



## Clinical Doctorate in Paediatric Dentistry (DDent)

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### **Title**

Dental Management of Children with X-Linked Hypophosphatemia (XLH): A scoping review and exploration of patient-reported outcome measure (PROM)

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### **Sponsored by:**

University College London (UCL)

**This study forms the research part of a professional doctorate in Paediatric  
Dentistry**

## **Declarations**

This research titled 'Dental Management of children with X-Linked Hypophosphatemia (XLH): A scoping review and exploration of patient-reported outcome measure (PROM)' was completed by myself and based on my own research and effort. Any additional work by others is fully acknowledged and referenced accordingly. This report has been submitted as part of professional doctorate in Paediatric Dentistry at UCL, but not submitted for any other qualification or publication.

Basmah Al-Otaibi

## Acknowledgement

*“It always seems impossible until it’s done.”*

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## **Covid-19 Pandemic Impact Statement**

The unprecedented global health crisis COVID-19 pandemic had disrupted routine healthcare services, altered patient accessibility, and introduced unforeseen challenges to conduct research projects efficiently. The student researcher was delayed in enrolling as a DDent student, commencing the programme in December 2020, which restricted their access to university campus and research topic information.

Prior to agreement on a specific research project, the topic underwent several changes to adapt with the uncertainties associated with the pandemic. Once a consensus was reached among researchers, the initial draft of the protocol was submitted end of the first academic year. Subsequently, obstacles such as delays in data collection, limitations of face-to-face appointments and changes in healthcare priorities necessitated an adaptive approach to the study design. Despite these challenges, this research endeavours to navigate and address the research topic while mitigating the significant impact of COVID-19 pandemic.

## Abstract

**Introduction:** X-Linked Hypophosphatemia (XLH) is a genetic multisystem disorder, characterised by low levels of phosphate in the blood causing distinctive skeletal and dental manifestations.

**Aims and objectives:** The aim was to review medical and dental management of paediatric patients with XLH in two parts; (i) the medical approach of XLH and its impact on dental manifestations such as recurrent spontaneous abscess (ii) the availability of dental guidelines, for instance whether endodontic treatment is superior to dental extraction for abscessed teeth.

The third part aimed to explore how paediatric patients with XLH seen at the Eastman Dental Hospital (EDH) feel about their dental health, using Patient-related outcome measure (PROM) questionnaire.

**Methods:** The eligibility for both scoping reviews was based on Population, Concept, and Context (PCC) framework. Population of interest in the medical and dental reviews were children under the age of 16 with XLH. The concept covered all available research in both fields of study, for medical review the timeframe was publications between 2018 and 2023, whereas dental review covered a wider duration from 2000 to 2022.

The third part was a service evaluation based in the paediatric department at EDH. The questionnaire was tailored according to clinician and patient input, as well as piloting the PROM with two XLH patients and their parents. The finalised questionnaire was then distributed to all eligible patients between July and December 2023.

**Results:** The first scoping review yielded 14 articles from 21 countries researching the dental implications of medical therapies of XLH, 4 studies (28.5%) were multicentred covering a wider range of patients. 7 studies (50%) were in favour of burosumab for children with XLH. The second review included 37 articles covering dental aspect of XLH. The most mentioned dental manifestation was recurrent spontaneous abscess with 31 articles (83.7%) followed by malocclusion and dental caries with 8 articles (21.6%). Endodontic treatment was preferred for abscessed permanent teeth, while extraction was the choice for primary abscessed teeth. For the service evaluation, 13 children (aged 7 to 16 years) participated. Three patients (23%) reported feeling unhappy with their teeth, with 9 patients (69%) undergoing dental extractions, and 4 (31%) underwent endodontic treatment.

**Conclusion:** The scoping review did not conclude one medical treatment was superior in preventing dental manifestations, due to limited evidence and novelty of burosumab. Also, there are no clinical guidelines on the dental management of XLH, it remains subjective. Finally, the PROM demonstrated a wide range of complications these patients face, allowing clinicians to monitor their individual progress to ensure the provided treatment addresses their concerns and meets their dental needs.

## Key Words

X-Linked hypophosphatemia, familial hypophosphatemic rickets, hereditary hypophosphatemic rickets, dental management, medical management, conventional treatment, burosumab, paediatric dentistry

## List of Abbreviations

<b>ADR</b>	Adverse Drug Reaction
<b>AE</b>	Adverse Event
<b>AI</b>	Amelogenesis Imperfecta
<b>AOB</b>	Anterior open bite
<b>BPABG</b>	British Paediatric and Adolescent Bone Group
<b>CDSR</b>	Cochrane Database of Systematic Reviews
<b>CEJ</b>	Cemento-enamel junction
<b>CF</b>	Cystic Fibrosis
<b>CINAHL</b>	Cumulated Index to Nursing and Allied Health Literature
<b>COVID-19</b>	Corona Virus Disease of 2019
<b>CT</b>	Conventional Treatment/Therapy
<b>DEJ</b>	Dentin-enamel junction
<b>DD</b>	Dentine dysplasia
<b>DI</b>	Dentinogenesis Imperfecta
<b>DMFT</b>	Decayed, Missing, Filled Teeth (permanent)
<b>DMP1</b>	Dentine matrix acidic protein 1
<b>EBSCO</b>	Elton B. Stephens CO (company)
<b>EDH</b>	Eastman Dental Hospital
<b>EMBASE</b>	Excerpta Medica Database
<b>FDA</b>	Food and Drug Administration
<b>FGF23</b>	Fibroblast Growth Factor 23
<b>FPM</b>	First permanent molar
<b>FS</b>	Fissure sealant
<b>FV</b>	Fluoride varnish
<b>GA</b>	General Anaesthesia
<b>GDP</b>	General Dental Practitioner
<b>GIC</b>	Glass ionomer cement
<b>GOSH</b>	Great Ormond Street Hospital, London
<b>GP</b>	General Practitioner

<b>HR</b>	Hypophosphatemic rickets
<b>HRQoL</b>	Health Related Quality of Life
<b>JBI</b>	Joanna Briggs Institute
<b>LA</b>	Local Anaesthesia
<b>LSMD</b>	Least Squares Means Difference
<b>MeSH</b>	Medical Subject Headings
<b>mg/dL</b>	Milligrams per decilitre
<b>MTA</b>	Mineral Trioxide Aggregate
<b>NHMRC</b>	National Health and Medical Research Council
<b>NHS</b>	National Health Service
<b>NICE</b>	National Institute for Health and Care Excellence
<b>NZ</b>	New Zealand
<b>OHI</b>	Oral Hygiene Instructions
<b>OHRQoL</b>	Oral Health Related Quality of Life
<b>OI</b>	Osteogenesis Imperfecta
<b>OPG</b>	Orthopantomogram
<b>PCC</b>	Population, Concept, Context
<b>PHEX</b>	Phosphate Regulating Endopeptidase X-Linked
<b>Pi/D</b>	Phosphate Salts and Active Vitamin D
<b>PMC</b>	Preformed Metal Cap
<b>PRISMA-Sc</b>	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
<b>PROMs</b>	Patient-Reported Outcome Measures
<b>PTH</b>	Parathyroid Hormone
<b>RCT</b>	Randomised controlled trial
<b>RCT</b>	Root canal treatment
<b>RGI-C</b>	Radiographic Global Impression of Change
<b>SD</b>	Standard Deviation
<b>XLH</b>	X-Linked Hypophosphatemia
<b>UAE</b>	United Arab Emirates
<b>UCL</b>	University College London
<b>UCLH</b>	University College London Hospital
<b>UK</b>	United Kingdom
<b>USA</b>	United States of America
<b>WHO</b>	World Health Organisation

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# **Chapter One: Literature Review**

# 1. BACKGROUND AND RATIONALE

## 1.1. Definition and prevalence of X-linked Hypophosphatemia

X-linked Hypophosphatemia (XLH) is a rare inherited disorder, characterized by low levels of phosphate in the blood. It is the most common form of familial hypophosphatemia with a prevalence of 1 in 20,000 individuals worldwide (Saraff et al., 2020). It manifests during childhood with distinctive clinical features of short stature, bone pain, skeletal deformities, and dental abnormalities. Disease awareness by healthcare providers is essential to be able to diagnose and manage promptly (Rothenbuhler et al., 2020).

## 1.2. Endocrine connection

Phosphate is an essential mineral in the human body, formed by combining phosphorus with oxygen. It is required for the adequate formation and growth of bones and teeth in children and later sustains their strength during adulthood. Maintaining physiological phosphate balance is critical for bone and teeth health. During phosphate homeostasis, endocrine regulators such as parathyroid hormone (PTH), vitamin D and fibroblast growth factor 23 (FGF23) target the intestines, kidneys, and bone (Penido and Alon, 2012). Dietary phosphate is absorbed by the small intestines, then stored in the skeletal system. The kidneys help control the amount of phosphate in the bloodstream and excrete excess phosphate in the urine. However, in XLH patients, more phosphate is excreted than stored, causing renal-phosphate wasting (Qadeer and Bashir, 2023).

## 1.3. Serum Phosphate

Serum phosphate concentrations measure the amount of phosphate in blood plasma. It may vary depending on patient's age, gender, and physiological state (Seefried et al., 2020). Levels may be within normal range or exhibit either an increase (hyperphosphatemia) or decrease (hypophosphatemia) in phosphate. Table 1.1. demonstrates the normal reference intervals of serum phosphate based on age group in milligrams per decilitre (mg/dL) (Ruppe, 2016).



**Table 1.1.** - Normal serum phosphate reference intervals based on age (Ruppe, 2016)

Age	mg/dL
<1 years	4.8 – 8.2
1 – 3 years	3.8 – 6.5
4 – 11 years	3.7 – 5.6
12 – 15 years	2.9 – 5.4
>15 years	2.7 – 4.7
Adults	2.5 – 4.5

The severity of hypophosphatemia is classified based on serum phosphate level, it could be mild, moderate, or severe. Mild or moderate decrease in concentration may not cause obvious clinical signs and symptoms, whereas a more severe decrease can lead to bone deformity and impaired growth. The specific levels to determine severity vary slightly among different sources and medical guidelines. Generally, mild hypophosphatemia ranges between 2 – 2.5 mg/dL, while moderate usually falls within 1 – 2 mg/dL. However, severe hypophosphatemia is determined when serum phosphate level is less than 1 mg/dL (Kiela and Ghishan, 2009). It is essential to interpret phosphate levels while considering the patient's age, gender, medical history, and presence of specific clinical features (Seefried et al., 2020).

## 1.4. Genetics

### 1.4.1. Gene mutation

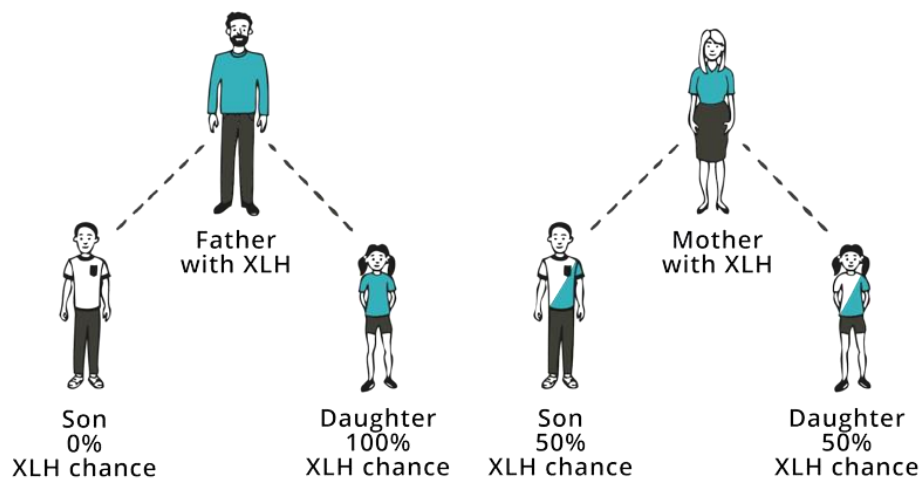
XLH is caused by a mutation in the Phosphate Regulating Endopeptidase X-Linked (PHEX) gene on the X chromosome. This gene is involved in bone and dental mineralisation and renal phosphate reabsorption. It is also responsible in regulating a protein known as fibroblast growth factor 23 (FGF23), which further participates in regulating phosphate in plasma and vitamin D metabolism in the body. The overactivity of FGF23 decreases the reabsorption of phosphate into the bloodstream by the kidneys leading to hypophosphatemia (Saraff et al., 2020).

### 1.4.2. Patten of inheritance

XLH has an X-linked dominant pattern of inheritance, which means only one X-chromosome that produces the altered PHEX is sufficient to cause the disorder. If a father has XLH, 0% of his sons will develop XLH, whereas 100% of his daughters will be diagnosed with XLH because they will inherit an X chromosome from with the mutated gene. However, if the mother

has XLH, her children both sons and daughters each have a 50% of developing XLH as shown in Fig 1.1. (XLH Link, 2023).

Although XLH is a genetic disorder, about 20-30% of people may develop XLH because of a spontaneous mutation which subsequently can be passed on to their future children. Genetic counseling and testing are recommended for affected families (Haffner et al., 2019).



**Fig 1.1.** XLH pattern of inheritance (XLH Link, 2023)

## 1.5. Clinical Features

Clinical features may vary between children and adults, they also vary from one person to the other. XLH manifests during late infancy when a child is beginning to walk. However, symptoms can appear at any age, and worsen or change over a period of time.

### 1.5.1. Childhood

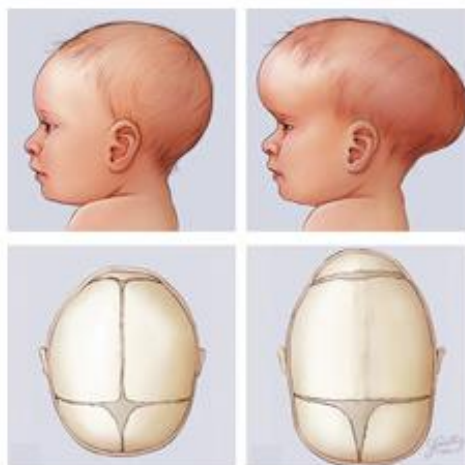
Rickets is one of the early signs of XLH, where growing bones in children soften and weaken. Distinctive features of the condition include short stature, abnormal gait, bone/joint pain, and skeletal deformities such as bowed legs. Figures 1.2. and 1.3. demonstrate the clinical and radiographic features of lower extremity deformities such as short stature with bowed legs (Haffner et al., 2019; Pereira et al., 2004). Cranial abnormalities are also observed including craniosynostosis, which is a birth defect where bones in the skull join early causing irregularities in the shape of the head as shown in Fig 1.4. (Sabeti et al., 2022). Parents usually report that their children are less energetic and experience fatigue which affects their quality of life (Haffner et al., 2019).



**Fig 1.2.** 9-year-old female with abnormalities of lower extremities characterised by bowing of legs (Pereira et al., 2004, pp.241-244)



**Fig 1.3.** Radiographs of lower extremities demonstrating short stature with bowed legs (Haffner et al., 2019, pp.435-455)



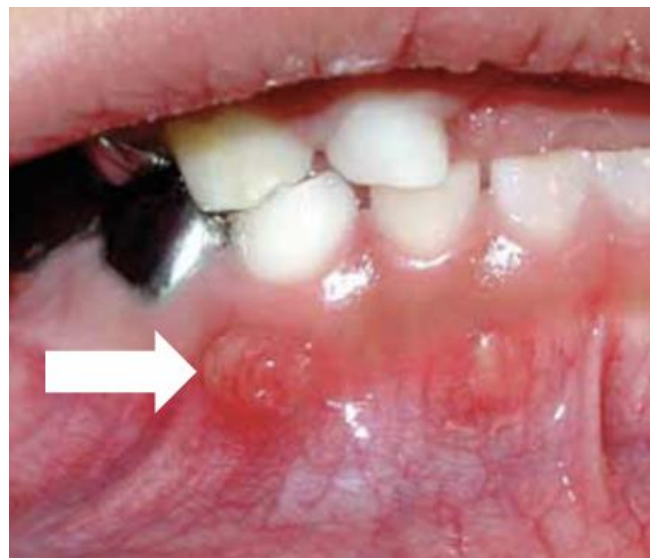
**Fig 1.4.** Left shows a normal brain vs. right a brain with craniosynostosis specifically sagittal synostosis (Sabeti et al., 2022)

### 1.5.2. Adulthood

Patients may continue to experience short stature, bowed legs and weakening of mature bone, which is referred to as osteomalacia. They may also develop new musculoskeletal symptoms later in life, including fractures, pseudofractures, osteoarthritis and hardening of tendons (enthesopathy), which can further burden their quality of life (Haffner et al., 2019). Other patients report increased muscle weakness and joint stiffness which can subsequently decrease their mobility and affect their daily function. Adult patients may also develop hearing loss or impairment of varying degrees, but the prevalence is uncertain and not reported in the literature (Baroncelli and Mora, 2021).

### 1.6. Dental Abnormalities

Children diagnosed with XLH may present with 'spontaneous' dental abscesses which is a bacterial infection without an apparent underlying condition such as dental caries or traumatic injuries, as shown in Fig. 1.5. (Hernández and Laguna, 2013). A study conducted by Al Juraihab, et al. (2021) stated that around 60% of patients with XLH develop recurrent dental abscesses in both primary and/or permanent teeth, and patients with one abscess will develop more. Whereas McWhorter and Seale, (1991) indicated that only 25% of their participants reported dental abscesses. Several studies have reported dental abscesses ranging from 25% to 51% of XLH patients aged 1 to 22 years, as shown in Table 1.2. (Dahir et al., 2020).

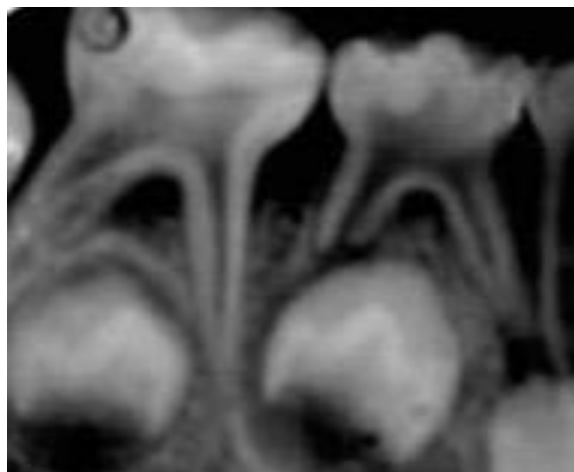


**Fig 1.5.** Arrow shows periapical abscesses with no clear evidence of decay or trauma (Hernández and Laguna, 2013, pp.101-108)

**Table 1.2.** - Percentages of Spontaneous Abscesses reported in the literature

Authors	Year	Study Design	Number of participants	Age range (years)	Abscess (%)
Baroncelli et al.	2006	Quasi-experiment	9	2 – 13.3	67%
Souza et al.	2010	Prospective study	14	4 - 26	7.1%
Rabbani et al.	2012	Cross Sectional	19	3 - 17	10.5%
Emma et al.	2019	Questionnaire	135	0 - 17	33%
Skrinar et al.	2019	Burden of Disease	90	1 - 18	51%
Dahir et al.	2020	Review	134	1 - 18	25% to 51%
Marin et al.	2021	Cross sectional	26 (6 children)	5 - 16	33%

It has been reported in the literature that incisors are highly susceptible to abscesses in comparison to canines and molars (Baroncelli et al., 2020). The reason behind their susceptibility to recurrent abscesses may be due to micro cracks in enamel or due to enlarged pulp chamber with prominent pulp horns extending to the dentino-enamel junction in both primary and permanent teeth, as shown in See Fig. 1.6. (Baroncelli et al., 2006). Other common dental complications include delayed eruption of primary and permanent teeth, thin enamel, abnormalities in dentine mineralisation and increased risk of periodontal disease (Souza et al., 2010). Such dental implications highlight the importance of a dentist as a member of the multidisciplinary team for XLH patients (Seow, 2003).



**Fig 1.6.** Periapical radiograph shows enlarged pulp chamber and horns with pathology associated to primary molars (Hernández and Laguna, 2013, pp.101-108)

## 1.7. Diagnosis

The diagnosis of XLH is based on clinical manifestations, radiographic evidence, family history, blood tests and genetic testing. Clinical features such as softening of bones, bowed legs, delayed growth and abnormal stature are bone complications also associated with Vitamin D deficiency, however XLH patients do not respond to Vitamin D and Calcium supplements (Hernández and Laguna, 2013).

## 1.8. Medical Management

### 1.8.1. Medical team

Early diagnosis and management are crucial during childhood when the skeleton is still at the developing stage, as this may improve patients' growth, height and dental health and prevent further invasive procedures (Souza et al., 2010). Due to the complexity of the condition a multidisciplinary team is required, including an endocrinologist, nephrologist, orthopaedic surgeon, pain specialist, psychologist, paediatric dentist, geneticist, physiotherapist, and dietician (Saraff et al., 2020).

### 1.8.2. Conventional therapy (CT)

Since 1975, conventional therapy was the only readily available treatment for XLH patients. The treatment includes oral phosphate supplements and active vitamin D derivatives. Alongside medications, patients may require corrective surgery to adjust certain clinical features such as bowing of legs (Martín Ramos et al., 2020). This therapy has been widely researched proving its success in managing bone pain, however children can still develop lower limb deformity hence requiring corrective surgery (Schindeler et al., 2020). This treatment has also been shown to improve dentine formation and mineralisation during tooth development, which may reduce the prevalence of dental abscess and prevent premature tooth loss (Gadion et al., 2022).

### 1.8.3. Novel therapy

In 2018, both the British Paediatric and Adolescent Bone Group (BPABG) and National Institute for Health and Care Excellence (NICE) approved and recommended the use of burosumab (Crysvita) for the treatment of XLH in children aged 6 months and older (Padidela et al., 2020). Burosumab is a fully human immunoglobulin G1 monoclonal antibody that binds and inhibits FGF23 activity which showed promising results in clinical trials and has been adopted worldwide as a first-line defence for XLH. It is administered as a subcutaneous

injection, once every 2 weeks for children from 6 months to 17 years of age (Schindeler et al., 2020).

This novel therapy leads to an increased phosphate absorption and renal phosphate reabsorption thereby improving overall serum phosphate levels and bone mineralisation (Lyseng-Willamson, 2018). Martín Ramos et al. (2020) evaluated the efficacy and safety of burosumab treatment in 6 paediatric patients after 1 year, assessing their height, weight, clinical features, and biochemical findings. The study concluded that burosumab was well-tolerated with no serious undesirable effects, recommending its use for the clinical management of XLH (Martín Ramos et al., 2020).

#### 1.8.4. Conventional vs Novel therapy

Imel et al. (2019) compared burosumab to conventional therapy in children, concluding that burosumab was superior in normalising serum phosphate and improving rickets severity, lower limb deformity, growth, and mobility. Overall, the benefits of burosumab are well-established in the literature, however, its impact on some phenotypic features of XLH such as dental abscess and craniosynostosis remain unclear (Schindeler et al., 2020). A phase III clinical trial comparing burosumab to conventional therapy stated that 28% of participants receiving burosumab developed dental abscesses in comparison to 9% in the conventional therapy group (Imel et al. 2019). Moreover, a longitudinal 10-year study (NCT03651505) due to be published in 2028 is currently investigating biomarkers, clinical assessments, and patient outcomes of burosumab and conventional therapy to provide a definitive conclusion as to their safety and efficacy (Schindeler et al., 2020). In chapter 2, a more detailed discussion of both methods of treatment and their impact on dental manifestations will be reviewed.

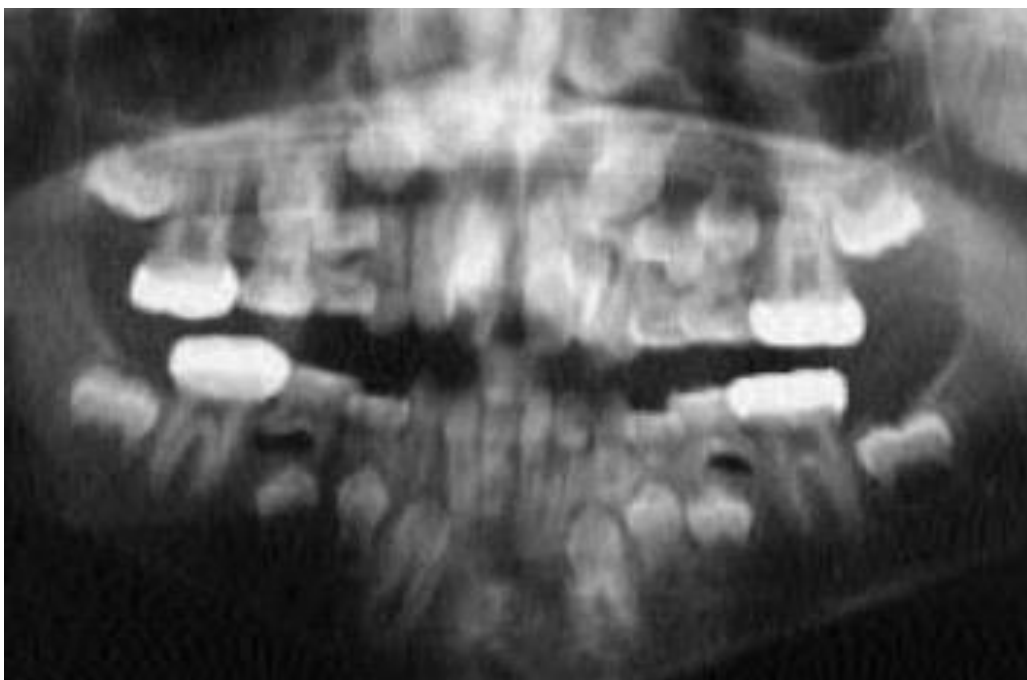
This disorder ultimately results in a reduced health-related quality of life (HRQoL) due to several skeletal abnormalities that affect their overall development. Children with XLH tend to endure multiple dental visits including emergency treatments from a young age because of oral manifestation of XLH. Therefore, their oral health-related quality of life (OHRQoL) is also affected which justifies the need for further investigation.

### 1.9. Dental Management

The appropriate management of dental complications of XLH remains controversial, some researchers advocate invasive treatments while others recommend following preventative measures (Batra et al., 2006). Furthermore, there is no specific guideline or care pathway for dentists to follow, the literature mainly recommends that children with XLH must be seen by a

dental professional twice a year for clinical examination and radiographs, if applicable (Haffiner et al. 2019). There is an established care pathway between Great Ormond Street Hospital (GOSH) and the Eastman Dental Hospital (EDH), with all patients referred for a dental evaluation by their medical team. Assessment in a specialised centre is valuable as practitioners may be more familiar with the complexity of the signs and symptoms of XLH, providing the appropriate management promptly (Nguyen et al., 2022). In Chapter 3, the dental management scoping review will be described in detail.

In terms of treatment options, most available research encourages the use of preventative measures as a first-line defence which includes topical fluoride application, pit and fissure sealants and overall maintenance of good oral hygiene to reduce the risk of spontaneous abscess (Batra et al. 2006). Prophylactic placement of preformed metal crowns without preparation to prevent risk of pulp exposure in primary and permanent molars has also been suggested as beneficial as shown in Fig. 1.7. (Baroncelli et al., 2006). However, Hernández and Laguna (2013) recommended that if a patient developed a dental abscess, then an aggressive pre-emptive treatment of choice should be to perform prophylactic pulpotomies with preformed metal crowns on all primary molars and resin restorations on anterior teeth. On the other hand, some authors indicated that extraction of teeth with abscesses is preferred as endodontic treatment may not be able to maintain asepsis (Pereira et al., 2004).



