3625-3632. https://doi.org/10.1210/JC.2015-2199

## Notes

* Original research.

*How to cite:* Escobar Arregocés FM. X-linked Hypophosphatemia and its Impact on Hard Tissues of the Oral Cavity. An Integrative Review. Univ Odontol. 2021; 40. https://doi.org/10.11144/Javeriana.uo40.xhih