**Fig 1.7.** Orthopantomogram (OPG) of XLH patient who had prophylactic stainless-steel crowns placed on the first permanent molars to prevent pulpal abscesses (Seow, 2003, pp.156-168)



## 1.10. Qualitative Research on XLH

A European multi-country qualitative study conducted by Lo et al. (2020) provided an in-depth analysis of pain, stiffness, mental health, dental health, and social life of adults with XLH, describing the psychological impact. The study did not include children's perspective as the participants were aged 26 years and above. Another qualitative study captured the burden of the disorder and improved the understanding of the symptom and treatment of XLH on both children and adults. It included 32 children and 18 adolescents from the United Kingdom (UK), United States of America (USA), and Australia. It highlighted that children's greatest burden was pain while adults' burden become more complex and multifactorial with the further need for interventions (Ferizovic et al., 2019). There is a lack of research focusing on children's preceptive, thus exploring, and measuring how XLH impacts their teeth and quality of life is required.

### 1.10.1. Oral Health-Related Quality of Life (OHRQoL)

OHRQoL has become an important aspect of clinical dentistry and dental research. In 2003, the World Health Organisation (WHO) recognised these questionnaires as a fundamental part of patients' general healthcare (Sischo and Broder, 2011). Yang et al. (2020) stated that several questionnaires have been developed and validated, for both adults and children to assess their quality of life in relation to their dental health. A thorough search of the literature showed two articles exploring OHRQoL in adults with XLH (Gjørup et al., 2020; Hanisch et al., 2019). A recent study by Nguyen et al. (2022) evaluated OHRQoL for both adults and children with XLH (21 patients including 7 children). They used guided theme interview, discussing different topics including, fear, anger, access to care, technical aspects, financial aspect, quality of life, OHRQoL, etc. It appeared that children were less impacted in their general and oral health than adults because they are referred and treated earlier (Nguyen et al., 2022).

### 1.10.2. Patient-reported outcome of measure (PROMs)

The healthcare system is shifting towards more patient-centred care. As a result, there was a consensus on the importance of including patients in the evaluation of their health condition and their viewpoint on the outcome of treatment (McGrath et al., 2012). Surveys such as PROMs were developed to explore patient's health outcome at a particular point in time as reported by the affected patient. They answer questions relevant to their symptoms, condition, dental health, and overall quality of life. Data collected from PROMs can be used longitudinally, as the survey may be obtained before and after treatment to monitor patient's progress and assess the impact of treatment on their condition (NHS, 2019).

Initially, PROMs were limited to four surgical procedures: varicose veins, hip and knee replacement, and hernia repair. However, there were noticeable efforts to investigate the feasibility of expanding routine measurements to a variety of chronic conditions, such as stroke, diabetes, asthma, and others. Evidence suggests it is possible for routine collection of PROMs to be implemented across a wide range of NHS departments (Devlin and Appleby, 2010). For instances, Cole et al. (2023) conducted a PROM of 48 adults with XLH based in the UK, measuring their health-related quality of life (HRQoL) including pain, fatigue, mental wellbeing, sleep quality and mobility issues. Results demonstrated worse outcomes in the majority of the measures assessed. Nevertheless, the study did not discuss the dental aspect of XLH, and paediatric input was not obtained.

In dentistry, PROMs can be used as a tool to elevate the quality of care provided and ensure patient involvement (Kingsley and Patel, 2017). There are few PROMs developed for dental services provided by the NHS. More recently, it has been used to assess dental conditions and treatments. Lyne et al. (2021) explored PROMs for children and young people with amelogenesis imperfecta (AI). Data demonstrated the range of issues AI patients face and managed to monitor their progress through treatment (Lyne et al., 2021). Furthermore, PROMs were used to compare two implant placement techniques, data collected after surgery and one year later to evaluate the clinical success of both treatments and patient satisfaction of the service (Almahrous et al., 2020). These studies illustrate the diverse application of PROMs in dental research highlighting the significance of understanding patients' experience and dental treatment beyond traditional clinical measures. Casaca et al. (2023), encouraged incorporating such questionnaires as part of quality improvement initiatives.

## 1.11. Aims and Objectives

The aim of this research project was to investigate the available literature on both the medical and dental management of children and young people with XLH. The scoping reviews evaluated the extent of published studies, focusing on the medical management of XLH and its impact on dental manifestations such as recurrent spontaneous abscess. Additionally, the research explored whether there were established guidelines suggesting dental treatment options for such manifestations.

### 1.11.1. Primary Objectives

- A. Medical Management of children and young people with XLH and its impact on dental manifestations: A Scoping Review
- B. Dental Management of children and young people with XLH: A Scoping Review
- C. Exploration of patient-reported outcome measure (PROM) of paediatric patients with XLH seen at EDH

#### 1.11.2. Secondary Objectives

- A. Gain a better understanding on whether one medical treatment is favourable for controlling or reducing dental implications of XLH
- B. Recognise the unmet dental needs associated with XLH
- C. Evaluate how XLH impacts patients' dental health and overall anxiety and whether they are satisfied with their teeth
- D. Identify the literature gap where future research may be essential

**Chapter Two: Medical  
Management of children and young  
people with X-Linked  
Hypophosphatemia (XLH) and its  
impact on dental manifestations: A  
Scoping Review**

## 2.1. Aim and Objectives

The aim of this review is to explore the available literature on medical management of children and young people with XLH. The review will systematically scope the extent of published studies focusing on the nature, range and extent of empirical research investigating the impact of medical management of XLH and their effect on dental manifestations such as recurrent spontaneous abscesses.

This review will aid in gaining a better understanding on whether one treatment option is favourable for controlling or reducing dental implications of XLH and will further identify the literature gap where future research may be essential.

## 2.2. Methodology

### 2.2.1. Review question

The review question was developed in collaboration with supervisors (SP and PA): Does the choice of medical management of paediatric patients with X-Linked Hypophosphatemia (XLH) have an impact on dental manifestations?

### 2.2.2. Protocol and registration

The current protocol is in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews (Peters et al., 2021) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation (Tricco et al., 2018). The final version of the protocol was registered with the Open Science Framework (<https://osf.io/y8d6q>).

### 2.2.3. Eligibility Criteria

For the following scoping review, the eligibility criteria were based on the Population, Concept and Context (PCC) framework, which is recommended by JBI as a guide to identify the main concepts necessary to answer the review question. **Population** included children and young people under the age of 16 years old, diagnosed with XLH. **Concept** covered all available research in the medical management of paediatric patients with XLH between 2018 to 2023. Publication years were chosen as burosumab therapy was approved by the Food and Drug Administration (FDA) in 2018, any research prior to 2018 would not provide the specific aim of this scoping review. **Context** considered all healthcare settings, with no cultural factors,

location, or gender specified. Furthermore, reviews including meta-analysis, systematic reviews, narrative reviews, mixed methods reviews, qualitative reviews, and rapid reviews must be identified and evaluated.

#### 2.2.3.1. Inclusion Criteria

- All publications considered, including case studies, cohort studies, cross-sectional studies, randomised controlled trials, observational studies, and narrative review articles
- Published between 2018 to 2023
- Involving XLH patients under 16 years old
- Published in English only
- Publications containing information on children and adults to be included only if results were presented separately for children

#### 2.2.3.2. Exclusion Criteria

- Non-peer-reviewed literature
- Reviews and Editorials
- Adult studies only
- Grey literature

#### 2.2.4. Type of Sources

All available studies meeting the eligibility criteria and addressing the review question were considered in this scoping review. Variety of study designs were included such as randomised controlled trials, non-randomised controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies were considered for inclusion.

Descriptive observational study designs such as case series, individual case reports and descriptive cross-sectional studies were also reviewed to determine their eligibility of inclusion. In addition, any other systematic or scoping reviews that meet the criteria were considered if determined relevant to the research question.

### 2.2.5. Search Strategy

The search strategy aimed to locate both published and unpublished studies. A preliminary limited search of MEDLINE and Cochrane Database of Systematic Reviews (CDSR) were undertaken to identify applicable articles on this topic. Search terms included keywords in the title, abstract and subject headings e.g., medical subject headings (MeSH) and embase subject headings (Emtree) as appropriate.

Relevant studies were identified by searching electronic databases of published peer reviewed literature including Medline, PubMed, Excerpta Medica database (EMBASE), Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science. Moreover, sources of unpublished studies were explored including NICE Evidence search, and NHS trust websites to determine eligibility.

The search strategy included all identified keywords and terms that were adapted for each database and information source. Subsequently the reference list of identified studies was then screened manually to further locate any additional studies relevant for this review.

### 2.2.6. Study/Source of Evidence Selection

Following the search, all identified citations were collected and uploaded into EndNote X9.3.3 (Clarivate Analytics, PA, USA) and duplicates were removed. A pilot data extraction was performed where titles and abstracts screened by two independent reviewers (BA and SP) for assessment against the inclusion criteria for the review.

Relevant sources were retrieved in full, and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia). The full text of selected citations were thoroughly assessed against the inclusion criteria by two independent reviewers (BA and SP). Any articles that are deemed relevant were included in the full-text review and reasons for any exclusion is documented and reported in the scoping review.

### 2.2.7. Data Extraction

In this scoping review, extracted data were incorporated by two independent reviewers (SP and PA) using a customised extraction tool developed by the authors. The tool compiled the

relevant data in a single excel spreadsheet on a Microsoft Excel software for validation and coding. It was modified and revised as necessary during the extraction process.

The final version of the tool included several variables, as shown in Appendix 1. The first section included general information of the article such as the study ID, title, names of the reviewers, type of publication (whether it is a journal article or book chapter), year of publication, country where the research was conducted, and name of all authors listed on paper. The second section mentioned the article's aim, design, and methodology. The third section demonstrated how the PCC framework was incorporated. The final section comprised of the main themes of this review including the Impact of conventional therapy (CT) to dental manifestations, the effect of burosumab (Novel therapy) to dental manifestations, comparison of conventional vs novel therapy and recommendations.

## 2.3. Results and Analysis

### 2.3.1. Preliminary Identification

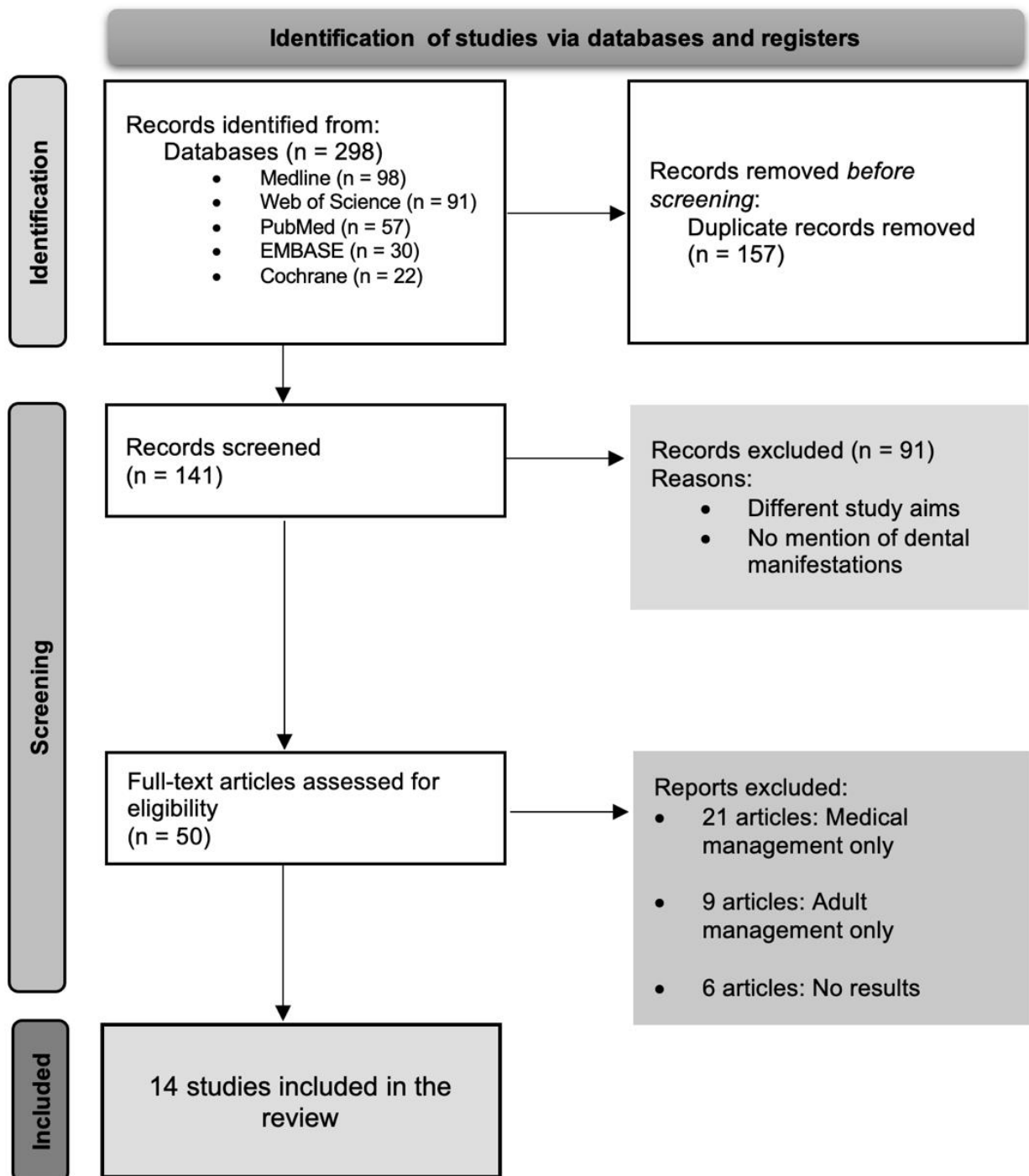
Initial screening resulted in identifying a total of 298 articles based on relevant keywords, publication period, and age group. In MEDLINE database, 98 titles were identified, while Web of Science yielded 91 titles. PubMed provided 57 titles, whereas EMBASE generated a total of 30 articles. The remaining 22 articles were identified from Cochrane library. Before further screening, EndNote X9.3.3 automatically removed 157 duplicate records which were obtained from multiple databases.

### 2.3.2. Screening

The abstract and methodology of 141 titles were screened to confirm they meet the inclusion criteria. Each article must include effect of medical management of XLH on dental manifestations on children and young people, or the article is excluded from the review.

A total of 91 titles were immediately excluded for not fulfilling the requirements of the PCC framework. Majority of excluded studies had different study aims, focusing on medical outcome of XLH therapy without mention of impact on dental manifestations such as recurrent spontaneous abscesses. After assessing eligibility of full-text, 36 studies were excluded for multiple reasons including medical management only, dental impact on adult patients only and 6 articles didn't have a conclusion yet. After thorough screening, 14 studies were deemed eligible for inclusion in this review as show in Fig 2.1.





**Fig 2.1.** PRISMA Flow diagram of identification and screening of studies

### 2.3.3. Reviewed Studies

The impact of medical management on children and adults has been extensively researched worldwide. While most published studies primarily concentrated on the medical improvement of XLH symptoms, there is only a brief reference to their dental improvements. This scoping review aims to explore whether there is enough evidence to suggest the superiority of one medical therapy over another concerning the improvement of dental manifestations of XLH.

21 countries researched the dental implications of different medical therapies of XLH with most of the research being conducted in Australia with 6 articles, followed by the USA. Nevertheless, 4 out of the 14 included studies were international and multicentred covering a wider range of patients. There was a variety of study designs included in the review, ranging from randomised controlled trial, open-label clinical trial, clinical guideline, literature reviews, case series, observational study, and retrospective study. Table 2.1. lists the articles included showing the author with study design, country of publication, number of patients and their age range, highlighting the specific aim.

The primary source of information in relation to the impact of medical management on dental health was from literature reviews accounting for 4 publications from 2018 to 2023. Whilst the highest level of evidence was obtained from 2 randomised controlled trials (RCT), Imel et al. (2019) was the only RCT to compare CT to burosumab. Nevertheless, a monocentric retrospective trial by Gadion et al. (2022) was the only study that focused on exploring the incidence of dental abscesses between both treatment options. Moreover, 4 studies had the same objective of assessing the efficacy and safety of burosumab in both medical and dental perspectives (Imel et al., 2019; Whyte et al., 2019; Martín Ramos et al., 2020 and Ward et al., 2022).

<b>Author</b>	<b>Year</b>	<b>Study Design</b>	<b>Aim</b>	<b>Country</b>	<b>Number of patients</b>	<b>Age (years)</b>
<i>Imel et al.</i>	2019	RCT	<b>Efficacy and safety of burosumab vs CT</b>	USA, Japan, UK, Sweden, South Korea, and Australia	61	1 - 12
<i>Whyte et al.</i>	2019	Open-label clinical trial	<b>Efficacy and safety of burosumab</b>	USA	13	1 - 4
<i>Padidela et al.</i>	2020	Clinical guidelines	<b>Review current evidence and provide expert recommendations</b>	UK	-	-
<i>Schindeler et al.</i>	2020	Review	<b>Summarise clinical trial data</b>	Australia	131	1 - 16
<i>Martín Ramos et al.</i>	2020	Case Series	<b>Efficacy and safety of burosumab</b>	Spain	5	6 - 16
<i>Bacchetta et al.</i>	2021	Review	<b>Discuss management of burosumab</b>	France	-	1 - 19
<i>Imel</i>	2021	Review	<b>Describe advances in management</b>	USA	-	-
<i>Brener et al.</i>	2022	Prospective case-control	<b>Explore the effect of burosumab</b>	Israel	10	4.3 - 15
<i>Gadion et al.</i>	2022	Retrospective	<b>Compare incidence of dental abscesses between burosumab and CT</b>	France	71	4 - 12

<i>Paloian et al.</i>	2022	Retrospective single-centre	<b>Assess effectiveness of burosumab</b>	USA	12	1 - 18
<i>Sandy et al.</i>	2022	Clinical Guideline	<b>Outline clinical practice guideline of burosumab</b>	Australia	-	-
<i>Trombetti et al.</i>	2022	Narrative literature review	<b>Provide clinical evidence on management</b>	Switzerland, Saudi Arabia, Italy, Spain, Belgium, Singapore, France, UK, Germany, Canada, Australia, Austria, Portugal, Bulgaria, and Argentina	2	Not specified
<i>Ward et al.</i>	2022	Randomised, active-controlled, open-label, phase III study	<b>Efficacy and safety of burosumab vs CT in younger and older children</b>	Canada, USA, Australia, Austria, UK, Japan, and Sweden	61	1 – 12
<i>Sandy et al.</i>	2023	Surveillance Units survey	<b>Investigate the prevalence of XLH and describe clinical characteristics of paediatric XLH</b>	Australia and New Zealand (NZ)	91	1 – 18

**Table 2.1.** - Summary of type and country of publication of included articles with aims of each study highlighted in **bold**

### 2.3.3.1. The Impact of conventional therapy (CT) to dental manifestations

Imel et al. (2019) conducted a randomised, active-controlled, open-label, phase 3 trial at 16 clinical sites in 6 countries: United States of America (USA), Japan, United Kingdom (UK), Sweden, South Korea, and Australia. The trial aimed to compare the efficacy and safety of converting to novel therapy versus continuing CT among 61 children with XLH aged from 1 to 12 years old. The study concluded that of the 32 patients randomly assigned to continue CT, 9% experienced dental abscesses and 6% dental caries, whereas 29 patients on burosumab had more frequent adverse events including 28% dental abscesses and 31% dental caries. A study by Sandy et al. (2023) investigated the prevalence of XLH in Australia and New Zealand while describing the clinical characteristics of the condition. Cross-sectional data was collected by surveillance units survey of 91 paediatric patients, 75 in Australia and 16 in New Zealand. 100% of patients in New Zealand received CT, and out of the 16 patients, only 6% reported spontaneous dental abscesses during the study.

Whyte et al. (2019) carried out a multicentre, open-label, phase 2 trial in the USA, aiming to assess the safety of burosumab in 13 children with XLH (aged 1-4 years). Prior to enrolment, a 4-year-old participant, who had received CT for 17 months, complained of dental abscesses and required extractions. Similarly, a case series in Spain, reported the findings of 5 XLH patients aged from 6 to 16 years old. 40% (n = 2) of patients experienced dental abscesses prior to the initiation of burosumab (Martín Ramos et al., 2020). Another retrospective single-centre study in the USA recruited 12 patients aged 1 to 18 years old previously treated with CT and about to transition to burosumab, 2 out of 12 (17%) patients reported a history of dental abscesses prior to the initiation of novel therapy (Paloian et al., 2022).

A review published by Schindeler et al. in 2020, evaluated the available clinical trial data looking into burosumab efficacy and safety in both adults and children with XLH. The review briefly mentioned the impact of CT on dental manifestations, stating that it remains a major challenge due to dental and periodontal complications, and recommended a more proactive approach to oral health to prevent dental abscesses. Another review of the use of burosumab in children with XLH by Imel (2021), stated that spontaneous dental abscesses and periodontal disease remain common in children and adults despite receiving CT. Bacchetta et al. (2021) published the practical clinical points from the French experience, following a panel discussion involving experts in the management of XLH. The review confirmed that CT should contribute to improving patients' dental health, however, such therapy has limitations leading to complications that may persist into adulthood.

The clinical efficacy and safety of conventional treatment is well-established in the literature. The treatment is known to enhance tissue defects, reduce the frequency of dental complications, and increase pain control (Chaussain-Miller et al., 2007). Trombetti et al. (2022) provided a narrative literature review, suggesting that the earlier CT is introduced during growth, the lower the incidence of recurrent dental abscesses and periodontitis. The review also demonstrated that such treatment provides an improvement in dentine and cementum mineralisation as shown in previous observational studies. Additionally, Gadion et al. (2022) conducted a monocentric retrospective study in France, which included a total of 71 children with XLH, 53.3% of whom received CT. The main objective of the study was to compare the incidence of dental abscesses in relation to the type of treatment provided. Like Trombetti et al. (2022), this study confirmed that when CT is introduced early, it improves dentine formation and mineralisation during dental development. Such improvement would lead to a lower occurrence of dental abscesses and reduce the likelihood of premature tooth loss.

#### 2.3.3.2. The effect of Burosumab (Novel therapy) to dental manifestations

The case series by Martín Ramos et al. (2020), demonstrated a positive outcome after receiving burosumab for one year, as none of the 5 paediatric patients reported dental problems during the treatment period. Additionally, Brener et al. (2022) conducted a prospective case-control observational study in Israel, recruiting a total of 10 children (age 4.3 – 15 years) with XLH. The aim was to explore the effect of novel therapy on dental health, dentition, and morphology. The study concluded that the incidence of spontaneous dental abscesses reduced throughout the three years of burosumab therapy, where only one patient out of 10 experienced recurrent dental abscesses until the tooth was extracted. Brener et al. (2022) concluded that increasing the serum phosphate intake may not counteract the abnormal enamel and primary dentine structure that was already formed; therefore, abscesses may remain to be an issue.

While burosumab has been shown to have a positive impact on patients, the majority of the relevant studies have cited the dental adverse events associated with such novel approach. For example, the phase 3 trial by Imel et al. (2019), randomly assigned 29 patients to receive burosumab, resulting in 31% experiencing dental caries and 28% complaining of dental abscesses. Similarly, reviews by Padidela et al. (2020) and Bacchettaa et al. (2021) stated that the most common side effects in burosumab is 35% dental abscesses and 11% dental caries. And as mentioned previously, Schindeler et al. (2020) reviewed the available clinical

evidence regarding burosumab therapy, confirming that the most significant adverse event in a paediatric care setting is the elevated incidence of dental abscesses related to burosumab therapy in comparison to placebo (31% with burosumab versus 6% with placebo).

### 2.3.3.3. Conventional vs Novel therapy

Table 2.2. below summarises the findings in the literature when comparing between treatment options in relation to their dental impact. A total of seven studies (50%) included in this scoping review were in favour of burosumab use for children with XLH. One impactful study was the monocentric retrospective trial by Gadion et al. (2022), which recruited 38 patients (53.3%) in the CT group and 33 (46.5%) in the novel group. The results indicated a significant reduction in the prevalence of dental abscesses among burosumab patients in comparison to those receiving CT (Gadion et al., 2022). Furthermore, after assessing the safety and efficacy of burosumab in younger children, Whyte et al. (2019) reported promising results in both medical and dental aspects. The phase 2 trial demonstrated that novel therapy improves serum phosphorus, rickets, and growth rates, while reducing dental complications (Whyte et al, 2019). This is further supported by an observational study by Brener et al. (2022), where CT was found to be insufficient in improving biochemical and radiological features of XLH, confirming that burosumab is more successful in normalising phosphate levels which would improve dentine mineralisation and decrease the likelihood of developing spontaneous dental abscesses.

Due to the substantial available evidence, the British Paediatric and Adolescent Bone Group (BPABG) clinical guidelines advocated the standardised introduction of burosumab for XLH paediatric and adolescent patients and recommended converting from CT to novel therapy (Padidela et al., 2020). Paloian et al. (2022) also agreed and proposed it as the preferred first-line treatment for children with XLH. Nevertheless, Bacchetta et al. (2021) added that a decision to discontinue CT and proceed with burosumab should depend on the medical team and their XLH severity criteria. One important criterion mentioned in the review, advised converting to bursosumab when a patient experiences dental abscess within the last 12 months.

<u>Author</u>	<u>Year</u>	<u>Findings</u>
Imel et al.	2019	Dental caries and abscesses more frequent in burosumab
Whyte et al.	2019	Burosumab had a more favourable outcome
Padidela et al.	2020	Supports the standardised introduction of burosumab
Schindeler et al.	2020	Adverse effects seen with burosumab are more than CT
Martín Ramos et al.	2020	Patients experienced more adverse effect with CT
Bacchetta et al.	2021	Burosumab was more effective than CT in children
Imel	2021	Both treatment options improved dentin-cementum volumes but did not improve mineral density
Brener et al.	2022	The frequency of dental abscesses decreased significantly throughout the three years of burosumab treatment
Gadion et al.	2022	Burosumab treatment appears to be associated with a reduction in the number of dental abscesses in XLH children, compared with CT
Paloian et al.	2022	Burosumab is safe and more effective than CT and recommends burosumab as the first-line therapy for children with XLH
Sandy et al.	2022	Increase in frequency of dental complications with burosumab, but the clinical relevance of this has not been determined
Trombetti et al.	2022	More events such as spontaneous dental necrosis in the burosumab arm than with CT
Ward et al.	2022	Dental caries, were reported more frequently with burosumab
Sandy et al.	2023	No statistically significant differences between treatment options when comparing clinical features and biochemistry

**Table 2.2.** - Summarised results of conventional (CT) vs burosumab on dental manifestations

(Red = CT is better, Yellow = No difference between treatment options, Green = Burosumab is better)



Despite these positive outcomes, it is essential to acknowledge and explore the potential limitations of the novel therapy. In this scoping review, five studies (35.7%) favoured CT over burosumab. Both Sandy et al. (2022) and Trombetti et al. (2022) included in their reviews the phase 3 RCT of burosumab versus CT by Imel et al. (2019), noting the increased frequency of dental complications in the burosumab group. Nevertheless, Sandy et al. (2022) emphasised that the clinical relevance of this conclusion cannot be attributed solely to the treatment choice. Alongside spontaneous dental abscesses, other adverse effects, such as dental caries and toothache, have been reported to be more frequent with burosumab (Imel et al., 2019; Ward et al., 2022). Furthermore, Schindeler et al. (2020) concurred that while the number of adverse effects (AEs) seen with burosumab appears to be greater than with CT, severe AEs linked to treatment remain rare.

Finally, three studies (21.4%) explored the similarities between treatment options. Sandy et al. (2023) observed no statistically significant difference between the two groups in relation to their clinical features or biochemistry. Similarly, Gadion et al. (2022) was unable to conclude a difference in the size of pulp chambers on consecutive radiographs between CT and burosumab. Nevertheless, Imel (2021) found that both treatment options enhanced dentin-cementum volumes but had no impact on mineral density.

#### 2.3.3.4. Recommendations

This scoping review investigated the specific recommendations regarding the management of XLH patients in a paediatric setting. Half of the studies (7 out of 14) discussed the need of further longitudinal and multicentre research with a larger number of patients to evaluate the clinical significance of each therapy on dental manifestations (Paloian et al., 2022). While Sandy et al. (2023), highlighted the importance of better understanding the mechanism of dental complications associated with XLH to help improve oral health. Other researchers such as Whyte et al. (2019) and Martín Ramos et al. (2020) recommended to focus on exploring the safety of burosumab and develop a universal criteria for its use.

The majority of the studies recommended the use of burosumab as a first-line treatment for children, however, two articles proposed initiating on CT and only consider converting to burosumab if patient is not responding well to treatment or if their XLH is deemed severe (Imel et al., 2019 and Trombetti et al., 2022). Their justification was regarding accessibility and cost-effectiveness, as there is a large annual cost of burosumab of around \$160,000 per paediatric patient which is 100-fold higher than CT (Goyal and Tandon, 2024). Nevertheless, there is

currently a clinical trial by the XLH Disease Monitoring programme (ClinicalTrials.gov No. NCT03651505) that will provide a 10-year longitudinal assessment of XLH patients on burosumab, evaluating its safety and efficacy, not only from a medical point of view but also dental and confirming its cost-effectiveness and availability (Ward et al., 2022).

The articles in this review indicated that management of XLH in children is multifactorial, and depends on early diagnosis, prompt intervention, patient compliance, and appropriate monitoring. As many parameters may contribute to treatment outcome, it is important to consider patient and family education, frequent medical and dental monitoring, and provide a multidisciplinary approach (Bacchetta et al., 2021). Although XLH is genetic, some families may be unaware of its medical and dental implications. Thus, it is essential to seize the opportunity to educate them on the specific clinical manifestations associated to the condition, and possible side effects of the treatment provided (Bacchetta et al., 2021). Sandy et al. (2022) also recommended patients attend for a thorough dental assessment prior to commencing XLH treatment whether they are currently experiencing dental issues or not. Additionally, advised dental professionals to encourage good oral hygiene regimens and schedule frequent dental check-ups. Since there is evidence of abnormal dental development associated with XLH, and patients tend to exhibit increased risk in dental abscess, dental caries and periodontal diseases, a 6-month review is crucial (Padidela et al. 2020). Finally, having a multidisciplinary team is an integral aspect of managing individuals with rare bone diseases, to address different complications significant to the condition (Sandy et al., 2022).

## 2.4. Discussion

Conventional therapy (CT) has been extensively researched and documented in the literature focusing mainly on its medical impact. Prior to the development of burosumab, the only available treatment included the intake of oral phosphate supplements and active vitamin D derivatives such as alfacalcidol (Martín Ramos et al., 2020). The appropriate dose of medication is prescribed by a Paediatric Endocrinologist and depended on the patient's age and severity of symptoms. The benefit of such treatment proved to have a positive outcome in terms of physical symptoms, improving growth, leg deformities, and overall pain (Trombetti et al., 2022). Nevertheless, adhering to CT may be difficult, as it requires taking medications several times a day, with an unpleasant taste, and gastrointestinal adverse effects. These aspects contribute further to the burden of disease and may lead to poor compliance (Sandy et al., 2022).

On the other hand, the approval of burosumab as a treatment option was a result of two decades of extensive clinical research, which included several phase 2 trials and one pivotal phase 3 study focusing on children with XLH (Martín Ramos et al., 2020). The evidence gathered over the years played a critical role in demonstrating the efficacy and safety of burosumab for paediatric patients above the age of one. Numerous studies included in this review have demonstrated a more favourable effect of this treatment on the overall health and growth of children. Additionally, a recent consensus statement has suggested that burosumab therapy should be recognised as the first-line treatment in children with XLH aged 1 year or older (Trombetti et al., 2022). Imel (2021) highlighted that the administration of burosumab as a subcutaneous injection every 2 weeks for children is more effective than daily multiple oral doses of conventional treatment.

The medical management prioritises the improvement of clinical features, with minimal consideration given to its impact on dental manifestations. There is a wide discussion comparing conventional and novel therapies, focusing on factors such as physical symptom alleviation, radiographic enhancement, and growth progression. However, there has been a recent interest in exploring the impact of treatment options on dental health. Several studies discussed the established potential of CT in improving dentine formation and mineralisation during tooth formation, which may reduce the prevalence of dental abscess and prevent premature tooth loss. Nevertheless, unlike conventional therapy, the impact of burosumab on the mineralisation of dental tissues and on oral complications remains unclear in the literature (Paloian et al., 2022).

Therefore, some researchers recommended introducing the medication as soon as an official XLH diagnosis is made to have a better outcome in dental development (Trombetti et al., 2022). Others suggested initiating with CT in milder cases, and to consider burosumab only when treatment response is inadequate (Imel et al., 2019). Gadion et al. (2022), further emphasised that using burosumab in cases of CT failure allows the comparison of both treatment options in the same child. The results in the monocentric retrospective study when comparing the incidence of abscesses in the same child, noted a clear advantage of burosumab use (Gadion et al., 2022).

Furthermore, demographic characteristics of patients receiving XLH treatment such as their age and gender may contribute to treatment outcomes. Ward et al. (2022) demonstrated that none of the younger patients who received burosumab experienced spontaneous dental abscesses, whereas such complication occurred in more than half of the older children receiving the same treatment. Nevertheless, Gadion et al. (2022) did not observe significant

difference in spontaneous abscess between the two age groups. However, they did observe a significant reduction in spontaneous dental abscesses among females in comparison to males. This gender discrepancy was not reported previously in the literature, a possible explanation could be the presence of a second non-mutated PHEX allele in females, which may partly counteract the mutated allele (Gadion et al., 2022).

## 2.5. Conclusion

In conclusion, the decision regarding the choice of medical management falls under the responsibilities of the XLH medical team, nevertheless, including paediatric dentists as part of the multidisciplinary team is essential to recognise their valid input on patients' dental health. This will allow for an open communication between members of the team, ensuring both medical and dental outcomes are optimal. It is not clinically justified for dental professionals to change the type of medical treatment, however if dental manifestations associated to XLH worsen, recommendations from a paediatric dentist to the patient's paediatric endocrinologist to explore more novel measures could be suggested.

The results obtained from this review cannot establish a direct cause-and-effect relationship between the treatment option and dental complications, as many factors may be involved. Many studies reported a reduced number of dental abscesses when treated with burosumab versus CT. Although these results are encouraging, studies did suggest that side effects such as dental abscesses and dental caries may be found in both treatments. However, if CT was introduced early it may help with improved dental development. Such a conclusion is not possible presently with burosumab due to its novelty, but after further longitudinal study and more insight, it might lead to the same conclusion. Finally, regardless of the treatment option provided, the main focus of a paediatric dentist is to maintain regular dental follow-ups, promote optimal oral hygiene regimen and promptly diagnose and treat any dental complications that may arise during childhood.

**Chapter Three:** Dental  
Management of children and young  
people with X-Linked  
Hypophosphatemia (XLH): A  
Scoping Review

### 3.1. Aim and Objectives

The aim of this scoping review was to explore the available literature on dental management of children and young people with XLH, focusing on the treatment options available for dental manifestations of XLH such as recurrent spontaneous abscesses.

This review aimed to gain a better understanding on the unmet dental needs associated with XLH and identifying the literature gap where future research may be focused.

### 3.2. Methodology

#### 3.2.1. Review question

The review question was developed in collaboration with supervisors (SP and PA): What is the dental management of children and young people under the age of 16 years old diagnosed with X-linked Hypophosphatemia (XLH)?

#### 3.2.2. Protocol and registration

The current protocol was in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews (Peters et al., 2021) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation (Tricco et al., 2018). The final version of the protocol was registered with the Open Science Framework in 20/3/2022 (<https://osf.io/qyuj3>).

#### 3.2.3. Keywords

The following key words were used to in the review: X-Linked hypophosphatemia, familial hypophosphatemic rickets, hereditary hypophosphatemic rickets, dental management, paediatric dentistry, and spontaneous abscess.

#### 3.2.4. Eligibility Criteria

For the following scoping review, the eligibility criteria were based on the Population, Concept and Context (PCC) framework, which is recommended by JBI as a guide to identify the main concepts necessary to answer the review question. **Population** included children and young people under the age of 16 years old, diagnosed with XLH. **Concept** covered all available research in the dental management of paediatric patients with XLH between 2000-2022.

**Context** considered all healthcare settings, with no cultural factors, location, or gender specified. Furthermore, original research articles and reviews including meta-analysis, systematic reviews, narrative reviews, mixed methods reviews, qualitative reviews, and rapid reviews to all be identified and evaluated.

#### 3.2.4.1. Inclusion Criteria

- All publications to be considered, including case studies, cohort studies, cross-sectional studies, randomised controlled trials, observational studies, and narrative review articles
- Published between 2000 to Feb 2022
- Involving XLH patients under 16 years old
- Published in English only
- Publications containing information on children and adults to be included only if results were presented separately for children

#### 3.2.4.2. Exclusion Criteria

- Non-peer-reviewed literature
- Reviews and Editorials
- Adult studies only
- Grey literature

#### 3.2.5. Type of Sources

This scoping review considered all available studies meeting the eligibility criteria and addressing the review question. Study designs included randomised controlled trials, non-randomised controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies were considered for inclusion.

Descriptive observational study designs including case series, individual case reports and descriptive cross-sectional studies were also reviewed for inclusion. Furthermore, qualitative studies were reported focusing on qualitative data. Any other systematic or scoping reviews that meet the inclusion criteria were considered, depending on the research question.

### 3.2.6. Search Strategy

The search strategy aimed to locate both published and unpublished studies. A preliminary limited search of MEDLINE and Cochrane Database of Systematic Reviews (CDSR) were undertaken to identify applicable articles on this topic. Search terms included keywords in the title, abstract and subject headings e.g., medical subject headings (MeSH) and embase subject headings (Emtree) as appropriate.

Relevant studies identified by searching electronic databases of published peer reviewed literature including Medline, PubMed, Excerpta Medica database (EMBASE), Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Google Scholar. Moreover, sources of unpublished studies or grey literature were searched including NICE Evidence search, medical and dental associations and NHS trust websites to determine eligibility.

The search strategy included all identified keywords and terms that were adapted for each database and information source. The reference list of included studies was then screened manually locating any additional studies that were relevant for this review.

### 3.2.7. Study/Source of Evidence Selection

Following the search, all identified citations were collected and uploaded into EndNote X9.3.3 (Clarivate Analytics, PA, USA) and duplicates were removed. A pilot data extraction was performed where titles and abstracts screened for assessment against the inclusion criteria for the review.

Relevant sources were retrieved in full, and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia). The full text of selected citations were thoroughly assessed against the inclusion criteria by two independent reviewers (BA and SP). Any articles that are deemed relevant were included in the full-text review and reasons for any exclusion is documented and reported in the scoping review.

### 3.2.8. Data Extraction

The extracted data involved specific details about the population, concept, context, study methods and key findings relevant to the review question in a single excel spreadsheet on a Microsoft Excel software for validation and coding. The tool was modified and revised as



necessary during the extraction process. The final version of the tool included several variables, as shown in Appendix 2. The first section included general information of the article such as the study ID, title, names of the reviewers, type of publication (whether it is a journal article or book chapter), year of publication, country where the research was conducted, and name of authors as listed on paper. The second section mentioned the article's aim and methodology. The third section demonstrated how the PCC framework was incorporated. The final section comprised of the main themes of the study: key dental features, key radiographic features, dental management of XLH and special clinical consideration.

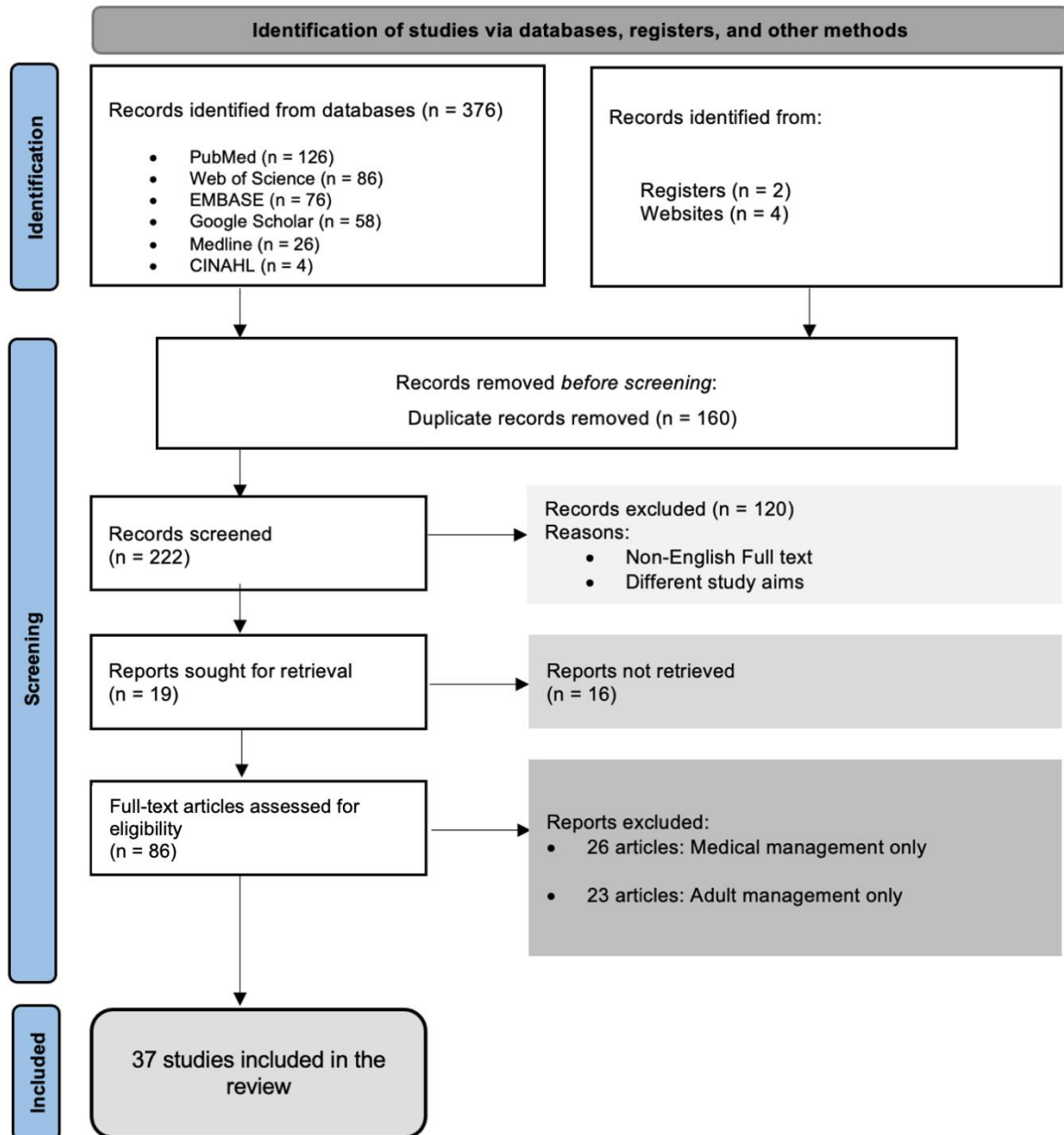
### 3.3. Results and Analysis

#### 3.3.1. Preliminary Identification

Initial screening identified a total of 382 articles based on relevant keywords, publication period, and age group via databases, registers, and other methods. In PubMed database, 126 titles were identified, while Web of Science yielded 86 titles, EMBASE provided 76 titles and MEDLINE generated a total of 26 articles (See Fig 3.1.). The remaining articles were identified from CINAHL, Google Scholar and other registries. Additionally, 4 titles were manually identified to ensure all type of evidence were included such as NICE Evidence search, medical and dental associations and NHS trust websites to determine possible eligibility. Before screening was carried out, EndNote X9.3.3 automatically removed 160 duplicate records obtained from several databases.

#### 3.3.2. Screening

Of the 222 titles screened to confirm they match the inclusion criteria stated previously in the methods section. 120 titles were excluded for not fulfilling the requirements of the PCC framework. The majority of excluded studies had different study aims, either focusing on dental management of adult patients only or their medical management. Other studies were excluded because they were not available in English and one article was unretrievable. After thorough screening, 37 studies were deemed eligible for full text assessment and included in this review as show in Fig 3.1.



**Fig 3.1.** PRISMA Flow diagram of identification and screening of studies

### 3.3.3. Reviewed Studies

Research on medical and dental management of XLH has been extensively studied worldwide. This scoping review demonstrated that 20 countries have explored the dental implication and management of XLH with most of the research being conducted in Europe. France is the most researched country on XLH with 6 articles followed by Brazil, Italy, UK, and USA with 4 each. There was a variety of research designs in the review, ranged from case reports, reviews, cross-sectionals, case controls, longitudinal cohort, and expert opinion. Table 3.1. lists the 37 articles included in the review demonstrating the publication year and type with the number and age range of patients involved.

Case reports and case series studies were the primary source of information in relation to dental manifestations with 22 published articles (59%), followed by 6 literature reviews (16%) and 4 cross-sectional studies (11%). Majority of case reports included 1 to 4 patients, 19 out of 22 case reports only presented one case, and the age range of cases were 3 to 16 years old. A total of 28 patients were reported, with the gender distribution of 21 males and 7 females. Additionally, included reviews were vague in stating the type of review being conducted, whether it is systematic, scoping or literature with no specific research question or strategy.

It is worth noting that no randomised control trial (RCT) or Cochrane review on the dental management were published during the period of identification or screening for this review. Furthermore, there was no research that compared two treatment options to determine the efficacy of one over the other. Sabandal et al. conducted a review in 2015 identifying the dental implications of XLH with suggested treatment options for XLH patients, including articles from 1971 to 2013, the review was broad including both paediatric and adult patients. Thus, a scoping review was justified to focus on paediatric patients alone.

Results were categorised into four main themes:

- Dental features, including the dental implications ranging from anomalies, restorative, endodontic, periodontal, and orthodontic perspective
- Radiographic features, demonstrating the possible radiographic findings affecting enamel, dentine, pulp, and roots
- Dental management of XLH to assess whether there were specific guideline clinicians can follow to manage recurrent complications associated with XLH
- Clinical considerations, discussed the specific treatment considerations mentioned in the current evidence

	<i>Author</i>	<i>Year</i>	<i>Article Type</i>	<i>Country</i>	<i>Number of Patients</i>	<i>Age (years)</i>	<i>Gender</i>
1.	Murayama et al.	2000	Case report	Japan	1	15	M
2.	Alexander et al.	2001	Clinical review and Case report	Australia	1	16	M
3.	Shroff et al.	2002	Case report	USA	4	3 – 7	3 M / 1 F
4.	Chaussain-Miller et al.	2003	Clinical trial	France	32	3 – 25	12 M / 20 F
5.	Seow	2003	Review	Australia	-	Paediatrics	-
6.	Baroncelli et al.	2006	Quasi-experiment	Italy	9	2 – 13.3	3 M / 6 F
7.	Batra et al.	2006	Case report	UK	1	3	M
8.	Su et al.	2007	Case report	China	1	3	F
9.	Douyere et al.	2009	Case report	France	1	4	M
10.	Souza et al.	2010	Prospective cohort study	Brazil	14	4 – 26	5 M / 9 F
11.	Al-Jundi and Hazza'a	2010	Controlled cross-sectional	Jordan	21	4 – 16	7 M / 14 F
12.	Al-Jundi et al.	2011	Case report	Jordan	1	15	M
13.	Rabbani et al.	2012	Cross sectional	Iran	19	3 – 17	8 M / 11 F
14.	Beltes and Zachou	2012	Case report	Greece	1	15	M
15.	Andersen et al.	2012	Cross sectional	Denmark	16	5.7 – 18	5 M / 11 F
16.	Vital et al.	2012	Review	France and USA	-	Paediatrics	-
17.	Soares et al.	2013	Case report	Brazil	2	6 and 10	1 M / 1 F
18.	Hernández and Laguna	2013	Case report	Mexico	1	4	M
19.	Souza et al.	2013	Case report	Brazil	1	5	M

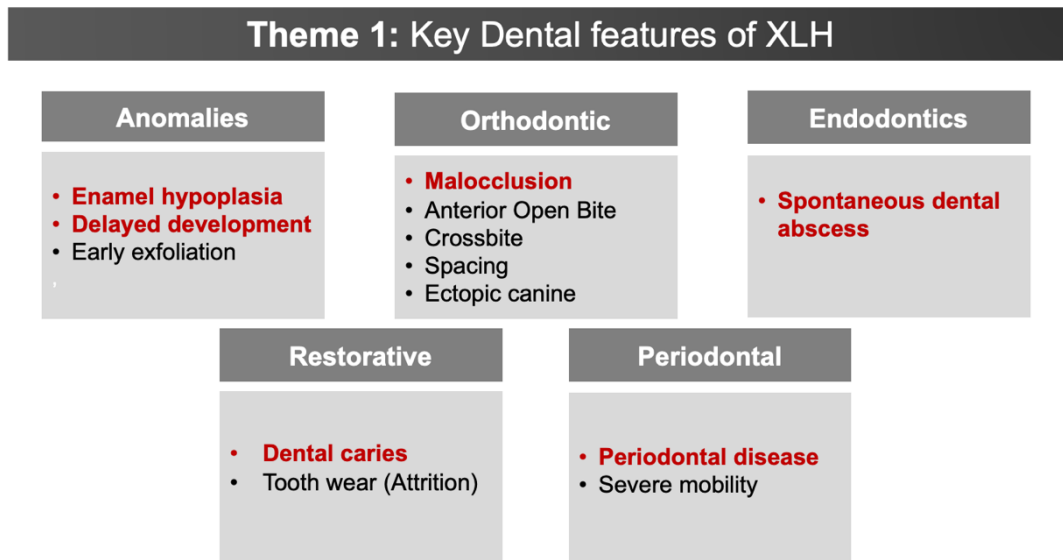
20.	Rathore et al.	2013	Case report	India	1	9	F
21.	Linglart et al.	2014	Review	France	-	Paediatrics	-
22.	Cremonesi et al.	2014	Case control	Italy	10	4 – 13	2 M / 8 F
23.	Sabandal et al.	2015	Review	Germany	-	Paediatrics	-
24.	Stinton et al.	2016	Case report	USA	1	14	M
25.	Lee et al.	2017	Case report	Korea	1	14	M
26.	Boukpepsi et al.	2017	Case series report	France	1	15	M
27.	Demirel et al.	2018	Case report	Turkey	1	4.5	F
28.	Paredes et al.	2018	Case report	Brazil	1	7	M
29.	Hughes and Hingston	2019	Case report	UK	1	3	M
30.	Makrygiannakis et al.	2020	Case report	Greece, UAE, and Cyprus	1	9	F
31.	Wato et al.	2020	Case report	Japan	1	1.5	M
32.	Marin et al.	2021	Cross-sectional	Chile and USA	6	5 – 16	3 M / 3 F
33.	Duplan et al.	2021	Expert opinion	France	-	Paediatrics	-
34.	Bradley et al.	2021	Case report	UK	1	16	M
35.	Baroncelli et al.	2021	Case control	Italy	24	3.8 – 8.2	9 M / 15 F
36.	Baroncelli and Mora	2021	Review	Italy	-	Paediatrics	-
37.	Gibson et al.	2021	Case report	UK	3	4 – 12	2 M / 1 F

**Table 3.1.** - Summary of articles included with year/type and country of publication

Gender: M = Male, F = Female, numbers indicate how many of each gender included

### 3.3.3.1. Theme 1: Key Dental features of XLH

Recognising dental manifestations of XLH is crucial, in milder cases, a paediatric dentist might be the first to identify the medical condition due to its distinctive dental characteristics (Seow, 2003). Fig 3.2. provides a summary of features frequently reported in the literature that will be discussed further in this chapter.



*Fig 3.2. Summary of key features of XLH with the red highlighting the most reported*

#### 3.3.3.1.1. Recurrent Spontaneous Dental Abscess

One of the main findings in XLH patients that was mentioned in 31 articles (83.7%) is recurrent spontaneous dental abscess in the absence of dental caries or trauma, which can affect both primary and permanent dentition (Linglart et al., 2014; Sabandal et al., 2015; Bradley et al., 2021). 6 out of 37 articles explored the prevalence of developing spontaneous tooth abscess. Table 3.2. outlined the prevalence of abscesses as reported in the literature, ranging from 7.1% to 100% in paediatric patients. Souza et al. (2010), conducted a prospective study in Brazil, aiming to verify the dental anomalies associated to XLH, they recruited 14 patients with age range of 4 to 26 years old, and only 1 participant (7.1%) experienced tooth abscess during the study. Similarly, Rabbani et al. (2012), published a cross-sectional study in Iran, recruiting and following up with 19 patients, age range of 3 to 17 years old for 3 years from 2008 to 2010. 2 patients (10.5%) reported dental abscesses, however nearly half of the patients experienced delay in eruption and enamel hypoplasia (47.7% and 42.1% respectively).

Baroncelli et al. in 2006 and 2021, concluded the same prevalence of spontaneous abscess of 67% in each trial. In 2006, a quasi-experiment of 9 patients between the age of 2 and 13.3

years, 6 out of 9 (67%) developed spontaneous abscesses. Whereas in 2021, the case control recruited more patients, 24 with age range of 4.2 to 7.4, and 16 of which (67%) reported a history of dental abscesses. The highest prevalence reported was by Shroff et al. (2002) who published a case report of 4 patients in the USA, with age range of 3 to 7 years old. All 4 patients (100%) presented with recurrent spontaneous tooth abscesses. This demonstrates a wide range in prevalence across the worldwide population.

**Table 3.2.** - Prevalence of Recurrent Spontaneous Dental Abscesses as reported in the literature

Authors	Year	Study Design	Number of participants	Age range (Years)	Abscess (%)
Shroff et al.	2002	Case report	4	3 - 7	100%
Baroncelli et al.	2006	Quasi-experiment	9	2 – 13.3	67%
Souza et al.	2010	Prospective study	14	4 - 26	7.1%
Rabbani et al.	2012	Cross Sectional	19	3 - 17	10.5%
Marin et al.	2021	Cross sectional	26 (6 children)	5 - 16	33%
Baroncelli et al.	2021	Case control	24	4.2 – 7.4	67%

Furthermore, Shroff et al. (2002) suggested that the first clinical abscess appears to occur prior to the age of 3 years and 9 months. This was supported by Fig 3.3. which shows dental abscesses of a 3-year-old male with XLH (Hughes and Hingston, 2019). Majority of articles confirmed that developing one dental abscess is a predictor of future abscesses (Beltes and Zachou, 2012). Seow (2003) published a literature review on unusual dental abscesses in children, stating that in XLH, the younger a patient exhibits their first abscess, the more severe the dental manifestations they will encounter in the future. One cross-sectional study in Denmark concluded that the number of affected teeth increase significantly with age. The study recruited a total of 52 patients, including 16 children with age range of 5.7 to 18 years old with the aim to assess and evaluate endodontically affected teeth (Andersen et al., 2012).

Alongside age, a few articles touched upon the influence of gender, Andersen et al. (2012) reported no statistical significance between gender difference with spontaneous abscesses. Nevertheless, Sanadal et al. (2015) review confirmed that gender distribution in published articles is balanced, they did note that post-puberty males developed more severe dental symptoms. Another trial by Chaussain-Miller et al. (2003) conducted a clinical trial in France, including 32 children, age range of 3 to 25, 20 females and 12 males, only 3 patients (9.4%) had developed spontaneous abscess on primary molars, and they were all boys.



**Fig 3.3.** Intraoral clinical photograph with arrows pointing out buccal sinuses on upper left central primary incisor (ULA) and lower right lateral primary incisor (LRB) in a 3-year-old male with XLH (Hughes and Hingston, 2019)

### 3.3.3.1.2. Malocclusion and Orthodontic implication

Following recurrent abscesses, malocclusion was the second most mentioned clinical feature, discussed in 8 articles (21.6%). The articles focused on anterior open bite (AOB), crossbite, canine malposition, skeletal abnormalities, and facial asymmetry. One prospective study of 14 patients, observed occlusal defects (AOB and/or crossbites) in 12 patients (85.7%) (Souza et al., 2010). Similarly, Hughes and Hingston (2019) published a case report of a 3-year-old male with XLH, it was noted that he has AOB and generalised spacing as seen in Fig 3.3. above.

The orthodontic treatment planning of XLH patients have been explored in the literature, with one case report by Makrygiannakis et al. (2020) providing clinical recommendations for orthodontists. The patient in the case report was a 9-year-old Caucasian female, with mild class III maxillary skeletal pattern and bilateral posterior crossbite. The success of orthodontic intervention confirms that patients with complex medical history can have the necessary treatment with no medical or dental complications (Makrygiannakis et al., 2020).

Other dental-related findings are delayed development, in both the primary and permanent dentitions (Lee et al., 2017). Delayed eruption and overall delayed dental development were reported in the literature 7 times (18.9%). Al-Jundi and Hazza'a (2010) assessed the dental development of XLH patients while comparing their results to healthy matched controls. The controlled cross-sectional study aimed to explore the relationship between medical management and dental development. They recruited 21 patients in Jordan, with age range of 4 to 16 years. Results show that 14 patients (66.6%) experienced significant dental delay varying from 0.2 to 2.5 years. Another previously mentioned cross-sectional by Rabbani et al. (2012), reported 9 out of 19 patients (47.7%) experienced delay in eruption during the three-year follow-up. This was further observed in a case report of a 14-year-old male with XLH in the USA who had delayed unerupted permanent teeth (Stinton et al., 2016). A more recent



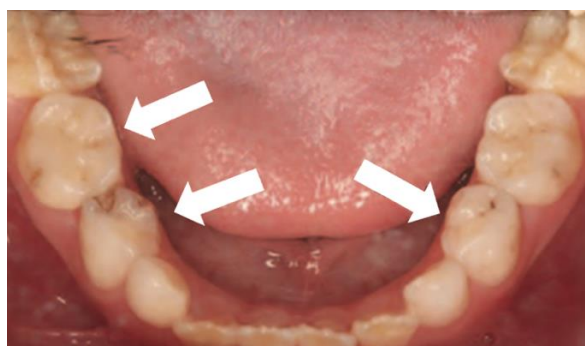
case review by Gibson et al. (2021), followed up with 7 XLH paediatric patients in the UK for 8 years, reporting the orthodontic clinical findings, including delayed dental development in 3 patients.

Less commonly reported were ectopic canines and facial asymmetry. A case report by Batra et al. (2006) in the UK, followed up with a 3-year-old male with XLH until the age of 11. They reported severely mispositioned canine which eventually required surgical removal. However, no other articles or trials reported such findings in their participants. Similarly, facial asymmetry was mentioned once in a case report of a 7-year-old male in Brazil (Paredes et al., 2018). Otherwise, facial asymmetry is not mentioned in any other case report or study.

### 3.3.3.1.3. Dental Caries and Attrition

Although articles state that spontaneous dental abscesses arise with the absence of dental caries or trauma, other causes of dental abscess may be due to dental caries. Caries have been reported in 8 out of 37 articles (21.6%) as a significant clinical finding of XLH patients. Marin et al. (2021), conducted a cross-sectional study comparing 6 XLH children (age range 5 to 16 years old) to the Chilean national average, and found that caries was higher in patients suffering XLH.

3 out of the 8 articles, were case reports of patients aged 4.5-, 9- and 15-year-old, all experiencing dental caries (Al-Jundi et al., 2011; Rathore et al., 2013 and Demireal et al., 2018). The case report from India, showed evidence of caries in all maxillary primary molars of the 9-year-old female (Rathore et al., 2013). Rabbani et al. (2012) also confirmed 9 out of 19 patients (47.7.%) reported dental caries. Fig 3.4. shows dental caries in primary teeth of an XLH paediatric patient (Liu et al., 2020). Additionally, in 2014, there was a case control observational study of 10 subjects with age range of 4 to 18 years old, where only 2 patients (20%) presented with clinically detectable dental caries, 8-year-old, and 10-year-old, however the remaining patients reported no carious lesions (Cremonesi et al., 2014).



**Fig 3.4.** Mandibular arch clinical photograph with dental caries in primary molars indicated by arrows (Liu et al., 2020)

Alongside dental caries, Duplan et al. (2021) published the French expert opinion regarding the dental manifestations of XLH with the exploration of prevention and appropriate management. They reported that attrition and incisal tooth wear is possible, thus requires monitoring and prevention. Fig 3.5. below demonstrates attrition of both upper primary central incisors, which in the case report of a 5-year-old male with XLH, was determined to be physiological, nevertheless, this patient suffered from recurrent spontaneous dental abscesses specifically to these teeth (Souza et al., 2013). Another similar case report from 2001, reported the clinical manifestations of a 16-year-old male with XLH, who reported experiencing necrotic pulp of teeth with incisal wear (Alexander et al., 2001).



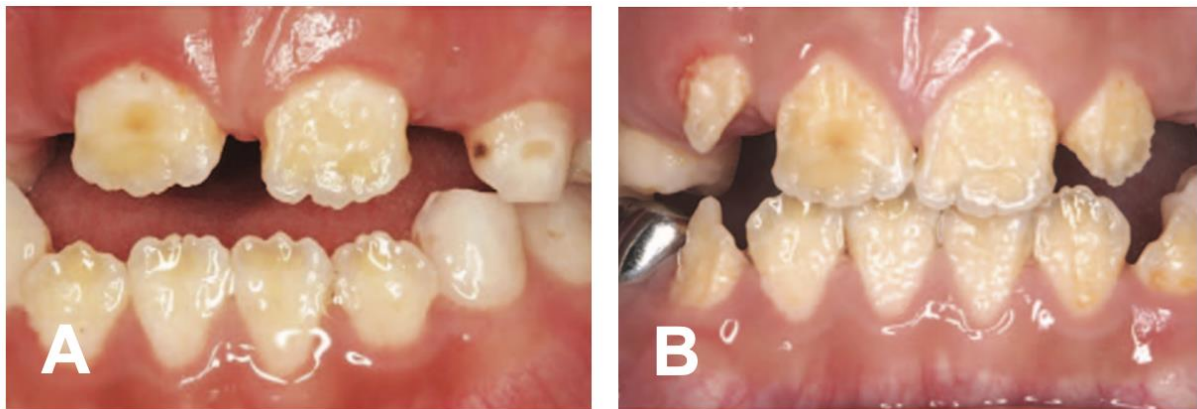
**Fig 3.5.** Maxillary arch clinical photograph demonstrating attrition of upper primary centrals (Souza et al., 2013)

#### 3.3.3.1.4. Dental Anomalies

Like development dental delay, enamel defects have been reported 7 times (18.9%) in this review, with hypoplasia being the most observed defect among XLH patients. 5 out of 7 articles reported enamel hypoplasia, which is a quantitative defect characterised by deficient thickness of enamel. One prospective cohort study by Souza et al. conducted in 2010, aimed to identify dental abnormalities of XLH paediatric patients, where they recruited 14 patients, with an age range of 4 to 26 years, concluding 8 patients (57.1%) were diagnosed with enamel hypoplasia. Another significant finding by Rabbani's cross-sectional study in 2012, reported that 8 out of 19 Iranian patients (42.1%) had enamel hypoplasia.

Moreover, Wato et al. (2020) published a case report of a Japanese male patient, who was clinically and radiographically monitored from 1 year and 5 months to 5 years and 7 months to observe any dental implications of XLH. The report observed colour change in primary anterior teeth, which is associated to the history of trauma, but also enamel hypoplasia was confirmed later. Also, the quasi-experiment in Italy, noticed that only 1 out of the 9 patients

(11.1%) had enamel hypoplasia, and two experienced enamel dyschromic alterations (22.2%). This signifies the importance of assessing dental anomalies in such cases, even if it is relatively rare (Baroncelli et al., 2006). One clinical trial investigated the frequency of enamel defects between permanent and primary teeth, they reported that white or brown enamel spots are more common on permanent teeth with 35%, in comparison to 8% in primary teeth (Chaussain-miller et al., 2003). Fig 3.6. demonstrated the same patient with 3 years difference, noticed that primary teeth appear to be less impacted, and permanent teeth deteriorated with time (Liu et al., 2020).



**Fig 3.6.** Frontal view clinical photographs of the same Chinese male with enamel hypoplasia  
(A) Age 10-years-old (B) Age 13 years old (Liu et al., 2020)

Other rare anomaly documented in the literature include premature or spontaneous exfoliation of teeth. Despite its rarity, it has been reported in 3 articles out of 37 (8.1%). Such abnormality was observed in Jordan, Brazil, and China, with varying ages of 3, 6 and 15 years old (Su et al., 2007; Al-Jundi et al., 2011; Soares et al., 2013). Differential medical diagnosis of this manifestation may be Papillon-Lefevre Syndrome; however, a thorough history taking, and clinical examination would determine the accurate diagnosis.

Another dental anomaly is fusion, which was reported twice in this review (5.4%), by case reports only. Fusion is a dental alteration characterised by the union of two separate developing tooth buds as seen in Fig 3.7. Such abnormality may be seen in primary and/or permanent dentition. However, in both case reports, it was only observed in primary teeth, no reports of fused permanent teeth (Hernández and Laguna, 2013; Souza et al., 2013).



**Fig 3.7.** *Intraoral clinical photograph of fused primary teeth (Souza et al., 2013)*

Finally, the rarest anomaly reported in an XLH patient was hypodontia, which was mentioned once by Lee et al. (2017). The case report is of a 14-year-old Korean male diagnosed with genetically missing upper left lateral incisor confirmed radiographically. No other mention of hypodontia in case reports or clinical trials, which may be an incidental finding.

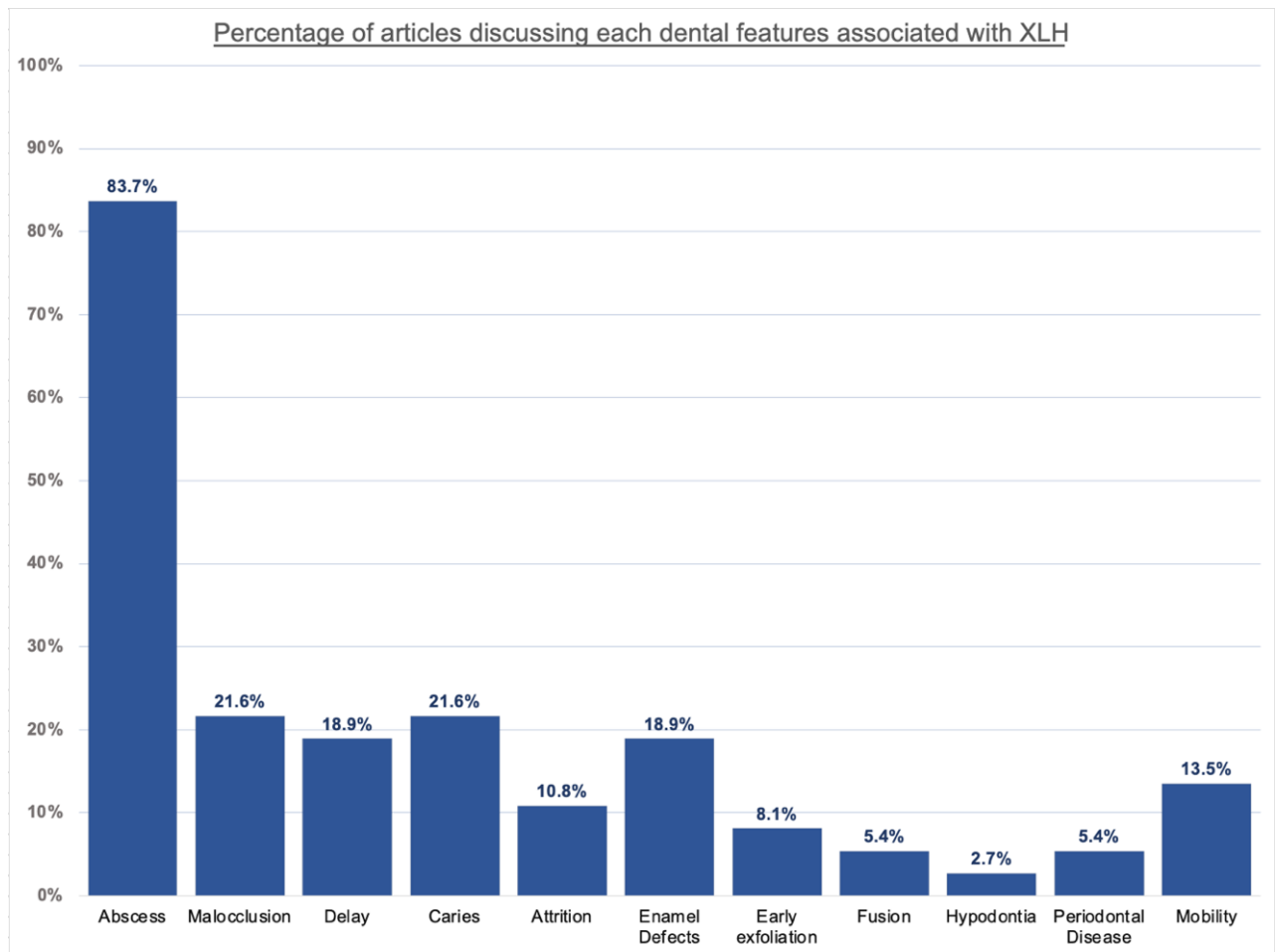
#### 3.3.3.1.5. Periodontal involvement

From this scoping review, the periodontal health of XLH patients has been the least investigated or discussed with only two studies, one in Jordan and the other in Iran. Al-Jundi et al. (2011) reported on a 15-year-old male patient with aggressive periodontitis, gingival inflammation, and poor oral hygiene. The detailed periodontal examination in this case revealed increased pocket depths with clinical attachment loss. Whereas Rabbani et al. (2012), reported two incidents of gingivitis, equivalent of 10.5% of participants in the cross-sectional study.

Furthermore, mobility was mentioned more frequently in 5 articles (13.5%), all of which were case reports. These reports were conducted in France, India, Brazil, Japan, and UK. 4 out of 5 were reporting increased mobility of primary teeth, for instance, Rathore et al. (2013) discussed manifestations of a 9-year-old female, who experienced mobility of maxillary primary molars. The only case report that explored mobility in permanent teeth was by Bradley et al. (2021), who evaluated a 16-year-old male with XLH. The clinical examination revealed upper left permanent central incisor (UL1) had a buccal swelling with grade 1 mobility (less than 1 mm movement horizontally). This confirms the importance of a thorough clinical examination.

The scoping review discussed all the possible dental manifestations that may be associated with XLH. The graph below summaries the key features, presenting recurrent spontaneous

dental abscesses as the most mentioned dental complication with 31 articles (83.7%) frequently associating it to XLH (See Fig 3.8). Malocclusion and dental caries follow with 21.6% each, as the second most featured clinical observation. However, the least discussed was hypodontia with one mention (2.7%), as it may be an incidental finding and unrelated to XLH as a medical condition.



**Fig 3.8.** Percentage of articles discussing the specific key features in the review

### 3.3.3.2. Theme 2: Key Radiographic features of XLH

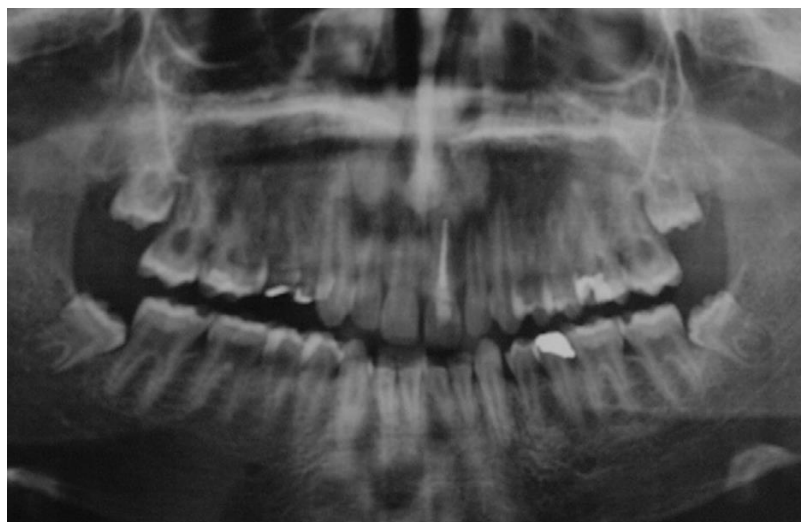
Accurately describing radiographic features is an essential clinical skill for any healthcare professional. When evaluating an XLH patient, a radiographic assessment may indicate several abnormalities affecting all dental tissues including, enamel, dentine, pulp, and root. Table 3.3. summarises the common radiographic features that will be discussed in this section.

**Table 3.3.** - Summary of key features of XLH as reported in the literature

Radiographic features
<ul style="list-style-type: none"><li>• Enlarged pulp chamber</li><li>• Pulp horns extending to DEJ</li><li>• Periapical radiolucency</li><li>• Taurodontism</li><li>• Short roots</li><li>• Thin enamel and dentine</li><li>• Root resorption</li><li>• Poorly defined lamina dura</li></ul>

### 3.3.3.2.1. Enamel

10 out of 37 articles (27%) explained the impact of such medical condition on the enamel layer of affected teeth. From this review, majority of the articles described the structure of enamel to be relatively normal but thin with evidence of microcracks. Such characteristics were mentioned 5 times, in 2 literature reviews, 2 case reports and 1 expert opinion. All supported that enamel layer will appear thinner with Duplan et al. (2021) suggesting slightly reduced radiopacity. Although the review by Linglart et al. (2014) confirmed that enamel is thinner, and dentine is more radiolucent. Two other case reports argued that not only is the enamel layer thin, but also dentine (Boukpepsi et al., 2017; Hughes and Hingston, 2019). Nevertheless, differentiating between enamel and dentine was discussed in a case report by Beltes and Zachou (2012), where they mentioned that there is evidence of a radiolucent band between the two layer as seen in Fig 3.9.



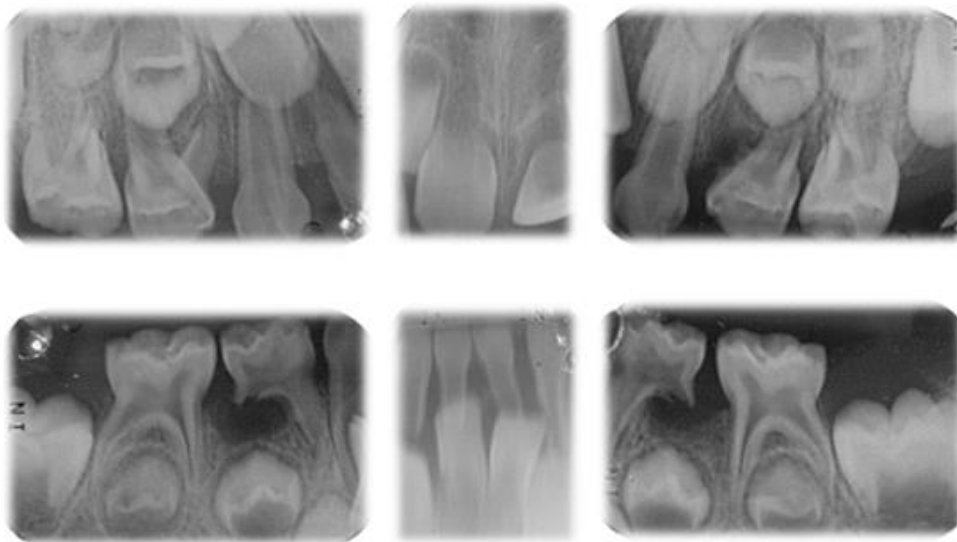
**Fig 3.9.** Evidence of radiolucent band between enamel and dentin (Beltes and Zachou, 2012)

Furthermore, enamel hypoplasia is a frequent clinical finding, which can be observed radiographically. 2 case reports recorded such radiographic finding in their results. Souza et al. (2010), found that 14.3% (2 out of 14) have both clinical and radiographic evidence of enamel hypoplasia. Rathore et al. (2013) also, presented a complex case of a 9-year-old patient with both enamel hypoplasia and dentine abnormalities. Although other studies have discussed hypoplasia as a clinical feature, they did not further elaborate on it radiographically.

### 3.3.3.2.2. Dentine

Of the 37 included studies, dentine was discussed more than enamel with 11 articles (29.7%). Generally, the affected teeth tend to exhibit a variety of dentinal defects. In the literature, the impact of XLH on dentine ranged from no affect to severe dentine abnormalities. Chaussain-Miller et al. (2003) confirmed that dentine is relatively normal in both primary and permanent dentitions. Nevertheless, the remaining 10 articles demonstrated the negative impact of XLH on such dental tissue.

Firstly, the detailed review by Seow (2003) on unusual dental abscesses, established that the dentine radiodensity is significantly reduced. The other literature review by Sabandal et al. (2015) determined the affected teeth tend to demonstrate significant dentinal defects that further lead to more dental complications. This is supported by both Souza et al. (2013) and Paredes et al. (2018), where they noted dental abnormalities such as irregular dentine layer in their patients (See Fig 3.10.). Another case report by Souza et al. (2010) also found radiographic evidence of dentine alterations in 14.3% patients (2 out 14).



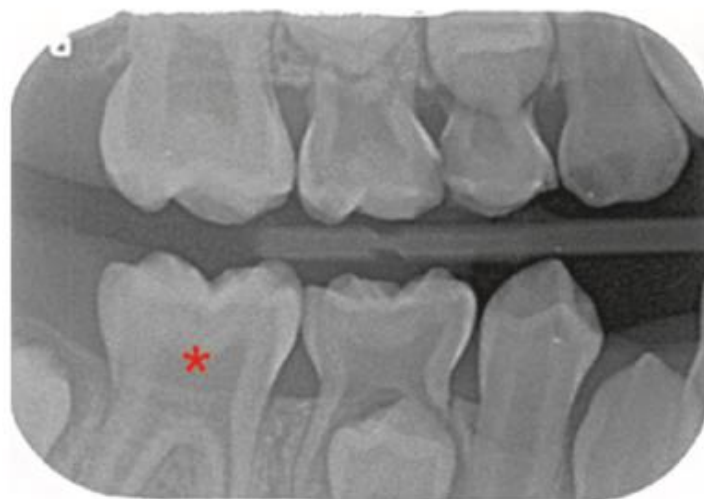
**Fig 3.10.** *Periapical radiographs of primary dentition showing irregular circumpulpal dentine (Paredes et al., 2018)*

Furthermore, as mentioned previously by Boukpepsi et al. (2017) and Hughes and Hingston (2019), both enamel and dentine are thin, this was further confirmed by Wato et al. (2020) who followed up with an XLH patient for 4 years until the age of 5, observing thinner dentine layer among other common radiographic features.

### 3.3.3.2.3. Pulp

The most significant radiographic finding in XLH patients is associated with the pulp, presenting as large chambers with abnormally high pulp horns extending to the dentino-enamel junction (DEJ). The statement “enlarged pulp chamber with prominent horns extending up to DEJ” was repeated a total of 13 times (35.1%) (Chaussain-Miller et al., 2003; Baroncelli et al., 2006; Su et al., 2007; Beltes and Zachou, 2012; Vital et al., 2012; Soares et al., 2013; Hernández and Laguna, 2013; Rathore et al., 2013; Linglart et al., 2014; Hughes and Hingston, 2019; Baroncelli et al., 2021; Duplan et al., 2021; Gibson et al., 2021). However, general characteristics of pulp whether the chamber or extension of horns was mentioned 29 times (78.4%).

In a prospective cohort study in Brazil, 6 out of 14 patients (42.8%) demonstrated radiographic evidence of enlarged pulp chambers (Souza et al., 2010). Such result was also obtained during the cross-sectional by Marin et al. (2021) with 94% of the patients showing pulpal chamber enlargement in both primary and permanent dentitions. Similarly, both Baroncelli et al. (2006) and Gibson et al. (2021) confirmed chamber enlargement with prominent pulp horns into tooth crown was a common finding in primary and permanent molars (See Fig 3.11).



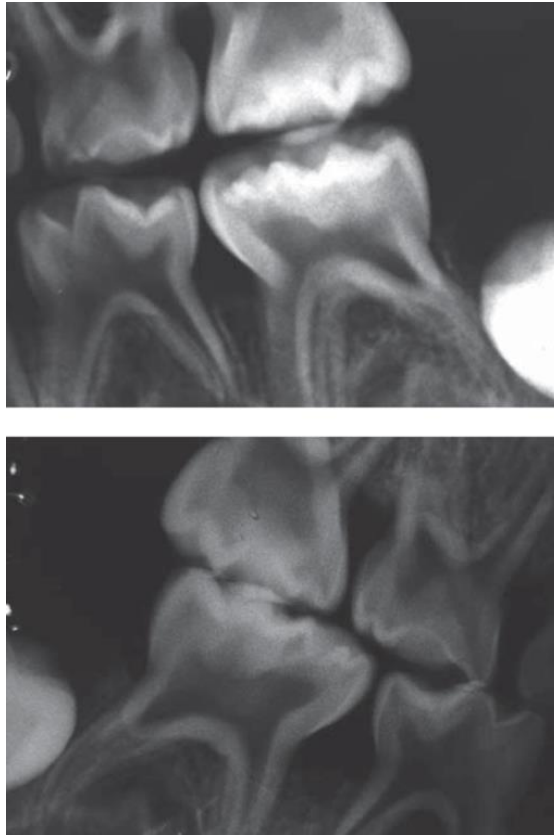
**Fig 3.11.** Horizontal bitewing of a 10-year-old XLH patient with evidence of enlarged pulp chamber and prominent pulp horns in both permanent and primary molars and (\*) shows Taurodontism of FPM (Duplan et al., 2021)



Furthermore, the clinical trial by Chaussain-Miller et al. (2003) also observed such pulpal enlargement with abnormally prominent pulp horns in both dentitions. Results from the trial showed that 70% of permanent teeth in paediatric patients had normal size pulp chamber, while 30% were enlarged. And in primary teeth, 88% exhibit normal pulp chamber and 12% were larger. Such outcomes may suggest that pulp is more affected in permanent teeth. This was identified by Rathore et al. (2013), who found all development permanent teeth in the case report, especially first permanent molars (FPMs) to have enlarged chambers. Whereas the case-control study by Cremonesi et al. (2014) detected 2 patients (20%) with such radiographic finding in the FPMs. Nevertheless, a few articles discussed the possibility pulp is less frequently affected in permanent teeth. This was supported by Su et al. (2007), who noted that the second primary molars, all exhibited large pulp horns extending to DEJ. And Soares et al. (2013) detected a close proximity of pulp horns to DEJ in all primary molars of a 6-year-old male.

Another important radiographic feature related to the pulp is taurodontism, which is often evident and specifically mentioned in 9 articles (24.3%) (Alexander et al., 2001; Chaussain-Miller et al., 2003; Seow, 2003; Rabbani et al., 2012; Soares et al., 2013; Linglart et al., 2014; Sabandal et al., 2015; Stinton et al., 2016; Gibson et al., 2021). The detection of taurodontism is discussed in a variety of study designs, 4 case report, 3 reviews, 1 clinical trial and 1 cross-sectional. One cross-sectional detected taurodontism in 15.8% of patients (3 out of 19) with age range of 3 to 17 years old, such finding was mainly observed in males, but the study did not specify if this was seen in permanent, primary or both dentitions (Rabbani et al., 2012). Nevertheless, Alexander et al. (2001) stated that such radiographic result is often observed in permanent molars, especially FPMs.

Alongside pulp chamber features, 2 articles briefly evaluated the radiographic effect of XLH on canals. For instance, Stinton et al. (2016) not only detected abnormalities in the pulp chamber, but also noted evidence of wider canal system. This was further confirmed by Bradley et al. (2021) where wide canal was seen in a patient presented with recurrent spontaneous signs of pulpal infection of otherwise intact teeth. Both case reports were of patients in the permanent dentition (14- and 16-year-old), nevertheless, Fig 3.12. demonstrates such finding in primary dentition as well (Souza et al., 2013).



**Fig 3.12.** Vertical bitewing radiograph of a patient in the primary dentition with evidence of enlarged pulp chambers with high horns extending to DEJ and wide canals (Souza et al., 2013)

#### 3.3.3.2.4. Root and surrounding structures

The impact of XLH is also observed around the root structures, causing noticeable changes and radiolucencies. Such changes are usually detected in the length, morphology, resorption, and maturation of dental roots. All of which were discussed 17 times in this review (45.9%). One relatively common radiographic finding is root resorption, with a total of 9 mentions in this review (24.3%). The highest level of evidence was the literature review by Sabandal et al. (2015) which elaborated that such resorption is more likely to be seen in primary dentition. This was supported by a case-control observational study which included a total of 10 paediatric patients, of which was an 8-year-old male with a fistula in the lower left second primary molar that resulted in a distal root resorption (Cremonesi et al., 2014).

The remaining 7 articles were all case reports, studying between 1 to 4 patients. Shroff et al. (2002) conducted a case study of 4 patients, one of which was a 4-year-old female with radiographs showing internal root resorption in 5 primary teeth and external resorption in 1 primary tooth. Similarly, a case report by Souares et al. (2013) evaluated 2 siblings, a 6-year-old male and his 10-year-old sister. The 6-year-old presented with advance root resorption in several primary teeth that led to premature exfoliation during early childhood (See Fig 3.13.).



**Fig 3.13.** Orthopantomograph (OPG) of a 6-year-old male with XLH, with classical radiographic features of enlarged pulp chambers in both primary and permanent dentition with evidence of premature loss of primary teeth (Soares et al., 2013)

Also, one case report that followed up with a 3-year-old patient until the age of 10, reported a spontaneous root resorption of lower left first primary molar when the patient was 5 years old, such finding was not mentioned in any other article (Batra et al., 2006). Nevertheless, not all reported resorptions were on primary teeth, Boukpepsi et al. (2017) published a case report of a 15-year-old male, in France with a periapical radiograph showing internal root resorption as seen in Fig 3.14. which was later endodontically treated.

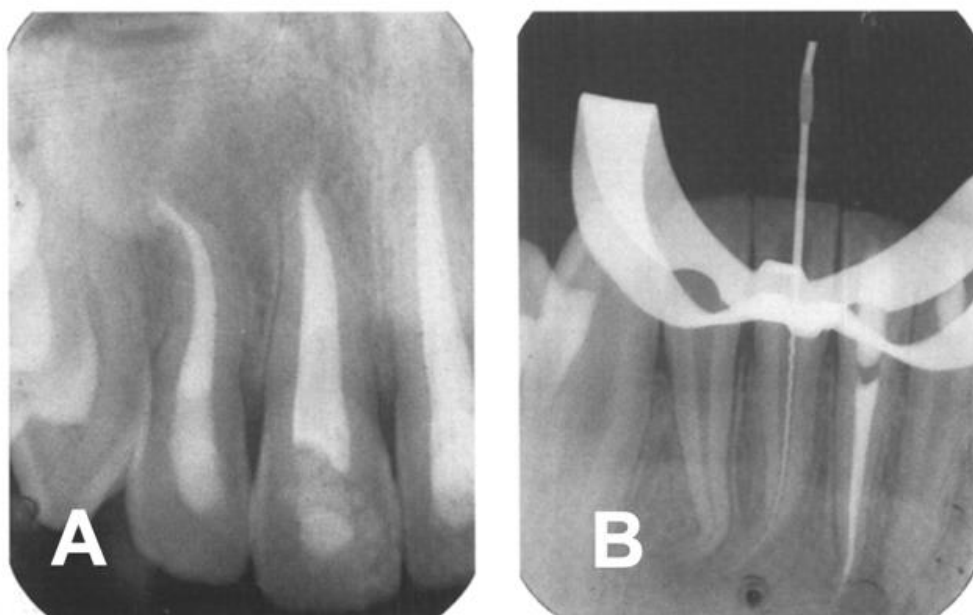


**Fig 3.14.** Periapical radiograph of lower left permanent central incisors with evidence of periapical lesion associated with internal and apical root resorption as indicated by the arrows (Boukpepsi et al., 2017)

Following root resorption, the discussion of length whether short or long was documented in 8 articles including 6 case reports, one literature review and one clinical trial. All case studies were reporting the outcome of a single XLH patient with age range of 3 to 16 years old, thus considering the impact on both primary and permanent dentitions. Most articles (7 out of 8)

agreed that with XLH, the roots are generally shorter than average in both dentitions (Murayama et al., 2000; Su et al., 2017; Rathore et al., 2013; Souza et al., 2013; Sabandal et al., 2015; Lee et al., 2017; Bradley et al., 2021). Su et al. (2007) specified short roots were often seen in mandibular central and lateral primary incisors. Nevertheless, Chaussain-Miller et al. (2003) observed the opposite in one of the 32 children recruited, stating that an Orthopantomograph (OPG) of a 15-year-old male with irregular compliance to medical treatment, showed short dental crowns and long roots.

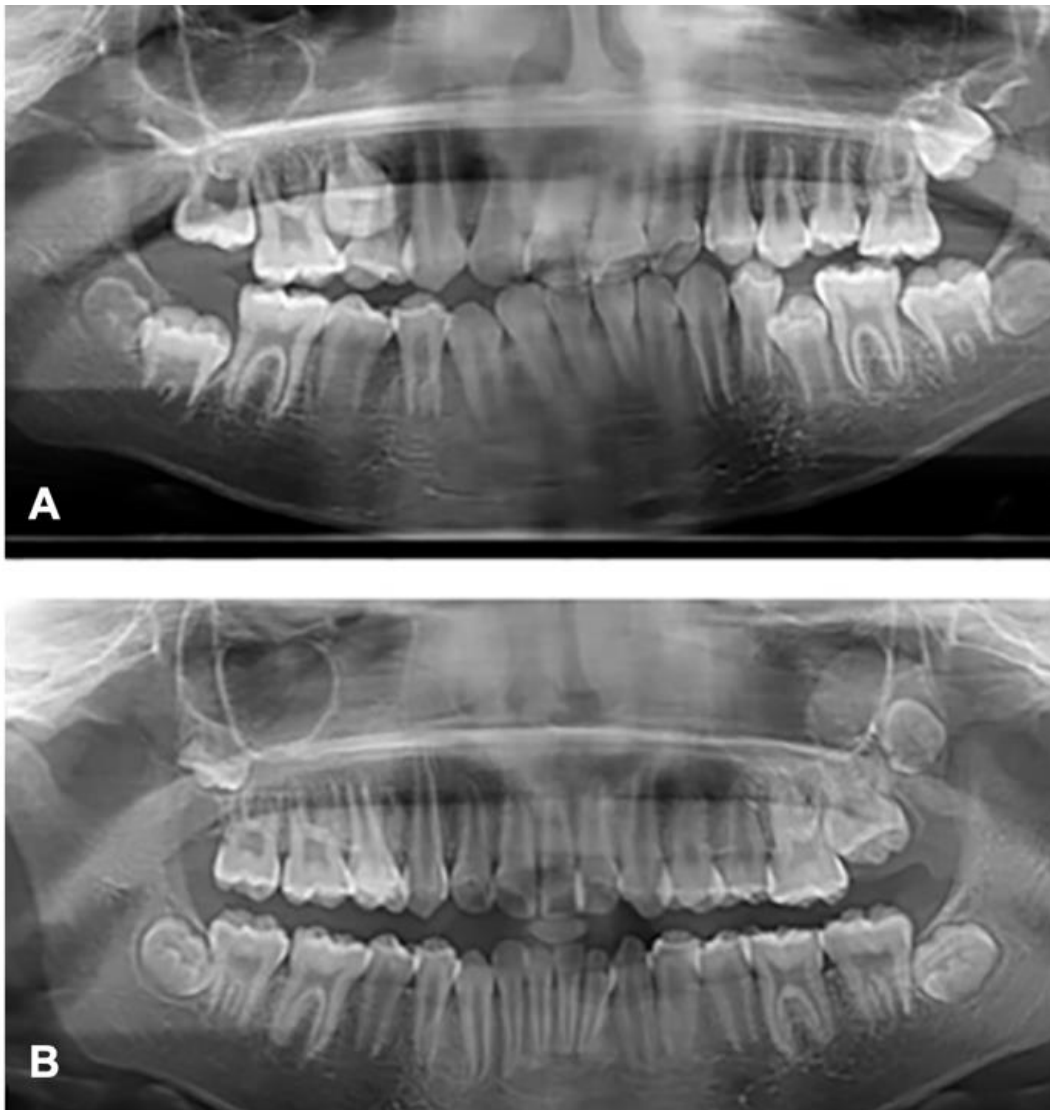
In terms of root morphology, Alexander et al. (2001) published a clinical review with a case report of a 16-year-old male diagnosed with XLH. The radiographic assessment demonstrated distinctive morphological changes, where upper right permanent lateral incisor and all four lower permanent incisors exhibited curvatures with evidence of periapical lesions that required endodontic treatment. Fig 3.15. show the periapical radiographs taken of upper and lower incisors revealing unusual root configurations. This was further supported by Duplan et al. (2021) and Gibson et al. (2021), who suggested a correlation between XLH and variation in shape and morphology.



**Fig 3.15.** (A) Periapical radiograph of successfully obturated upper right permanent lateral incisor with unusual root configuration (B) Periapical radiograph of lower permanent incisors with similar root curvatures mid-endodontic treatment (Alexander et al., 2001)

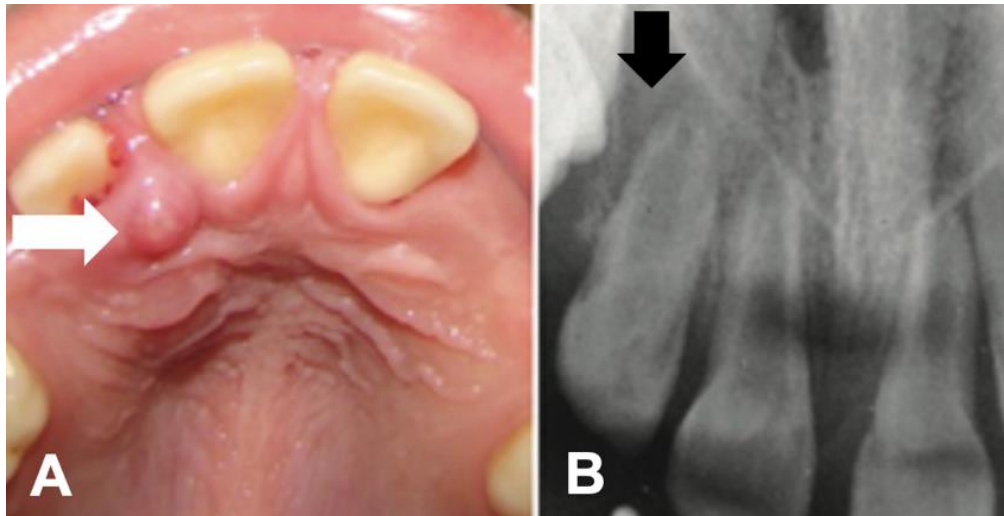
A rare radiographic observation that was mentioned twice in the 37 articles was root development and maturity. Although Chaussain-Miller et al. (2003) confirmed that most patients (78.5%) had normal root maturation of their permanent dentition with no sign of delay. Nevertheless, a case report by Gibson et al. (2021) followed up with 3 patients, one of which

was a 10-year-old female requiring fixed orthodontic treatment but exhibited developmental delay in root length and maturation as seen in Fig 3.16A. The OPG was repeated at the age of 13.5 years, which demonstrated slow progression (Fig 3.16B). Consequently, this led to postponing treatment until she showed appropriate development at the age of 14 and 6 months.



**Fig 3.16.** (A) OPG at the age of 10 years with evidence of immature root development  
(B) Repeat OPG of the same patient at the age of 13.5 years showing slow progression  
(Gibson et al., 2021)

Since recurrent spontaneous dental abscess is a significant clinical finding for XLH patients, it is frequently confirmed by a periapical radiolucency as a radiographic evidence (See Fig 3.17.). Such feature was covered 11 times (29.7%) in the included studies. Like the previous obtained results, majority were from case reports (8 out of 11). The remaining outcomes were from 1 literature review and 2 cross-sectional study.



**Fig 3.17. (A)** Clinical evidence of dental abscess associated to upper right permanent lateral incisor **(B)** Intraoral radiograph indicating periapical radiolucency related to the abscess (Soares et al., 2013)

One of the cross-sectionals aimed to describe the endodontic and periapical status of permanent teeth in XLH patients. 16 children were radiographically assessed, resulting in a total of five treated teeth, all were either incisors or canines. One lower lateral permanent incisor had a periapical radiolucency and required endodontic treatment, whereas the remaining four teeth were previously treated with signs of healing and lack of periapical radiolucencies (Andersen et al., 2012). The other cross-sectional by Marin et al. (2021) suggested that 74% of patients would exhibit radiolucent apical lesions during their lifetime. This is further reinforced as majority of the case reports (7 out of 8) observed periapical radiolucency of affected teeth (Murayama et al., 2000; Shroff et al., 2002; Beltes and Zachou, 2012; Demirel et al., 2018; Hughes and Hingston, 2019; Wato et al., 2020; Bradley et al., 2021). Such finding was not observed by Makrygiannakis et al. (2020) who aimed to provide orthodontic treatment for a 9-year-old female with mild Class III malocclusion.

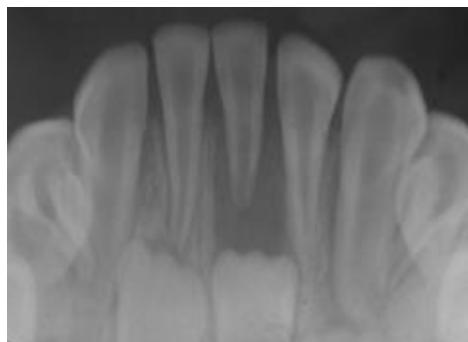
Other major findings were associated with periodontal ligament (PDL) and lamina dura. Lamina dura mentioned a total of 8 times (21.6%), whereas PDL only twice (5.4%). A case report in Japan, evaluated a 15-year-old male with XLH, clinically and radiographically. Among other relevant radiographic findings such as enlarged pulp, reduced dentine radiodensity and taurodontism, Fig 3.18. shows impact of XLH on lamina dura especially on incisors and premolars. It also shows root dysplasia of the lower left first premolar (Murayama et al., 2000).



**Fig 3.18.** Intraoral radiograph showing root dysplasia and absence of lamina dura in both lower left central permanent incisor and lower left first premolar (Murayama et al., 2000)

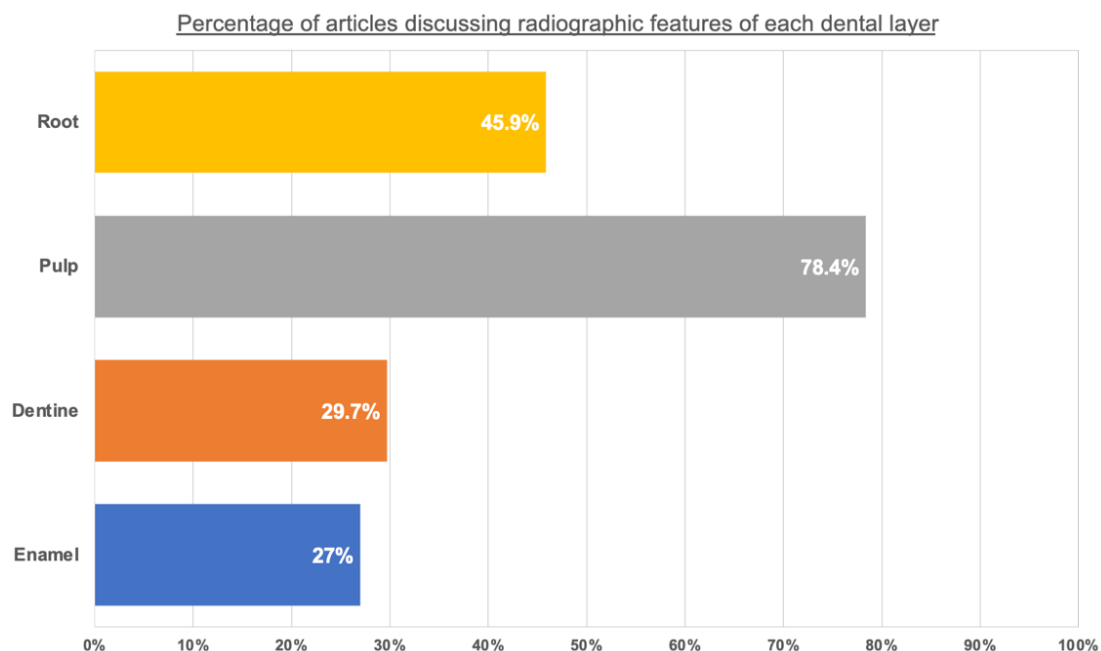
Generally, all 8 articles suggested that lamina dura would appear to be radiographically absent. This was confirmed by Sabandal et al. (2015), stating that such structure is poorly defined on an intraoral radiograph. A case report of a 14-year-old male in Korea showed that such absence may be complete or partial (Lee et al., 2017). Another report observed that such absence is evident in some areas in the permanent dentition of a 15-year-old male from Greece. The lamina dura in primary teeth were evaluated, were a 5-year-old male demonstrated poorly outlined structures (Souza et al., 2013). Moreover, Al-Jundi et al. (2011) provided a case report that showed both reduced radiopacity of lamina dura and evidence of widened PDL space. Such widening of PDL was documented in one other case report by Stinton et al. (2016) of a 14-year-old male with XLH.

Finally, the impact on alveolar bone was discussed in 5 articles (13.5%). 4 out of 5 were case reports, including patients with age range of 3 to 9 years old (Su et al., 2007; Douyere et al., 2009; Rathore et al., 2013; Souza et al., 2013). While the clinical trial by Chaussain-Miller et al. (2003) confirmed that 100% of patients demonstrated normal radiodensity of alveolar bone. The remaining studies detected hypoplastic alveolar ridge as a radiographic finding with XLH. Nevertheless, Douyere et al. (2009) evaluated a 4-year-old male clinically and radiographically, observing severe alveolar bone loss (See Fig 3.19.).



**Fig 3.19.** Intraoral radiograph of lower right central primary incisor with severe alveolar bone loss (Douyere et al., 2009)

Fig 3.20 provides a summary of the overall percentage of articles mentioning each dental layer and the associated radiographic features observed in the literature. Since dental abscesses were the most repeated clinical feature, pulp was the most discussed radiographic finding with 78.4% (29 out of 37 articles). Followed by dental root with nearly half the articles (45.9%) discussing distinctive changes in length, morphology, or formation. Both enamel and dentine were mentioned simultaneously with close percentages of 27% and 29.7% respectively.



**Fig 3.20.** Overall percentages of articles in the literature covering radiographic features depending on each dental layer

### 3.3.3.3. Theme 3: Dental management of XLH

Table 3.4. aimed to provide a concise list of all key features and dental management as suggested by the literature. There is currently no set guideline on clinical recommendations of dental manifestations associated with XLH, however from 1971 several studies have been published to explore treatment options and assess their success (Sabandal et al., 2015). The availability of tailored guideline for XLH dental management would allow clinicians - whether specialised or not - to establish an appropriate treatment plan in managing features such as recurrent dental abscesses. However, this review will discuss each aspect of dental management as reported by the literature.

#### 3.3.3.3.1. Preventive Care

XLH patients require comprehensive preventive measures throughout their dental journey, as signified by the number of articles detailing the specific precautions dental professionals should implement. Nearly half of the studies (45.9%) explored the options to maintain optimal



oral hygiene and reduce the likelihood of dental complications. The success of dental care relies not only on treatment provided, but also on preventative actions taken by the patient and the providing clinician.

Like all paediatric patients, oral hygiene instruction (OHI) is an essential part of any dental visit, aiming to reinforce an optimal daily routine. For XLH patients specifically, 7 articles emphasised the importance of maintaining good oral hygiene (Murayama et al., 2000; Baroncelli et al., 2006; Souza et al., 2010; Rabbani et al., 2012; Cremonesi et al., 2014; Makrygiannakis et al., 2020; Baroncelli and Mora, 2021). However, out of the 7 articles, only one elaborated on the specific hygiene instructions to provide patients and their families. Cremonesi et al. (2014) advised to educate patients on ideal toothbrushing and flossing techniques, while providing dietary recommendations such as avoiding cariogenic foods. This is considered the first line of defence against dental caries and/or abscesses (Cremonesi et al., 2014).

Additionally, topical application of fluoride varnish was recommended by 8 articles in this review. Literature suggests applying fluoride varnish (22,600 ppm) every 3-months as preventive measure (Murayama et al., 2000; Baroncelli et al., 2006; Su et al., 2007; Douyere et al., 2009; Souza et al., 2010; Rabbani et al., 2012; Sabandal et al., 2015; Baroncelli and Mora, 2021). For primary dentition, Su et al. (2007) specified applying the varnish to anterior teeth and use fissure sealants for primary molars. Topical application of fluoride varnish is confirmed to be appropriate evidence-based practice. Nevertheless, the quasi-experiment by Baroncelli et al. (2006) provided an outdated recommendation, which is the administration of systemic fluoride. This practice is no longer clinically justified, and application of varnish for both dentitions is sufficient.

Alongside OHI and fluoride varnish application, pit and fissure sealants are another clinical recommendation covered 12 times in this review from various study designs and methodologies (Baroncelli et al., 2006; Batra et al., 2006; Su et al., 2007; Douyere et al., 2009; Souza et al., 2010; Rabbani et al., 2012; Vital et al., 2012; Rathore et al., 2013; Linglart et al., 2014; Sabandal et al., 2015; Duplan et al., 2021; Baroncelli and Mora, 2021). Such approach is suggested to protect occlusal surfaces of both dentitions by preventing bacterial invasions to the pulp (Vital et al., 2012). Baroncelli et al. (2006) further elaborated sealants would reduce the risk of developing recurrent spontaneous abscesses as it has the potential to prevent the penetration of microorganisms through dentinal abnormalities and irregularities.

Batra et al. (2006) and Douyere et al. (2009) suggested placing fissure sealants on permanent molars as a prophylactic measure. Su et al. (2007) supported such treatment to primary molars as well permanent. To prevent dental abscesses, Linglart et al. (2014) instructed sealing tooth surfaces of both dentitions as soon as clinically possible. Moreover, the choice of sealant material was a major factor, as 5 articles advised the use of flowable resin composite (Douyere et al., 2009; Rathore et al., 2013; Linglart et al., 2014; Sabandal et al., 2015; Duplan et al., 2021). The initial reference to recommend such material for fissure sealants was by Douyere et al. (2009), which also specified to reapply after 10 months to ensure its clinically intact. Additionally, the use of flowable resin was not only suggested for permanent teeth, but also for primary molars (Rathore et al., 2013; Sabandal et al., 2015; Duplan et al., 2021).

Finally, frequent dental visits were suggested by 12 authors to ensure close monitoring and follow up (Alexander et al., 2001; Baroncelli et al., 2006, Souza et al., 2010; Rabbani et al., 2012; Vital et al., 2012; Soares et al., 2013; Rathore et al., 2013; Sabandal et al., 2015; Hughes and Hingston, 2019; Makrygiannakis et al., 2020; Duplan et al., 2021; Baroncelli and Mora, 2021). Due to patients' history with recurrent spontaneous abscesses, Alexander et al. (2001) recommended regular reviews as more dental complications in the future may arise. Thus, dental care involving detailed history taking and periodic examination with periodontal health assessment is essential (Rabbani et al., 2012; Makrygiannakis et al., 2020). Both Vital et al. (2012) and Baroncelli and Mora (2021) advised dental assessments should be carried out twice a year (i.e., every 6 months). Nevertheless, Soares et al. (2013) explained that XLH paediatric patients should be treated as high-carries risk patients with recall intervals of 3-months instead of 6-months. Although the expert opinion by Duplan et al. (2021) confirmed intervals between appointments of 6 to 12 months for XLH patients is appropriate. Hughes and Hingston (2019) debated that a shorter interval such as 3 to 6 months is more realistic. Literature also implied dental care should be provided by a specialist, such as paediatric dentist to deliver prompt diagnosis, tailored treatment plan and early intervention (Baroncelli et al., 2006).

### 3.3.3.3.2. Endodontic

The most covered dental management approach in this scoping review is endodontic treatment with a total of 23 articles (62.1%). The treatment is indicated as an appropriate treatment measure for abscessed teeth (Alexander et al., 2001). Hernández and Laguna (2013) decided to proceed with pulpectomy on abscessed primary teeth with evidence of fistula, while providing prophylactic pulpotomies on the remaining asymptomatic primary teeth. The justification of such approach was based on the premise that if a patient experiences one

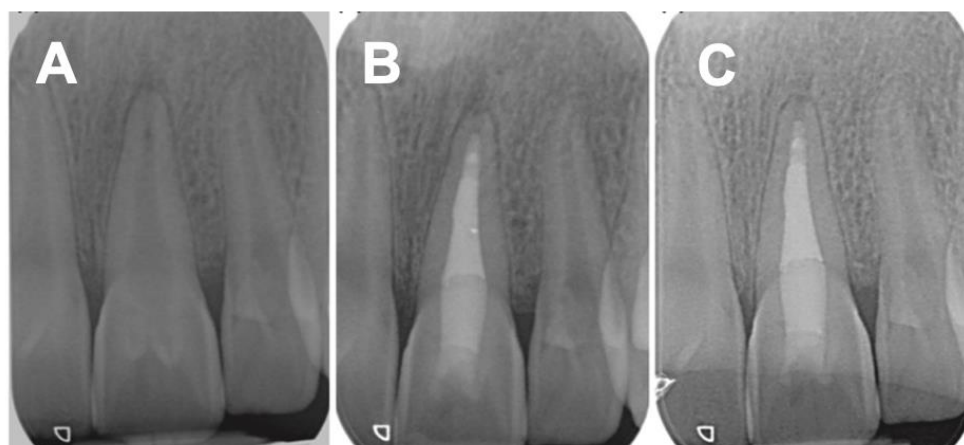
abscess, they are likely to be susceptible to develop more. Another case report aimed to evaluate the impact of aggressive preventative pulp therapy for 4 young patients (age range 3 to 7 years old), results confirmed the management failed clinically (Shroff et al., 2002). Rabbani et al. (2012) suggested that this treatment does not provide any benefit in maintaining the primary dentition of XLH paediatric patients. Nevertheless, pulp therapy remains an option for primary teeth when justified, for instance, a 5-year-old male with multiple recurrent infections underwent pulpectomy of all abscessed anterior and posterior primary teeth, and in his six-month follow up, the child did not show any clinical signs of recurrent abscesses, proving success of treatment (Souza et al., 2013).

The remaining articles highlighted the options for abscessed permanent teeth. Unlike primary teeth, root canal treatment (RCT) as a preventive measure was not explored. RCT is considered when there are clinical signs and symptoms of dental infections. Murayama et al. (2000) was the only article in this review to discuss incision and drainage of an abscess to relieve pain. In this case report, no dental or periodontal abnormalities identified, nevertheless due to recurrent abscesses, RCT was performed (Murayama et al., 2000). Beltes and Zachou (2012) published a case report of a 15-year-old male in Greece with multiple RCTs due spontaneous abscesses, and during his 6-month, 1-year and 2-year follow-ups, radiographic assessment revealed signs of bone healing with absence of clinical complications.

Two trials evaluated the number of patients with endodontically treated teeth. Chaussain-Miller et al. (2003) found 10 out of 32 patients required RCT (6 males and 4 females), indicating the mean percentage of treated teeth per patient is low (4%). The other trial explained 1 out of 9 patients underwent endodontic treatment due to abscess formations, patient was 13.3 years old, she was the eldest participant. When abscesses occur, conventional endodontic treatment should be performed on permanent teeth (Vital et al., 2012). Both Linglart et al. (2014) and Sabandal et al. (2015) suggested conventional endodontic treatment for abscessed permanent teeth, followed by a definitive restoration such as a crown. This was demonstrated in a case report by Lee et al. (2017), where a 14-year-old male required RCTs to manage 3 abscessed first permanent molars, all of which were restored with definitive crowns.

When providing RCT, quality of root filling should be excellent, Boukpepsi et al. (2017) recommended filling the access cavity with GIC and restore with resin composite or definitive crown, depending on the tooth and remaining structure. Thermoplasticised obturation technique is the ideal choice, however in cases such as Fig 3.21. where a 16-year-old male

has wide canal and an open apex, it is suggested to place mineral trioxide aggregate (MTA) plug.



**Fig 3.21. (A)** Periapical radiograph of upper left central incisor with dens in dente, wide canal, open apex, and apical radiolucency **(B)** Post-RCT demonstrating satisfactory root filling **(C)** 8-month review radiograph with evidence of healing (Bradley et al., 2021)

### 3.3.3.3.3. Extraction

An alternative treatment option for primary or permanent abscessed teeth is dental extraction which was suggested 37.8% (14 out of 37) in this scoping review. To prevent further abscess formation of primary teeth, Batra et al. (2006) recommended extractions under local anaesthesia (LA) as a first-line treatment. This was encouraged by Vital et al. (2012), who elaborated that when a primary tooth presents with an abscess, then dental extraction is the favoured treatment option as endodontic may not prevent recurrent abscesses, leading to further dental complications which may impact the developing permanent successor. Additionally, this was supported by Cremonesi et al. (2014) and Hughes and Hingston (2019), both of which recommended to extract primary teeth instead of attempting to provide endodontic treatment. Soares et al. (2013) also suggested to consider extraction if no adequate bone support or endodontic treatment is unfeasible. One case report provided the necessary treatment for a 4-year-old male with XLH experiencing recurrent abscesses and severe mobility, a clinical decision was made to extract 5 primary teeth as endodontic treatment is not justified in this case (Douyere et al., 2009).

When obtaining dental history of another 4-year-old male patient, from the case report it was evident that all abscessed primary teeth were extracted by their previous dentist (Hernández and Laguna, 2013). However, Al-Jundi et al. (2011) mentioned early loss of FPMs in their case report was due to caries instead of recurrent dental abscesses. Thus, it is fundamental to obtain a thorough history to determine the cause of early loss or extraction. It is also important to investigate the frequency of antibiotic intake. 3 articles discussed providing antibiotics prior

to extractions, however, this does not seem to be a standard practice of care but instead a clinical decision by the dentist (Hughes and Hingston, 2019; Duplan et al., 2021). Baroncelli and Mora (2021) suggested considering antibiotics only if the acute abscess is severe, specifying the choice of antibiotics would be amoxicillin and metronidazole.

#### 3.3.3.3.4. Restorative

Providing an appropriate restorative treatment may prevent further complications and lead to increased dental longevity. Such aspect of management was discussed 35.1% (13 out of 37), covering a variety of treatment options such as, prophylactic preformed metal crowns (PMCs), resin composite restoration, glass ionomer cement (GIC), lab-fabricated crowns and/or definitive crowns.

For anterior teeth, the main management strategy focuses on preventing pulpal abscesses. For primary incisors, Seow (2003) recommended restoring teeth when possible and suggested using resin composite as the ideal restorative material of choice. Nevertheless, Hernández, and Laguna (2013) suggested an alternative material such as GIC to provide a more conservative treatment, avoiding the need of etching or rinsing. One unconventional treatment was provided by Hughes and Hingston (2019) for a 3-year-old male patient. Treatment required silicone impressions followed by laboratory-fabricated full coverage composite crowns to restore maxillary lateral incisors and all canines. Fig 3.22. shows post-operative results after cementing crowns with opaque Panavia, demonstrating excellent margins and overall aesthetics.



**Fig 3.22.** Post-treatment of a 3-year-old patient with full coverage crowns on anterior teeth and Prophylactic PMCs on posterior teeth (Hughes and Hingston, 2019)

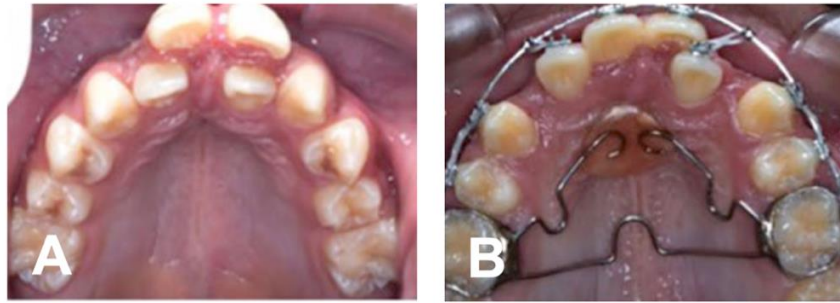
On the other hand, Cremonesi et al. (2014) suggested to provide restorations for anterior permanent teeth when possible and make a clinical decision on which teeth to restore. Nevertheless, all 3 studies recommended restoring incisors or canines with resin composite as the only suitable dental material (Boukepssi et al., 2017 and Demirel et al., 2018).

For posterior primary teeth, 8 articles suggested PMCs, whether as prophylactic measure or after endodontic treatment. Murayama et al. (2000) confirmed that prophylactic PMCs of teeth with no evidence of dental caries is effective in preventing tooth wear or enamel microfracture. Seow (2003) recommended to provide such approach without preparation utilising the Hall technique to reduce the risk of pulpal exposure that may occur with conventional techniques. This was the technique used by Hughes and Hingston (2019) as seen in Fig 3.22 for prophylactic placement of PMCs on all primary molars.

However, restoring permanent posterior teeth would require a more definitive and long-term management. Thus, Seow (2003) suggested as soon as molars are partially erupting, restoring the occlusal surfaces with dental material such as resin composite would protect the teeth from developing dental abscesses. For abscessed permanent molars, clinical recommendation was to provide RCT followed by a definitive crown. The material and type of crown was not specified, but options may range from gold or stainless steel to porcelain. Alexander et al. (2001) recommended the use of full veneer gold crowns.

#### 3.3.3.3.5. Orthodontic

Orthodontic assessment is an essential part of examining a patient in the mixed dentition to evaluate their malocclusion and determine any orthodontic needs. However, with XLH patients, because of the recurrent spontaneous abscesses and increased evidence of root resorption, some orthodontists may be reluctant to provide the necessary treatment and advise to accept the malocclusion. Nevertheless, out of the 5 articles (13.5%) that explored orthodontic interventions, 3 concluded that such treatment is not contraindicated if XLH is medically well-managed and patients proved to have optimal oral hygiene (Vital et al., 2012; Linglart et al., 2014; Makrygiannakis et al., 2020). The case report by Makrygiannakis et al. (2020) discussed the importance of closely collaborating with the patient's medical team to ensure no complications arise from the treatment. Fig 3.23. shows the possibility of providing a successful orthodontic treatment.



**Fig 3.23.** (A) Pre-orthodontic treatment (B) Mid-orthodontic treatment (Gibson et al., 2021)

The remaining 2 articles were case reports that explored the use of space maintenance in certain situations (Soares et al., 2013; Souza et al., 2013). For instance, Soares et al. (2013) suggested to consider space maintainer when needed. Whereas Souza et al. (2013) explained that due to early loss of primary molars, some clinicians proceed with fixed space maintainers to prevent crowding in the future (See Fig 3.24.). However, it is important to recall Soares et al. (2013) statement that ‘XLH paediatric patients should be treated as part of high-carries risk category’, thus a space maintainer may be contraindicated and should rely on a justified clinical decision.



**Fig 3.24.** Fixed space maintainers for both upper and lower arches (Souza et al., 2013)

### 3.3.3.3.6. Periodontal

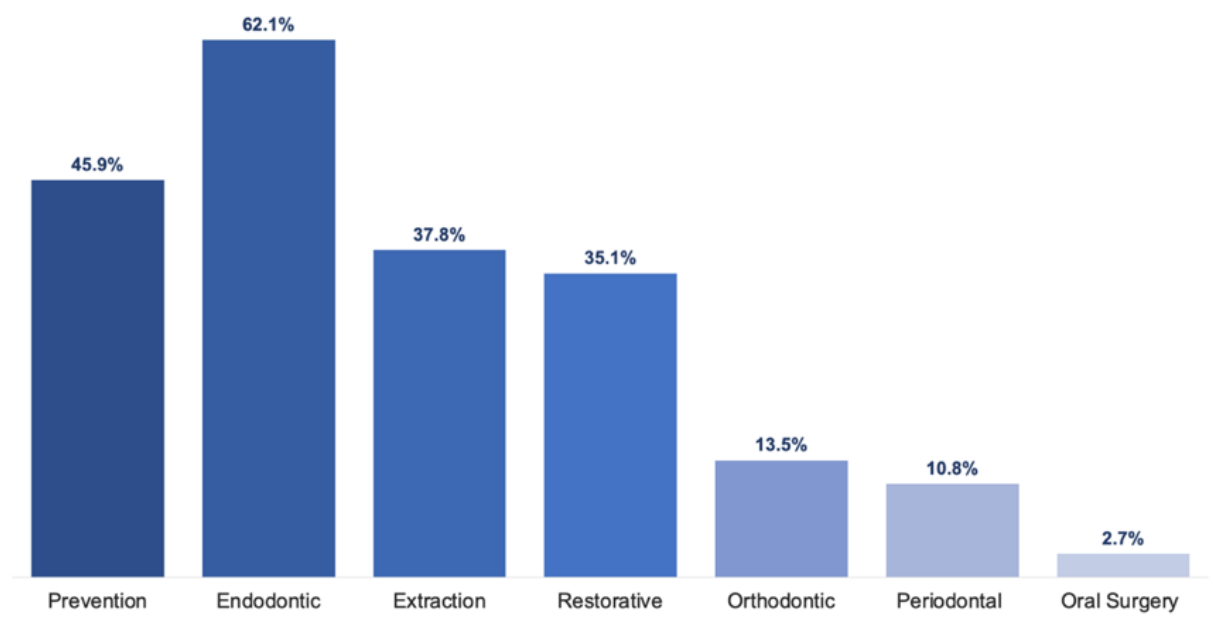
Documenting Basic Periodontal Examination (BPE) score of all patients above the age of 7 is standard practice. Such assessment would determine if there were any periodontal involvement and whether a referral to a specialist is needed. 4 out of 37 articles (10.8%) discussed periodontal management. In a case report by Al-Jundi et al. (2011), referral to the periodontal for scaling and polishing was advised, with the need to prescribe chlorhexidine gel 0.2%. Similarly, Douyere et al. (2009) proposed prophylactic ultrasonic or hand scaling every 3 to 6 months. This was further supported by Soares et al. (2013) as they suggested to closely monitor XLH patients and assess every 3 months when periodontal disease is evident. Of all articles included, only one patient needed a full-mouth debridement, such case is rare for a young patient, but a proper assessment was useful to determine this promptly (Stinton et al., 2016).

### 3.3.3.3.7. Oral Surgery

Finally, the oral surgery department is needed as part of the multidisciplinary team, especially in cases where ectopic canine is evident. This feature was only discussed in one publication (2.7%) (Batra et al., 2006). Nevertheless, such finding may be associated to other XLH patients. Thus, the clinical decision of appropriate management would depend on a collaboration between paediatric dentist, orthodontist, and oral surgeon to determine whether such ectopic tooth can be aligned or should be extracted.

To summarise the key aspects of dental management, Fig 3.25. demonstrates the overall percentages of each included treatment, confirming that endodontics is the most discussed, while oral surgery is the least. The graph shows that endodontic therapy is the most recommended management of dental abscesses with 62.1%, followed by dental extraction with 37.8%. However, regarding the general management, preventative approach was advised by nearly half the articles with 45.9%. The least discussed treatments were periodontal and oral surgery with 10.8% and 2.7% respectively. Nevertheless, 13.5% demonstrated that orthodontic treatment is not contraindicated, leading to successful outcomes without complications with the need of close monitoring.

Percentage of articles discussing different aspects of dental management



**Fig 3.25.** Percentage of articles discussing different aspects of dental management in the review



**Table 3.4. - Summary of scoping review results of dental features and management**

<b>Author</b>	<b>Dental Findings</b>	<b>Dental management</b>
<b>Murayama et al.</b>	Recurrent spontaneous abscess	Incision and drainage, endodontic treatment, PMC for primary molars
<b>Alexander et al.</b>	Recurrent spontaneous abscess, incisal wear	Endodontic treatment, PMC for primary molars and gold crown for permanent molars
<b>Shroff et al.</b>	Recurrent spontaneous abscess	Prophylactic pulpotomy and stainless-steel crown of primary molars
<b>Chaussain-Miller et al.</b>	Recurrent spontaneous abscess, enamel defects	Endodontic treatment
<b>Seow</b>	Recurrent spontaneous abscess	Resin composite (primary incisors and partially erupted permanent molars) and prophylactic PMC (primary and permanent molars)
<b>Baroncelli et al.</b>	Recurrent spontaneous abscess, enamel hypoplasia	Endodontic treatment
<b>Batra et al.</b>	Recurrent spontaneous abscess, AOB, mal-positioned canine	Extraction of primary teeth with history of abscess, prophylactic PMC remaining primary molars, fissures sealants of permanent teeth
<b>Su et al.</b>	Early spontaneous exfoliation intact primary teeth	Topical fluoride and fissure sealants to primary molars
<b>Douyere et al.</b>	Recurrent spontaneous abscesses, severe mobility	Topical fluoride, extraction, endodontic treatment, fluid resin composite on all occlusal surfaces and prophylactic fissure sealants on FPMs
<b>Souza et al.</b>	Recurrent spontaneous abscesses, enamel hypoplasia, malocclusion	Topical fluoride, fissure sealants and maintenance of good oral hygiene
<b>Al-Jundi and Hazza'a</b>	Delayed dental development, malocclusion	Early intervention to prevent permanent deficit in development
<b>Al-Jundi et al.</b>	Spontaneous loss of permanent teeth, caries, and malocclusion	Referral to periodontal department, scaling, chlorhexidine gel 0.2%, extraction, and removable prosthesis

<b><i>Rabbani et al.</i></b>	Recurrent spontaneous abscess, caries, delay in eruption, enamel hypoplasia	Topical fluoride, fissure sealants and maintenance of good oral hygiene
<b><i>Beltes and Zachou</i></b>	Recurrent spontaneous abscess	Endodontic treatment, prophylactic PMC of primary molars
<b><i>Andersen et al.</i></b>	Recurrent spontaneous abscess	Endodontic treatment and preventative dental care
<b><i>Vital et al.</i></b>	Recurrent spontaneous abscess, severe dental anomalies	Early sealants, endodontic treatment of permanent teeth, extraction of primary teeth, and prevention of attrition
<b><i>Soares et al.</i></b>	Recurrent spontaneous abscess, premature tooth loss	Extraction, endodontic treatment, composite and/or sealants
<b><i>Hernández and Laguna</i></b>	Recurrent spontaneous abscess, fistula, fusion of primary teeth	Pulpectomies, prophylactic pulpotomies, PMC in primary molars, and composite resin in anterior teeth
<b><i>Souza et al.</i></b>	Recurrent spontaneous abscess, wear, fusion of primary teeth	Extraction, endodontic treatment, and space maintainer
<b><i>Rathore et al.</i></b>	Edentulous mandibular arch, caries, mobility	Pulpotomies of carious primary molars and preventive resin restorations on the remaining molars
<b><i>Linglart et al.</i></b>	Recurrent spontaneous abscess, enamel microcracks	Endodontic treatment, extraction for primary and sealant with resin
<b><i>Cremonesi et al.</i></b>	Recurrent spontaneous abscess, caries, enamel hypoplasia	Extraction of primary abscessed teeth, endodontic treatment of permanent teeth, and restorations
<b><i>Sabandal et al.</i></b>	Recurrent spontaneous abscess, delayed eruption	RCT of permanent teeth followed by definitive crown and prophylactic PMC of primary molars
<b><i>Stinton et al.</i></b>	Recurrent spontaneous abscess, delayed dental development	Emergency extraction and full-mouth debridement
<b><i>Lee et al.</i></b>	Recurrent spontaneous abscess, delayed eruption, hypodontia	Endodontic treatment

<b><i>Boukpepsi et al.</i></b>	Recurrent spontaneous abscess	Antibiotics and endodontic treatment
<b><i>Demireal et al.</i></b>	Recurrent spontaneous abscess, caries, deep palatal vault	Extraction, and restoration with resin composite
<b><i>Paredes et al.</i></b>	Recurrent spontaneous abscess, facial asymmetry, mobility	Extraction
<b><i>Hughes and Hingston</i></b>	Recurrent spontaneous abscess, delayed eruption, AOB, caries	Antibiotics, prophylactic PMC of all primary molars (hall technique), lab-made full coverage composite crowns of anterior teeth and extraction of abscessed teeth
<b><i>Makrygiannakis et al.</i></b>	Class III maxillary skeletal pattern, posterior crossbite	Orthodontic treatment with fixed appliance
<b><i>Wato et al.</i></b>	Tooth colour change, mobility, and enamel hypoplasia	Endodontic treatment
<b><i>Marin et al.</i></b>	Recurrent spontaneous abscess, caries	Endodontic treatment
<b><i>Duplan et al.</i></b>	Recurrent spontaneous abscess, enamel hypoplasia, attrition, caries, malocclusion	Endodontic treatment or extraction of abscessed teeth, fissure sealants
<b><i>Bradley et al.</i></b>	Recurrent spontaneous abscess, sinus, and mobility	Endodontic treatment (MTA plug)
<b><i>Baroncelli et al.</i></b>	Recurrent spontaneous abscess	
<b><i>Baroncelli and Mora</i></b>	Recurrent spontaneous abscesses with fistulae	Topical fluoride, fissure sealants and maintenance of good oral hygiene, extraction, endodontic treatment
<b><i>Gibson et al.</i></b>	Recurrent spontaneous abscess, delayed dental development	Endodontic treatment, extraction for orthodontic reasons, orthodontic treatment

#### 3.3.3.4. Theme 4: Special clinical considerations

In this section, a detailed discussion of the specific clinical considerations in the current literature will be reported. The recommendations focused on medical and dental managements, to assess any improvements or adjustments in standard of care is required.

##### 3.3.3.4.1 Medical management

6 articles have discussed the importance of early medical intervention to guarantee optimal medical and dental outcomes. Souza et al. (2010) and Rathore et al. (2013) reported that early diagnosis and treatment may potentially prevent dental abscess formation in the future. This was reinforced by Al-Jundi and Hazza'a (2010), as any delay in commencing medical treatment can lead to abnormalities in dental development especially on permanent dentition and subsequently cause recurrent abscesses. The controlled cross-sectional also explained that patients who were diagnosed with XLH after the age of 2, may suffer more dental manifestations that may not be corrected in the future in comparison to patients diagnosed early (Al-Jundi and Hazza'a, 2010).

As discussed in Chapter 2, conventional therapy (CT) demonstrated properties that may prevent dental anomalies by enhancing dental mineralisation and formation. Thus, Rabbani et al. (2012) suggested to continue with such treatment as it may avoid dental complications. A useful observation in the review by Vital et al. (2012) confirmed the importance of good patient compliance in medical management, especially during their growth period, as this may lead to fewer dental anomalies in their permanent dentition, subsequently leading to less dental infections.

##### 3.3.3.4.2 Preventive measures

The recommendations surrounding prevention measures were substantial, as they have the potential to reduce dental complications associated with XLH such as recurrent abscesses, dental caries, or attrition (Su et al., 2007). Such approach consists of oral hygiene instructions, fluoride varnish, fissure sealant and regular reviews. Studies have shown that specific measures like topical fluoride application and pit and fissure sealants may prevent endodontic complications (Peredes et al., 2018). Although the use of pit and fissure sealant was encouraged by many articles, Alexander et al. (2001) claimed that acid may penetrate pulp chambers through enamel microfractures. Thus, the article recommended an alternative material such as GIC. However, since then, there has been updates regarding the material of choice, confirming flowable resin composite as the ideal choice (Duplan et al., 2021).

#### 3.3.3.4.3 Dental management

The flowchart below summarises the proposed dental management of common dental features based on the literature reviewed (See Fig 3.26). This might aid dental professionals, especially if they have never treated an XLH patient and are not aware of their dental implications. This may guide them to deliver the standard of care expected, while including various specialities to consult and develop a tailored and individual treatment plan.

Treatment options of complications such as spontaneous dental abscesses vary, some recommend attempting root canal treatment, whereas others suggest extraction. The choice of treatment is subjective, as it depends on patient's age, dental development stage, presence of dental anomalies, compliance, expectations and XLH severity. Also, Souza et al. (2013) suggested the prognosis of abscessed teeth tend to be significantly poor, thus outcome of treatment may be unsuccessful. Nevertheless, Alexander et al. (2001) determined that pulp therapy is possible in XLH patients, proposing a clinical decision is important before proceeding with extraction option only. As stated by Batra et al. (2006) extraction of abscessed teeth at initial presentation is controversial, but in certain cases RCT success is doubtful thus extraction may be the only appropriate choice.

In the primary dentition, infection may spread rapidly in the jawbone, confirming extraction is often necessary (Linglart et al., 2014). Another review suggested that treatment should depend on extent of infection, history of recurrence and exfoliation timing. Both Shroff et al. (2002) and Demirel et al. (2018) advised against prophylactic pulp therapy of primary teeth due to lack of evidence available in the literature. The results obtained from the case report by Shroff et al. (2002) indicate that prophylactic pulpotomies on primary teeth is unsuccessful and should not be recommended. Such approach is outdated with high failure rates. Thus, extraction may be preferable in abscessed primary teeth (Hughes and Hingston, 2019).

Whereas in the permanent dentition, authors preferred endodontic treatment over extractions for functional and aesthetic reasons (Beltes and Zachou, 2012). Extraction of permanent teeth were only considered if there is evidence of recurrent lesions post-RCT, subsequently followed by prosthodontic replacement of extracted tooth (Cremonesi et al., 2014). However, the review by Baroncelli and Mora (2021) preferred re-treatment over extractions. Thus, it remains a clinical decision made with the patient and their parents, discussing risks and benefits of both treatment options to obtain a valid informed consent.

To provide excellent quality endodontic treatment, the accuracy of working length (WL) is necessary. Sabandal et al. (2015) suggested using electronic apex locator to determine the accurate length. However, Lee et al. (2017) recommended after establishing the WL by an apex locator, to confirm it with a periapical radiograph. This was similar to Boukpepsi et al. (2017) who confirmed the length electronically and radiographically. Regarding the quality of root canal filling, the final obturation must be well-condensed with no voids, to prevent chances of re-infection (Sabandal et al., 2015). Alongside void-free obturation, ensuring excellent apical and coronal seal is fundamental to prevent re-contamination (Hughes and Hingston, 2019). Sabandal et al. (2015), Paredes et al. (2018) and Hughes and Hingston (2019) all suggested thermoplasticised gutta percha obturation techniques are ideal.

Additionally, Boukpepsi et al. (2017) recommended performing treatment under operative microscope, however this may not be accessible to all clinicians. In cases where a permanent tooth is immature with incomplete root development, it is essential to follow careful copious irrigation and placement of an apical plug using mineral trioxide aggregate (MTA) (Sabandal et al., 2015; Bradley et al., 2021). Post-RCT, it is advised to schedule the patient for a 6-month review. During the review visit, clinical and radiographic examinations would determine the outcome of endodontic treatment and whether signs of healing are observed (Boukpepsi et al., 2017; Beltes and Zachou, 2012). Clinically, a comprehensive endodontic assessment is performed including tenderness to percussion, tenderness to palpation, evidence of abscesses, degree of mobility, and periodontal pocket depth. However, this is only justified in certain situations and should not be routine practice (Bradley et al., 2021).

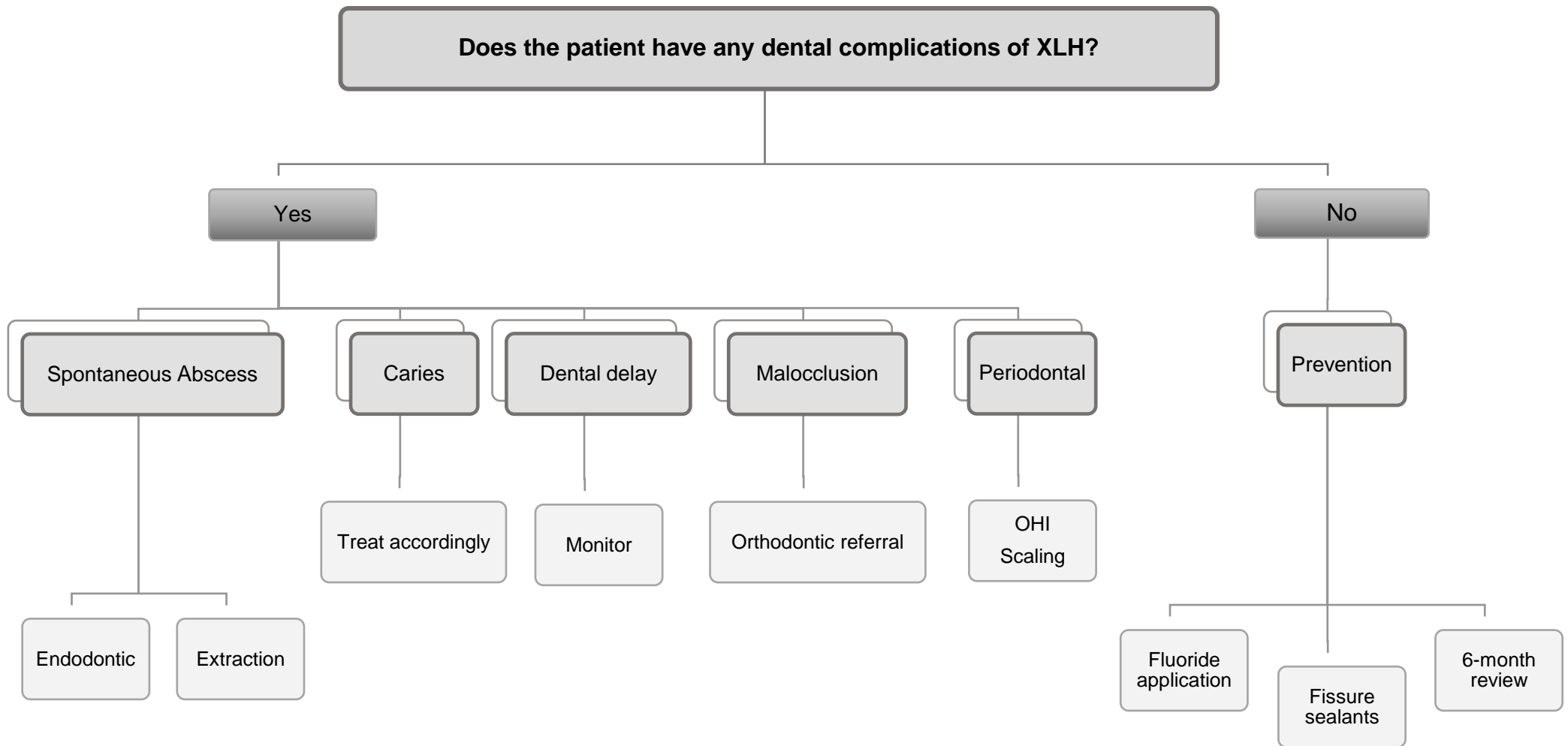
From a restorative point of view, conservative measures should be the preferred treatment of choice. When feasible, invasive procedures should be avoided, as they may require extensive reduction of dental structures. This was suggested by 3 articles, reporting to limit crown preparation, as this may compromise the pulp and lead to an inadvertent exposure (Murayama et al., 2000; Alexander et al., 2001; Batra et al., 2006). Thus, recommendations for the dental management to proceed with non-invasive procedures such as hall technique especially for primary molars when indicated.

Although historically prophylactic placement of PMCs for all primary molars was recommended to protect teeth from abscesses. And Hughes and Hingston (2019) further outlined their potential benefit in preventing attrition and enamel microfracture. A few studies have proposed to replace the systematic crowning of primary molars to sealing occlusal aspects with resin composite instead (Douyere et al., 2009). While some authors advised

PMCs may prevent pulp necrosis in primary molars, Vital et al. (2012) debated that the current evidence indicates the benefit of PMCs is not as effective as resin sealants.

Furthermore, since resin composite is the material of choice, determining the bonding system is important to ensure strength and retention. 4 articles have explored the etching system, with 100% of studies recommending self-etch over total-etch (Douyere et al., 2009; Beltes and Zachou, 2012; Cremonesi et al., 2014; Sabandal et al., 2015). Results demonstrate that self-etching system is easily applied for paediatric patients, as it does not require rinsing with decreased procedure time (Douyere et al., 2009). Due to its low viscosity, it has shown to fill the enamel microcracks without damage, further preventing microorganism from invading pulp tissue (Cremonesi et al., 2014). Douyere et al. (2009), also advised the reapplication of resin sealants after 10 months, with regular reviews. This was encouraged by Beltes and Zachou (2012), confirming this procedure must be repeated annually due to the wear of material until the permanent successor is erupted. Sabandal et al. (2015) confirmed self-etching is advisable, as prolonged etching or total-etching system may pose a risk of pulp irritation. From this scoping review, only one article established that the bonding strength of resin composites may be reduced for XLH patients due to dental abnormalities (Sabandal et al., 2015). Thus, careful clinical evaluation is needed to provide an optimal retentive restoration that will last.

Finally, as mentioned in the previous section, orthodontic treatment is not contraindicated, and should be offered to patients if there is evidence of an orthodontic need (Duplan et al., 2021). Some orthodontists may be reluctant due to the potential increased risk of root resorption, nevertheless, Makrygiannakis et al. (2020) emphasised there is currently no available data to suggest such an operative complication. Baroncelli and Mora (2021) argued that if medical management is optimal and no evidence of dental pathologies, orthodontic intervention should not be avoided. However, Makrygiannakis et al. (2020) also highlighted the importance of close monitoring especially for XLH patients and to consider pausing treatment if spontaneous abscesses occur.



**Fig 3.26.** Summary of proposed Dental Management of dental features based on the literature review



### 3.4. Discussion

Medical management of XLH is extensively documented in the literature, with considerably less research conducted on dental management and its long-term effects (Liu et al., 2020). Since XLH is relatively rare, some dental professionals may not have encountered a patient with such medical condition. The ability to recognise XLH solely from its dental manifestations is significant, as in milder cases, a dentist may be the first to identify a systemic involvement from the dental implications (Seow, 2003).

The most relevant dental manifestation of XLH is recurrent spontaneous dental abscess in the absence of dental caries or trauma (Baroncelli et al., 2021). It is important to comprehend when a patient develops one tooth abscess, their likelihood of experiencing more in the future is high (Beltes and Zachou, 2012). Therefore, a dentist should take a detailed medical and dental history, assessing the frequency of abscesses and success of previous dental treatments. Such approach would allow to accurately determine the severity of XLH, providing a vigilant and appropriate treatment plan. Baroncelli et al. (2021), also highlighted which teeth were affected with dental infection the most. The trial in Italy reported that incisors were affected most followed by canines then molars. Both Sabandal et al. (2015) and Andersen et al. (2012) reported the same results adding that premolars tend to be the least affected. The order is influenced by eruption sequence and the natural rate of tooth wear from mastication (Andersen et al., 2012).

Furthermore, dental professionals should be able to identify features associated with other dental anomalies (Seow, 2003). When assessing clinical and radiographic findings associated with XLH, it is valuable to consider and exclude potential differential diagnoses such as Dentinogenesis Imperfecta (DI), Dentine Dysplasia (DD), or Osteogenesis Imperfecta (OI). Thus, understanding the pathogenesis of different anomalies, and their specific features, would aid in accurate diagnosis, and prompt medical and dental interventions (Sabandal et al., 2015).

There are several factors that may influence dental or medical manifestations, such as age, gender, and patient compliance. A clear correlation has been established between the severity of dental features and the age at which the first dental complication occurs (Sabandal et al., 2015). The younger the patient is when they develop their first dental abscess, the more severe the dental complications may be in the future (Beltes and Zachou, 2012). Andersen et al. (2012) concluded that the number of affected teeth with dental abnormalities may increase

significantly with age. A few articles also discussed the impact of gender, Andersen et al. (2012) reported no statistical significance between gender regarding spontaneous abscesses. Nevertheless, Sabandal et al. (2015) suggested male patients tend to exhibit more severe dental symptoms in comparison to females. Another study by Chaussain-Miller et al. (2003) demonstrated only 3 patients (9.4%) had spontaneous dental abscesses and all were male. This may be attributed to the lyonization hypothesis, where one of the X-chromosomes in a female is inactivated during development thus reducing extent of dental abnormalities (Linglart et al., 2014). Additionally, an insightful observation from Vital et al. (2012) signified the importance of good patient compliance during medical treatment, particularly around growth periods. Such compliance may result in fewer dental manifestations in the permanent dentition, consequently reducing the occurrence of dental infections.

This scoping review focused on exploring the clinical recommendations for dental management, which included oral hygiene instructions, fluoride varnish, fissure sealants, monitor enamel microcracks, dietary advice and frequent monitoring (Sabandal et al., 2015). Such preventative measure is considered a standard of care for all patients, regardless of their medical history, nevertheless, there are specific recommendations to follow with XLH paediatric patients. For instance, when sealing occlusal structures of posterior teeth of primary or permanent teeth, using self-etching system and flowable resin composite are advised (Douyere et al., 2009; Beltes and Zachou, 2012). If a clinical decision is made to place a PMC on a primary molar, then utilising the Hall technique with no crown preparations is preferred (Hughes and Hingston, 2019).

Generally, the aim of dental management is to prevent or limit abscess formation (Paredes et al., 2018). In cases where endodontic complications arise, a primary abscessed tooth should be extracted, whereas if the tooth is permanent, endodontic treatment is encouraged, unless clinically unfeasible (Cremonesi et al., 2014). Nevertheless, the results obtained from this review cannot definitively determine whether endodontic treatment is superior to extraction, as such comparison between treatments was not provided. Therefore, clinical decision should be discussed with patient and their parents to understand the risks and benefits of both treatment options.

Finally, having an open communication between all members of the multidisciplinary team is essential to ensure optimal dental and medical health outcomes. The team may consider consulting specialists from different dental departments when justified. For instance, some patients may require the intervention of an orthodontist or a consultation from a periodontist,

as features of XLH may vary widely in severity and appropriate management may require a collaboration between departments. Thus, providing a tailored and individualised plan is advised.

### 3.5. Conclusion

In conclusion, dental manifestations associated with XLH, and their dental managements are sufficiently documented in the literature. Dental professionals should be able to recognise clinical and radiographic features of XLH, due to its distinctive characteristics. They should also be able to distinguish XLH specific dental complications from other dental anomalies, to prevent misdiagnosis and unsuitable treatment measures.

This scoping review highlighted the most common dental feature frequently seen in XLH patients is recurrent spontaneous dental abscesses, in caries-free teeth with no history of trauma. Results of the review suggested the importance of early diagnosis and intervention for both dental and medical managements to prevent further complications. When an abscess is identified, prompt management is necessary, for primary teeth extraction is advised and for permanent, endodontic treatment is preferred. This review cannot conclusively state one treatment option is superior from the other, however, several articles confirmed the benefit of carrying out endodontic treatment over extractions. Nevertheless, prevention is key in managing XLH patients, with periodic examinations, oral hygiene instructions, fluoride varnish application, and fissure sealants with close monitoring every 3 to 6 months.

Finally, although there is substantial evidence on XLH, there remains to be a lack of clinical guidance for dental professionals on the recommended management of certain dental manifestations. Since most articles in this review were case reports, the treatment measure provided may not necessarily be applicable to a wider population. Thus, choice of treatment remains subjective and based on clinical justification. This review suggests additional research to compare between treatment options, determining which choice will ensure the better dental health outcome for children.

**Chapter Four:** Exploration of  
Patient-Reported Outcome Measure  
(PROM) of children and young  
people with X-Linked  
Hypophosphatemia (XLH)

## 4.1. Aims and Objectives

The aim of this service evaluation was to understand how children and young people with XLH seen at the Eastman Dental Hospital (EDH) felt about their dental health using Patient-reported outcome measures (PROMs), including:

- How often patients experienced physical symptoms such as pain, sensitivity and/or difficulty eating/brushing
- Whether they had experienced recurrent spontaneous abscesses
- How XLH impacted their overall dental anxiety
- What was their dental treatment experience and frequency of emergency dental visits
- Whether they are satisfied with their smile/teeth

## 4.2. Methods

### 4.2.1. Participants

The prevalence of XLH is relatively rare, it varies across the literature between 1 in 20,000 to 1 in 200,000 individuals worldwide (Sandy et al., 2023). Initially, 2 national specialist-led units based in London were planned to participate in data collection, Eastman Dental Hospital (EDH) and Great Ormond Street Hospital (GOSH). However, after obtaining the list of eligible paediatric patients at both departments it was confirmed that they were identical, therefore it was decided to proceed with gathering data only from EDH.

### 4.2.2. Development and pilot of the questionnaire

The questionnaire was developed in July 2023 by the student using the Amelogenesis Imperfecta (AI) PROM created by Lyne et al (2021) as a reference guide. The PROM results obtained by Lyne et al. (2021) can be used longitudinally, where patients can retake the survey after the treatment provided to monitor patients' progress and overall satisfaction of care.

The PROM in this service evaluation was designed to be concise and straightforward, comprising of 11 multiple-choice questions and one open-ended question. This format enabled patients to share their individual perspectives on how XLH impacts their dental health and overall quality of life.

Due to the rarity of XLH and limited availability of patients, the questionnaire underwent a pilot phase with two participants and their parents. The participants selected were aged 7 and 12

years, representing both genders. Following the feedback obtained from the pilot evaluation, appropriate changes were made to the XLH PROM as outlined in Table 4.1 below.

**Table 4.1. - Feedback and necessary changes made following the PROMs pilot**

Area of questionnaire	Comments from pilot	Changes made to final PROMs
<b>Overall appearance and general comments</b>	<p>One child wanted more pictures</p> <p>One parent suggested changing “Always” option to “Often”</p> <p>All children and parents thought it was easy and age appropriate</p>	<p>A simple picture was added to the cover page and face scales above the answer</p> <p>Changed any “Always” answer to “Often”</p>
<b>Question 2</b>	One parent suggested to reword “difficulty eating”	Reworded to “hard to eat”
<b>Question 4</b>	Parent and child didn’t understand “salty taste”	Reworded to “bad (bitter) taste” to signify the presence of pus
<b>Question 5</b>	Child didn’t understand the word “swelling”	Included “bump (swelling)”
<b>Questions 10 and 11</b>	Both questions were open-ended, and parents thought it would be difficult for a child to answer independently	To simplify the questionnaire, options were included, but children may still require the assistance of their parents

Furthermore, it was essential to confirm the reading age of the final questionnaire, which was 7 years old according to Readable website. Nevertheless, parents were encouraged to help their children complete the questions if deemed necessary. Finally, to enhance accessibility, the final questionnaire featured scale faces to represent the emotions corresponding to each answer. The final version of the questionnaire is shown in Fig 4.1.

# X-Linked Hypophosphatemia (XLH)

## Patient Survey



Thank you for helping us with our survey. We would like to ask you a few questions about how X-Linked Hypophosphatemia (XLH) affects your teeth and gum.

Please turn the page and answer the questions. When you are finished, please give it back to the dentist.

**Circle your answers like the example below:**

1. Do your teeth cause you pain or sensitivity?	Often	<b>Sometimes</b>	Never
---	-------	------------------	-------

**The dentist will fill out the following information for you**

**Age:** ..... years




**Gender:** M / F / X

**Relevant Medical History:**

**Medications:**

**Dental treatment stage:** Pre-treatment / Mid-treatment / Post-treatment

**Attendance:** Regular / Under review only / Discharged

Please circle ONE answer			
1. Do your teeth cause you pain or sensitivity?	Often	Sometimes	Never
2. Do you find it hard to eat foods you like because of your teeth?	Often	Sometimes	Never
3. Does it hurt when you brush your teeth?	Often	Sometimes	Never
4. Do you ever feel you have bad (bitter) taste in your mouth?	Often	Sometimes	Never
5. Do you often get a bump (swelling) around your teeth or gum?	Often	Sometimes	Never
6. Do you feel scared (sad) about going to the dentist?	Often	Sometimes	Never
7. Did you ever have a bad experience with a dentist?	Often	Sometimes	Never
8. Do you feel happy with your teeth?	No		Yes
9. How many times do you visit the dentist every year?	More than 5 times	2-4 times	1-2 times
10. How many visits this year because you were in pain? (i.e., emergency visit)	More than once	Once	Never
11. What treatments did you get at the dentist?	Extractions	Fillings	Only check-ups
12. Is there anything else you would like to tell us about XLH and how it affects your teeth and smile?			

**Fig 4.1.** XLH PROMs



### 4.2.3. Data Collection

The intention was to include every paediatric patient diagnosed with XLH currently under the care of EDH or recently discharged. Eligible patients were identified using the patient electronic healthcare records system 'Epic'. To confirm eligibility, the student first searched for an official diagnosis letter from their healthcare provider in the media section and then established when their upcoming dental visit in the department. If patients did not have a future appointment scheduled, they were contacted via telephone and email to assess their interest in participating, which included a brief explanation of the service evaluation.

When contacted via telephone, patients and their parents were given two options to answer the PROM, either during their next face-to-face visit at the department or online. The majority of parents opted to answer the online version of the questionnaire. Parents were aware that the questionnaire needed to be completed by the patient to obtain their perspective and experience with XLH. They were also informed that participating in the questionnaire was voluntary and anonymous ensuring no identifiable information was collected. Additionally, patients and their guardian needed to provide verbal consent and assent to complete the PROM. Data analysis included descriptive statistics using Microsoft Excel sheet.

### 4.3. Results

Thirteen patients (7 females and 6 males, with age range of 7-16 years) completed the questionnaire between July and December 2023, all participants had been seen at both EDH and GOSH. The student collected all the data included in the analysis, 4 patients (31%) were seen face-to-face, and 9 patients (69%) completed the online PROM version. No patients refused to participate. Individual codes were given after inputting the data into a Microsoft Excel sheet.

Table 4.2. demonstrates the overall sample characteristics collected: age, gender, XLH medications, stage of dental treatment and attendance status with each individual response to questions 1 through 10. To easily interpret results, each participant was given a unique code in which the letter P stands for patient, followed by a number (e.g., P001, P002, P003, etc).

ID	Age	Gender	XLH management	Dental Treatment Stage	Attendance	Q1. Pain or Sensitivity	Q2. Difficulty eating	Q3. Difficulty Brushing	Q4. Bitter Taste	Q5. Swelling	Q6. Dental anxiety	Q7. Bad experience	Q8. Happy about teeth?	Q9. Number of dental visits per year	Q10. Emergency dental visit this year?
P001	7	F	Both	Post	Discharged	Sometimes	Never	Sometimes	Never	Never	Never	Never	Y	2 - 4	Never
P002	14	F	Both	Post	Discharged	Sometimes	Often	Never	Often	Never	Never	Never	N	More than 5	Never
P003	10	F	Burosumab	Post	Discharged	Sometimes	Never	Never	Sometimes	Sometimes	Never	Never	Y	1 - 2	Once
P004	7	F	Both	Post	Review	Sometimes	Never	Sometimes	Never	Sometimes	Never	Never	Y	1 - 2	Never
P005	12	F	Both	Post	Discharged	Sometimes	Never	Never	Never	Never	Sometimes	Never	Y	1 - 2	Never
P006	7	F	Burosumab	Post	Review	Never	Never	Never	Never	Sometimes	Often	Never	Y	1 - 2	Never
P007	8	F	Burosumab	Post	Review	Sometimes	Never	Never	Sometimes	Often	Often	Never	Y	1 - 2	More than once
P008	12	M	Burosumab	Pre	Review	Sometimes	Never	Never	Never	Never	Never	Never	N	2 - 4	Never
P009	12	M	Both	Mid	Regular	Never	Never	Never	Never	Never	Never	Never	Y	2 - 4	Never
P010	16	M	Burosumab	Mid	Regular	Often	Sometimes	Sometimes	Never	Often	Never	Never	Y	More than 5	More than once
P011	16	M	Both	Mid	Regular	Often	Sometimes	Sometimes	Sometimes	Often	Never	Sometimes	N	More than 5	More than once
P012	9	M	Both	Post	Review	Never	Never	Never	Sometimes	Sometimes	Sometimes	Sometimes	Y	2 - 4	Never
P013	10	M	Both	Post	Review	Never	Never	Never	Sometimes	Sometimes	Sometimes	Sometimes	Y	More than 5	Never

**Table 4.2.** - Summary of results obtained including demographic characteristics and responses from Q1 to 10 with patients ID codes

**N.B.** F = Female, M = Male, Y = Yes, N = No

For the XLH medical management, all 13 patients (100%) were on burosumab treatment, while 8 (62%) were also on Vitamin D supplementations (cholecalciferol). All participants were receiving medical treatment in the same hospital. However, in terms of dental management, 9 patients (69%) answered the questionnaire post-dental treatment, and only one patient (8%) is pre-dental treatment. All participating females were post-dental treatment (n = 7). Additionally, nearly half of the participants were considered 'under review' (46%, n = 6), while the remaining patients either discharged or regularly attending the department for treatment (See Table 4.3.)

		Female n (7)	Male n (6)	Total n (13)
<b>Age (yrs)</b>	Mean	9.29	12.50	10.77
	Standard Deviation	2.812	2.950	3.219
	Range	7-14	9-16	7-16
<b>Medications</b>	Burosumab only	3 (43%)	2 (33%)	5 (38%)
	Burosumab and cholecalciferol	4 (57%)	4 (67%)	8 (62%)
<b>Dental Treatment Stage</b>	Pre-Treatment	0 (0%)	1 (17%)	1 (8%)
	Mid-Treatment	0 (0%)	3 (50%)	3 (23%)
	Post-Treatment	7 (100%)	2 (33%)	9 (69%)
<b>Attendance status</b>	Regular attender	0 (0%)	3 (50%)	3 (23%)
	Under Review	3 (43%)	3 (50%)	6 (46%)
	Discharged	4 (57%)	0 (0%)	4 (31%)

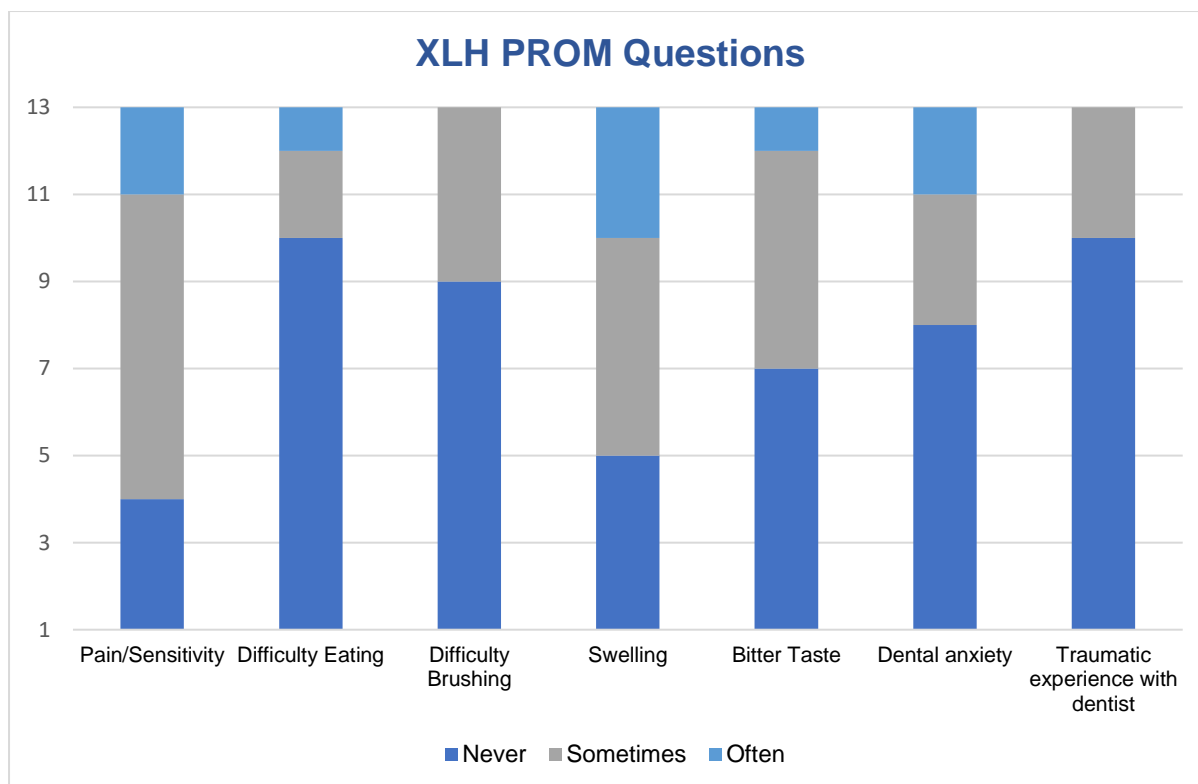
**Table 4.3.** - Overall sample characteristics

Patient responses to PROM questions (1 to 7) were summarised in Table 4.4. and shown in Fig 4.2. All questions were answered fully, with no missing data reported of any of the participants. The 'Often' response was reported the most in swelling question (Q4) with 23% (n = 3), followed by dental anxiety and pain/sensitivity with 15% (n =2) each. Additionally, more than half the participants (54%, n = 7) reported that they 'Sometimes' experience pain and/or sensitivity from their teeth. Remaining questions (2 to 7) had 'Never' as the most reported response, with 10 patients (77%) never having difficulty eating or traumatic experience with

dentist, 9 patients (69%) never having difficulty brushing and 8 patients (62%) never experiencing dental anxiety (See Fig 4.2.).

	<b>Responses</b>	<b>Frequency</b>
<b>Q1. Pain/Sensitivity</b>	Often	2 (15%)
	Sometimes	7 (54%)
	Never	4 (31%)
<b>Q2. Difficulty eating</b>	Often	1 (8%)
	Sometimes	2 (15%)
	Never	10 (77%)
<b>Q3. Difficulty brushing</b>	Often	0 (0%)
	Sometimes	4 (31%)
	Never	9 (69%)
<b>Q4. Swelling</b>	Often	3 (23%)
	Sometimes	5 (38%)
	Never	5 (38%)
<b>Q5. Bitter Taste</b>	Often	1 (8%)
	Sometimes	5 (38%)
	Never	7 (54%)
<b>Q6. Dental anxiety</b>	Often	2 (15%)
	Sometimes	3 (23%)
	Never	8 (62%)
<b>Q7. Traumatic experience with dentist</b>	Often	0 (0%)
	Sometimes	3 (23%)
	Never	10 (77%)

**Table 4.4.** - Summary of PROM responses including frequency and percentages of each



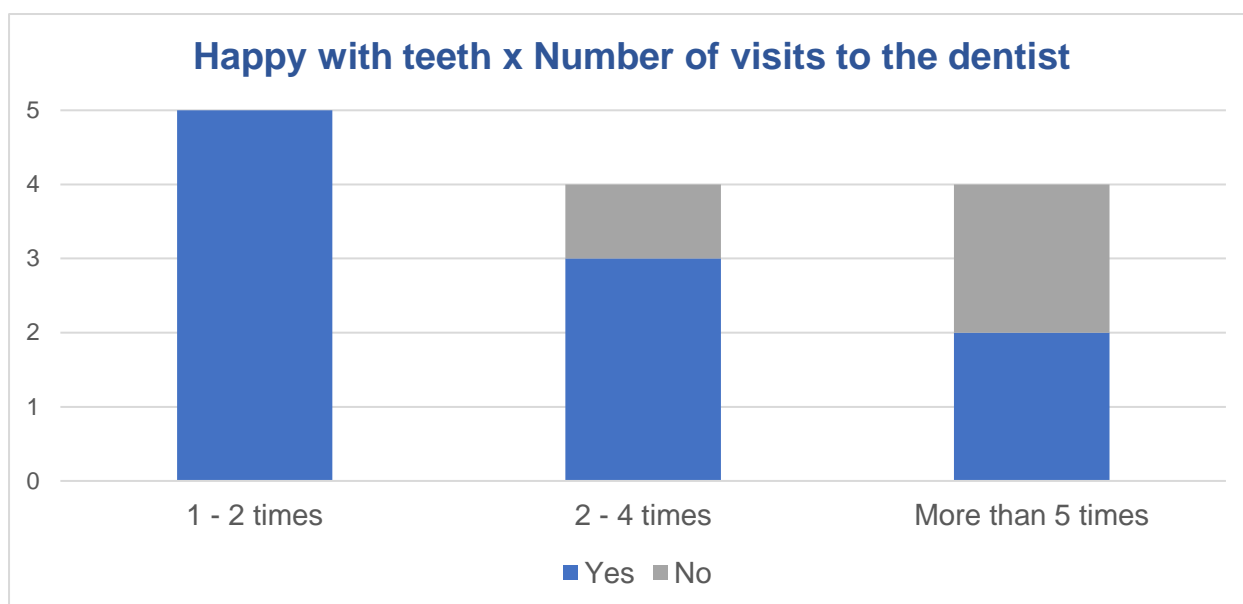
**Fig 4.2.** Bar chart showing PROM responses from 13 participants (Question 1 to 7)

Question 8 was a yes/no question that focused on whether patients felt happy about their teeth and smile. The majority of patients answered 'Yes' (77%, n = 10), 6 females and 4 males reported they were happy as shown in Table 4.5. However, 3 patients (23%) stated they were unhappy, each at a different stage of dental treatment, P002 was post-dental treatment, P008 pre-treatment and P011 was mid-treatment. These patients were 12, 14 and 16 years of age, indicating that they were in the permanent dentition. Notably, the other 3 patients in the same stage of dental development (codes: P005, P009, P010) reported they were happy with their teeth/smile. This suggests that the dental age may not play a major role in patients' level of happiness or satisfaction. However, this was small sample, and further studies are needed to investigate this.

Moreover, 4 patients (31%) with the codes: P002, P010, P011, P013 have reported attending to the dentist 'more than 5 times a year'. It is important to note that both P002 and P011 also reported being unhappy with their teeth. Fig 4.3. demonstrates patient responses to question 8 in relation to the number of visits to the dentist every year (Question 9), showing all patients who attend 1-2 times a year were happy with their teeth. Whereas 50% of patients (2 out of 4) attending more than 5 times a year were unhappy.

**Table 4.5.** - Responses of Question 8 and 9

		Female n (7)	Male n (6)	Total n (13)
<b>Q8.</b> Do you feel happy with your teeth?	No	1 (14%)	2 (33%)	3 (23%)
	Yes	6 (86%)	4 (67%)	10 (77%)
<b>Q9.</b> How many times do you visit the dentist every year?	1 - 2 times	5 (71.4%)	0 (0%)	5 (38%)
	2 - 4 times	1 (14.3%)	3 (50%)	4 (31%)
	More than 5 times	1 (14.3%)	3 (50%)	4 (31%)



**Fig 4.3.** Cross tab between happy with teeth and number of visits to the dentist per year

For further elaboration, question 10 aimed to explore the amount of emergency dental visits per year. Although P002 and P008 expressed dissatisfaction of their teeth in question 8, they have reported not attending for an emergency dental visit this year. Nevertheless, this was not the case for P011, who needed to attend emergency dental visits more than once this year, alongside more than 5 regular dental visits. The remaining two patients who reported going for an emergency visit more than once this year (P007 and P010) were happy with their teeth. Reason for the emergency visits was not explored in the questionnaire.

Question 11 asked 'What treatments did you get at the dentist?' to explore the extent of patients' dental experience. The options included were limited to 'Extractions', 'Fillings' and 'Only check-ups' to ease answering the questionnaire. The majority of patients also wrote additional treatments they received such as root canal treatment (RCT) and fissure sealants (protective coating). Table 4.6. provides an individual summary of dental treatment received for each participant by code.

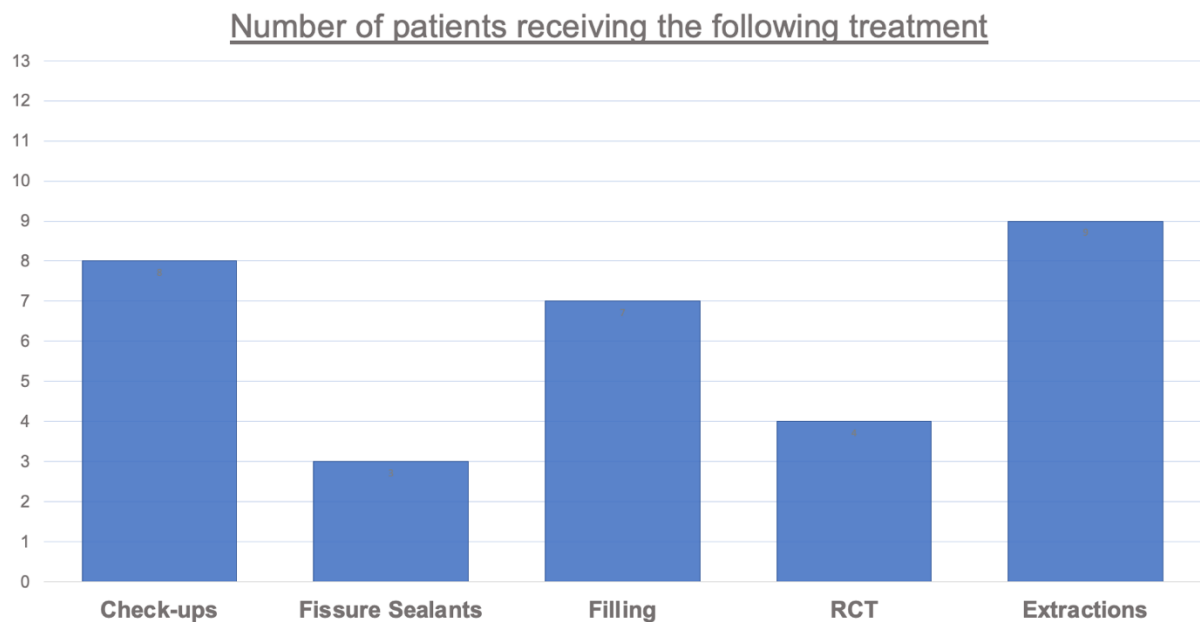
**Table 4.6. - Check list of dental treatments received for each participant by ID code**

ID	Check up	Fissure sealants	Filling	Root canal treatment	Extractions
P001	✓				✓ (GA)
P002					✓
P003	✓		✓		✓
P004	✓				
P005	✓		✓		✓
P006	✓	✓			
P007			✓ (PMC)		
P008					✓
P009	✓		✓ (PMC)		✓
P010				✓	✓
P011			✓	✓	
P012	✓	✓	✓	✓	✓
P013	✓	✓	✓	✓	✓

As shown in Table 4.6. there was a variety of treatments received by each participant, 23% (n = 3) needed extractions, fillings, and regular check-ups (P003, P005, P009). The 2 patients who received the most number of treatments were P012 and P013, both males and in the mixed dentition. According to Table 4.2. both P012 and P013 reported 'sometimes' having dental anxiety and a traumatic dental experience (Question 6 and 7), however none of them needed an emergency dental visit and they were generally happy with their smile.

When comparing patient's happiness and the treatment provided, out of the 3 patients who were unhappy with their teeth (P002, P008, P011), 2 experienced extractions and one underwent endodontic and restorative treatments. Yet other patients have had similar invasive procedures and remained happy about their overall dental experience and smile.

Additionally, 3 patients were in the early mixed dentition, one reported only requiring check-ups (P004), while P006 required fissure sealants as well. However, another participating 7-year-old (P001) reported experiencing extractions under general anaesthesia (GA). It was also noted that dental extraction experience was similar between mixed and permanent dentitions (4 and 5 patients respectively). Thus, dental development stage may not be a factor in the number and extent of treatment received. Fig 4.4. shows the total number of patients receiving different dental treatments with 9 patients (69%) experiencing dental extractions, followed by 8 (61.5%) needing regular dental check-ups. Nevertheless, four out of the 13 patients (31%) reported undergoing RCT in the past, with the least treatment being fissure sealants with a total of 3 patients (23%).



**Fig 4.4.** Total number of patients receiving different dental treatments

Lastly, 11 out of 13 participants (85%) made additional comments to the open-ended question (Question 12). It is worth noting that some parents also included their opinion in this section. Comments obtained are summarised in Table 4.7. covering aspects such as function, aesthetic, psychological, dental, and medical.



**Table 4.7. - Summary of additional comments obtained from PROM including patients ID code, gender, and age for each comment**

Aspect	Comments
<b>Function</b>	<p>'Thanks to Eastman help I'm able to eat food and not limited to certain things' – P001, F, 7 years</p> <p>'I had perfect teeth, later my problems started when more teeth growing' – P008, M, 12 years</p> <p>'I could never bite into apples or nuts' – P002, F, 14 years</p>
<b>Aesthetic</b>	<p>'I have missing front teeth, and don't like the gaps' – P005, F, 12 years</p>
<b>Psychological</b>	<p>'I became a slow eater; my friends would finish their lunches and I barely began' – P002, F, 14 years</p> <p>'I'm now happy because I don't have infections' – P013, M, 10 years</p> <p>'XLH gives me a lot of pain and infections, it gets bad out of nowhere. When it gets really bad it gives me a headache and I can't stay still' – P011, M, 16 years</p> <p>'My teeth seem worse than my sisters' – P007, F, 8 years</p>
<b>Dental</b>	<p>'I didn't need an extraction for over a year. Before that I have had around 5 teeth taken' – P009, M, 12 years.</p> <p>'I go to the dentist a lot' – P010, M, 16 years</p> <p>'It's been a year since my last problem, before that I used to go to the dentist a lot' – P012, M, 9 years</p> <p>'They told me I can't get braces because of XLH, which is unfair' – P013, M, 10 years</p>
<b>Medical</b>	<p>'I'm better after treatment for XLH, stronger bone and teeth' – P003, F, 10 years</p> <p>'I think my XLH is in good condition' – P005, F, 12 years</p>
<b>Parent's input</b>	<p>'As her father I worry about the amount of dental treatment she will need'</p> <p>'We are very happy with Burosumab, but NICE has not approved it for adult patients, so we are worried about our sons' future'</p> <p>'I have been shamed for choosing root canal for both my boys, but I don't regret it'</p> <p>'A dentist once suggested to extract all the baby teeth if they have one abscess, which is extreme'</p>

The comments provided were consistent with the results obtained from the questionnaire. For instance, P002 reported functional and psychological impacts and stated she was unhappy about her teeth or smile in question 8. Similarly, P011, was yet another patient reporting dissatisfaction of dental health, he disclosed that 'XLH gives him a lot of pain and infections' with more than 5 dental visits per year and more than one emergency visit this year, this may be indicative to why he answered 'No'.

#### 4.4. Discussion

The impact of an XLH diagnosis can persist from early childhood through to adulthood, subjecting patients to lifelong physical, dental, psychosocial, and financial burden. Although dental manifestations and management of XLH are documented in the literature, there is a demand in exploring the burden of the disease on paediatric patient's dental and oral health-related quality of life (OHRQoL). Both Hanisch et al. (2019) in Germany and Gjorup et al. (2020) in Denmark, investigated the OHRQoL of adults with XLH, concluding that they experience higher negative impact, and their quality of life is reduced, however, children and young people's input was not considered. Nevertheless, a study by Nguyen et al. (2022), involving semi-structured interviews of 21 participants, including 8 children in France was conducted to explore their OHRQoL. The results of the interviews highlighted the challenges XLH patients face, including difficulty in finding a dental professional with sufficient knowledge of their medical condition. However, children appeared to be less affected in their general and oral health than adults as they are referred and treated promptly (Nguyen et al., 2022).

In the UK, Cole et al. (2023) published a PROM of 48 adults with XLH, assessing their overall health-related quality of life (HRQoL) including pain, fatigue, mobility, sleep, and mental health. A third of the participants reported worse outcomes in fatigue, depression, quality sleep and chronic illnesses. However, no consideration of dental impact or paediatric patient input. Additionally, Cole et al. (2023) concluded that more research is needed to examine why there is a discrepancy between participants, including the characteristics which result in a good health outcome.

The PROM developed in this study is the first to involve paediatric patients with XLH, exploring how their medical health affects their overall dental health and experience. During history taking, children may be reluctant to express verbally how they feel about XLH and its impact on their teeth, thus, by answering the questionnaire, dental professionals will be able to further understand the patient's experience. The result from the PROM offers an opportunity to open

discussion and provides a better understanding on the need for tailored and individualised dental treatment plan.

It was essential to obtain the choice of medical treatment, whether participants were on conventional treatment or burosumab therapy. All 13 patients were on burosumab injections every 2 weeks, and 8 patients (62%) were also provided with vitamin D supplementation. The combination of conventional and novel therapy may be due to severity of their symptoms, medical expert choice or personal preference, however this was not investigated. No patients reported receiving only conventional treatment for their XLH, as burosumab is becoming the first-line therapy for children with XLH (Paloian et al., 2022). A PROM developed by Padidela et al. (2021) reviewed the results of a randomised, controlled, phase 3 trial of burosumab versus conventional therapy in children with XLH, investigating HRQoL but not exploring dental health. It concluded that changing to burosumab improved patient's outcome. It would have been beneficial to include dental outcomes to be able to determine if one treatment option is superior, as XLH has significant dental impacts.

Most participants (69%, n = 9) included were post-dental treatment, they were either discharged back to their general dental practitioner (GDP) or under review at EDH. It would have been beneficial to obtain PROM for all patients at each stage to compare the influence of dental treatments on their overall dental experience. However, it was not feasible to collect data 'pre-treatment' as most may have had treatment prior to being seen at EDH, as only 1 participant (8%) was pre-treatment and only seen before for routine dental check-ups.

Furthermore, patients reported a variety of concerns about their teeth and smile, the most common was pain and/or sensitivity, followed by swelling. This result is consistent with recognised dental manifestations of XLH as described by Seow (2003). However, 'Never' was the most reported response with the majority of patients never having difficulty eating, brushing, bitter taste, dental anxiety, or traumatic experience with a dentist. This may indicate that receiving prompt and adequate medical treatment for XLH may be essential in improving their health and reduce dental symptoms. Nevertheless, this cannot be concluded from this study, and further longitudinal studies required to make such conclusion.

Question 12 was open-ended allowing participants to include any additional comments they may have regarding their XLH and its impact on their teeth or smile. 11 patients (85%) took the opportunity to include their opinion, and some comments were made by their parents, as they were present when patients are filling the questionnaire. Certain parents experienced the

impact of XLH, leading them to advocate for their children's overall medical and dental health. Others were overwhelmed with the amount of treatment they received and hoped for their children to achieve a better outcome with less burden. A few parents expressed their fear and disappointment about NICE guidance (2023) recently rejecting their funding for burosumab as a therapy for adults with XLH. Parents are concerned for their children's future, and whether burosumab will have withdrawal symptoms or if they rely solely on conventional treatment, will they achieve comparable health outcomes as seen with burosumab. In June 2024, NICE has amended their guidance, approving the access of burosumab to all patients with an official diagnosis of XLH in England, Wales and Northern Ireland (XLH UK organisation, 2024). Another parent stated that they were shamed by different dentists about choosing root canal treatment for their children instead of extractions.

This simple questionnaire was developed to aid patients in stating their concerns and needs and assist the dental team in tailoring appropriate treatment plan. This tool should be used repeatedly at several stages in their development as part of treatment planning to address their personal concerns and highlight whether a specific treatment provided a successful outcome.

#### 4.4.1. Limitations

This service evaluation has several limitations, including a small sample size, consisting of mainly patients post dental treatment. When collecting participants' medication list, all 13 patients were on burosumab therapy, 8 of which were also receiving conventional therapy. It would have been beneficial to explore when patients started burosumab therapy to understand its impact on XLH. Additionally, including participants on conventional therapy only would allow to compare results between each type of therapy. However, since burosumab is the first-line treatment, it was challenging to allocate patients on Oral phosphate and Vitamin D supplementations alone.

The PROM questionnaire could have been further modified, as Question 8 only explored the satisfaction of their teeth and smile, when it should have included 'if not happy, why?' to explore the possibility that they are bothered with appearance or malocclusion instead of dental manifestations of XLH. Question 11 included limited dental treatment options to make it easy for patients, nevertheless some participants added other treatments such as RCT and silver caps to expand on their answer. Having more treatment options in the questionnaire would have been beneficial, to compare whether patients who received extensive dental

treatment were more dentally anxious or assess the level of pain or satisfaction between patients who had extractions versus RCT. Additionally, exploring the modality of treatment such as local anaesthesia, inhalation sedation or general anaesthesia would have been useful, to correlate the results to level of anxiety or pain.

Furthermore, the questionnaire was based on an AI PROM developed by Lyne et al. (2021) which also included AI-relevant questions such as being bullied or missing school. These aspects were not included in this version of XLH PROM, in hindsight missing school may have been relevant for XLH patients as having recurrent spontaneous abscess would lead to an impact on their school attendance.

During the time of data collection, the youngest patient eligible to participate was 7 years old, thus the age range in this study was 7-16 years old. The average age of participants was 10 years old, with almost equal number of girls and boys in the sample (7 females and 6 males). Nevertheless, to provide a better representation of a specialist paediatric dental setting, it would have been beneficial to obtain data from younger patients. Currently, the analysed results are of patients in either mixed or permanent dentition, indicating a lack of input from patients in the primary dentition. A wider age range would have been valuable to assess the impact of XLH during different developmental stages.

The majority of participants opted to answer the online version of the questionnaire, thus there is a possibility their answers were influenced by their parents' point of view. Finally, such study requires a long-term service evaluation with a larger sample size, including majority of pre-treatment patients and following them through their journey until treatment is completed.

#### 4.5. Conclusion

This service evaluation, which involved the development and use of an XLH-specific PROM highlighted the range of challenges children and young people with XLH face, from pain and sensitivity to recurrent swelling. The individual issues they endured were not linked to the frequency of emergency visits or recurrent abscesses. Also, results obtained suggest that children who were post-treatment and attend regular check-ups only have high levels of satisfaction with their teeth. Hence, a timely diagnosis and referral to a specialised care centre is crucial to avoid deterioration in their dental health, which may lead to dissatisfaction. Finally, clinicians can employ this questionnaire at different stages of a patient's development and throughout treatment to explore all their individual concerns and assess whether an improvement in their patient-reported outcome is observed.

## **Chapter Five: Recommendations for Future Research and Limitations of current study**

X-Linked Hypophosphatemia (XLH) is a rare genetic multisystem disorder, characterised by low levels of phosphate in the blood. Although it is the most common form of familial hypophosphatemia, it is relatively rare with a prevalence of 1 in 20,000 individuals worldwide (Saraff et al., 2020). It exhibits distinctive clinical features of short stature, skeletal deformities, and dental manifestations. Such chronic disease significantly impacts the health-related quality of life (HRQoL) affecting patients from early childhood to adulthood. Disease awareness by healthcare professionals is essential to be able to diagnose and treat promptly and effectively (Rothenbuhler et al., 2020). Nevertheless, knowledge of this condition seems to be limited to a few specialised centres, and requires multidisciplinary care involving endocrinologists, nephrologists, psychologists, physiotherapists, geneticists, and dentists while liaising with patient group representatives (Haffner et al., 2019).

## 5.1. Recommendations

### 5.1.1. Medical Management

The scoping review provided an insightful perspective regarding the medical management of XLH and its impact on dental features. While some authors preferred the use of burosumab, other specialists continue to recommend conventional treatment (CT), mainly due to their lack of experience with novel measures in a paediatric clinical setting (Paloian et al., 2022). The findings of the review cannot conclude that one option is superior in improving dental outcome or preventing dental complications, nevertheless, the majority of the studies reported a reduction in dental abscesses with burosumab versus CT. Despite the encouraging results, the dental adverse effects are present in both treatment options. CT has been extensively researched since 1975, confirming that if introduced early enough, it may lead to significant improvements in dental development. However, the impact of burosumab on dental development remains uncertain due to its novelty and limited research.

Clinical practice recommendations and guidelines have been developed concerning the diagnosis and medical management of XLH with some reference of the dental impact. There remains a lack of research available regarding paediatric dental management, and further longitudinal and multicentre trials with a larger number of participants to establish clinical significance of such medical treatments on dental manifestations is required. Based on the identified themes, there are several suggestions for future studies and areas of further exploration, such as longitudinal assessment of XLH patients on burosumab, evaluating its safety and efficacy, not only from a medical point of view but also dental and confirming its cost-effectiveness and availability (Haffner et al., 2019; Padidela et al., 2020; Sandy et al.,

2022). Currently, there is no conclusive evidence that burosumab is cost-effective and no guarantee that such treatment option will be accessible to all XLH patients worldwide (Haffner et al., 2019). By addressing these areas in future research, the influence on paediatric dentistry can be further understood, leading to better experiences for young patients and their families.

Educating patients and their families on the specific clinical implications associated to XLH, and possible dental adverse effects of the treatment provided may improve awareness on what is perceived as a dental emergency (Bacchetta et al., 2021). Also, parents should be informed on the importance of a dental assessment prior to commencing XLH treatment and the need of frequent dental check-ups every 6 months. Additionally, dental professionals are encouraged to reinforce oral hygiene instructions, monitor dental development, and look out for dental abscesses, caries, or periodontal diseases. Finally, having a multidisciplinary team, including both medical and dental specialists is a fundamental part of management.

An attempt made to discuss XLH in general, highlighting the shift in medical management and the confusion associated with dental management. Any recommendations regarding medical or dental management will need to be updated when more evidence on novel therapy emerges. Also, few limitations of each chapter are mentioned to explore how improvements can be made in the future. Nevertheless, several topics for future studies are highlighted in Table 5.1.

Future research topics
<ul style="list-style-type: none"><li>• Explore the effect of XLH on school, social life and mental wellbeing</li><li>• Develop clinical and/or radiologic criteria to establish safety of treatment</li><li>• Evaluate the long-term safety of burosumab in infants and adolescents</li><li>• Evaluate the long-term efficacy of burosumab with respect to dental features</li><li>• Explore the likelihood of burosumab preventing spontaneous dental abscesses</li><li>• Determine cost-effectiveness of burosumab and/or CT in paediatric settings</li><li>• Compare root canal treatment vs. dental extraction to treat recurrent abscesses</li><li>• Explore oral health-related quality of life (OHRQoL) of children with XLH</li></ul>

**Table 5.1.** - Summary of suggested research topics for the future (Haffner et al., 2019)



### 5.1.2. Dental Management

The review concluded that there is currently no standardised clinical guidelines available for dentists to follow when treating patients with XLH. Dental professionals should be aware of manifestations associated with XLH; a dentist can be the first healthcare professional to determine a systemic involvement (Seow, 2003). Several studies advised reducing time between dental recalls when a patient is in the high caries risk category. Like the medical review, educating patients and their parents about dental manifestations is a critical aspect of effective management, as highlighted in the included studies. Nonetheless, these recommendations are not XLH specific and appear to apply to all patients regardless of their medical history, since providing optimal dental treatment is the standard practice of care.

Table 5.2. outlines the dental considerations for XLH as documented in the literature. Most studies focused on preventive measures such as the application of fluoride varnish and placement of fissure sealants in both primary and permanent dentitions. This approach may limit the need for invasive approach, consequently reducing the burden of care and extent of required dental treatment. Additionally, involving several dental specialities in the multidisciplinary team is recommended.

Moreover, when providing a restoration, it is suggested to follow self-etching system instead of total etching, the literature elaborated that total etch has the potential of causing pulpal irritation, which in turn can lead to spontaneous abscesses (Cremonesi et al., 2014). The choice of restoration will depend on the dental development stage, however if a preformed metal crown (PMC) is considered, then implementing the hall technique is crucial to avoid drilling into dental tissue which may weaken the tooth and lead to infection (Sabandal et al., 2015).

Alongside dental extractions, root canal treatment is the other preferred option for managing dental abscesses. For XLH patients, it is important to ensure they receive excellent endodontic treatment with no voids and good apical and coronal seal. Anything less than optimal may cause continuous spontaneous abscesses and increase the likelihood of re-treatment or ultimately extraction. Several studies recommended obturating with thermoplastic, however the literature elaborated the importance of choosing an appropriate root filling material which depends on the stage of root development (Vital et al., 2012).

**Special clinical considerations include:**

- Avoid invasive treatments
- Prioritize preventative measures
- Orthodontic assessment when patient in the late mixed dentition
- Self-etching system instead of total etching
- Preformed metal crowns (PMC) using hall technique
- Provide excellent endodontic treatment

**Table 5.2.** - Summary of clinical considerations for dental professionals as stated in the literature

There is a need to develop a thorough clinical guideline for XLH dental manifestations, to aid inexperienced dentists to manage such complex cases without the need to refer to specialised centres especially when there are limited accessibility or availability. This would allow delivering proper dental management in an emergency setting.

### 5.1.3. PROMs

Following the results obtained from both medical and dental scoping reviews, it was deemed necessary to explore the patient-reported outcome measure (PROM) developed specifically for XLH children and young patients. The service evaluation aimed to highlight the range of challenges patients tend to face, from dental pain or sensitivity to spontaneous abscesses. Results from the questionnaire would help improve dental management practices and lead to a better understanding on how the choice of treatment may impact dental experience and overall quality of life.

The questionnaire can be collected during routine dental visits, either pre-, mid-, or post-dental treatment. Answers obtained at the initial dental visit can be beneficial as it establishes a baseline result, nevertheless obtaining feedback at several time frames would allow for a more impactful conclusion. For example, comparing a patient's pre- and post-treatment results may show a significant change in levels of pain or variation in dental anxiety perception. Another way can be to assess the answers of a patient with history of recurrent spontaneous abscess

before and after receiving endodontic treatment to confirm if the treatment provided was useful in managing symptoms.

Furthermore, when analysing data, it was noticed that all 13 patients were receiving medical treatment at the same establishment, 8 of which were given both CT and burosumab while the rest were treated with burosumab alone. Recommendations to investigate the impact of combining both treatments together to assess if such approach may lead to a better dental outcome in the future.

Finally, PROMs may indicate a need to explore oral health-related quality of life (OHRQoL) of paediatric patients to better understand the impact of XLH on their dental needs and overall quality of life. The results from such study may then lead to the development of a care pathway for clinicians to follow. There is currently an established care pathway between Great Ormond Street Hospital (GOSH) and Eastman Dental Hospital (EDH), as all patients are referred for a dental evaluation by their medical team with or without confirmation of dental implications. Dental assessment in a specialised centre is crucial as specialists may be more familiar with the complexity of XLH and its dental manifestations leading to appropriate necessary management (Nguyen et al., 2022).

## 5.2. General Limitations

Both scoping reviews had similar limitations to reflect upon. The medical management review only found 2 articles comparing treatment options and their impact on dental manifestations, whereas the remaining studies were investigating the safety of burosumab and benefits of converting to such novel approach. Similarly, the dental aspect of XLH was extensively researched with multiple studies addressing the specific aim of the review since 1971. Nevertheless, there was no clinical trial that compared two treatment options, for example root canal treatment versus dental extraction of abscessed teeth, which may determine the efficacy and superiority of one treatment over the other. This, however, may not be feasible or ethical, but would provide a better understanding on the appropriate dental managements for such manifestations. Thus, there is a need for additional randomised controlled trials and Cochrane reviews to establish relevant and conclusive evidence.

The inclusion criteria for the search strategy considered all types of publications from 2018 to 2023 for the medical review, as burosumab was approved in 2018. Whereas the dental management review covered a larger timeframe from 2000 to February 2022. However,

Sabandal et al. conducted a thorough dental management review in 2015, including studies from 1971 to 2013 that identified dental complications of XLH and discussed possible dental treatments for both adults and paediatric patients. Upon reflection, the current review should have included studies from 2014 to 2022 instead, this would have allowed for a more concise and easy-to-follow review, with no mention of repetitive or out-dated management regarding implications such as spontaneous dental abscesses.

Furthermore, the inclusion criteria for both reviews stated that any study included should discuss XLH patients 16 years or under. The age range was wide, covering patients from 3 to 16 years old. However, gender was not well-distributed, for instance in the dental review the 22 case reports included a total of 28 patients, 21 of which were males, while the remaining 7 were females. This may not provide a proper female perspective about XLH and its dental management.

Additionally, the vast variety of study designs and methodologies posed a challenge in drawing cohesive conclusions. It is important to note, majority of the studies were limited to single centres instead of being multicentred and international with large sample size. Also, the medical scoping review explored management from the point of view of 21 countries, with the majority being in Australia, USA, and UK. On the other hand, the current dental review defined dental implications and suggested management from 20 different countries with most of the studies being in Europe, specifically France followed by Italy, Brazil, USA, and UK. This may not provide an inclusive perspective on global dental practices. Therefore, such geographical bias may limit the application of results to the worldwide population.

The data extraction of both reviews was finalised within a specific time frame, thus the inclusion of more recent or relevant studies was not possible. Currently, the results of the review cannot confirm one treatment to be superior from a dental standpoint. Nevertheless, the clinical trial scheduled for publication in 2028, will address the identified gaps in the literature and will further increase knowledge and quality of management.

In terms of the service evaluation, it has several limitations discussed previously in more detail in Chapter 4. Generally, data collection was restricted to a small sample size due to time restraint and limited availability of patients in the department. Medical history of each patient was evaluated, with all participants on burosumab, while 8 (out of 13 patients) were on both novel and conventional treatments. It is important to mention that there was no inclusion of

patients on CT only, which would have allowed for a wider comparison between therapies. However, since burosumab is the first-line treatment, it was challenging to allocate patients on conventional therapy alone.

During the time of data collection, the youngest eligible patient was 7 years old, with an overall age range of 7 to 16 years. Nonetheless, for a more accurate representation of a specialist paediatric centre, there was a need to include younger patients. As a wider age range would enable the assessment of XLH during different dental development stages. The current analysed results are of patients in either mixed or permanent dentitions, indicating a lack of input from patients in the primary dentition. Therefore, to obtain significant results in the future, a long-term service evaluation with several cycles, larger sample size and wider age range is required. This means including patients before receiving dental treatment and following them through their dental journey until it is complete to evaluate and compare all their results.

Several modifications of the questionnaire (XLH PROM) would have been beneficial. Question 8 explored patients' happiness about their teeth but did not ask for further elaboration to why some may not be happy. Thus, including an option for a descriptive answer from those who answered 'no', could have led to the conclusion that patients are unhappy with appearance or malocclusion and not the dental manifestations such as spontaneous abscesses. Moreover, Question 11 explored the treatments each patient received, but the included options were few to choose from. The questionnaire overlooked significant treatments the majority of XLH paediatric patients may have received such as root canal treatment (RCT) and silver caps. Including more treatment options was important, as it would have allowed to compare whether patients who received extensive dental treatment were more dentally anxious or assess the level of pain or satisfaction between patients who had extractions versus RCT.

Finally, majority of patients and their parents opted to answer the online version of the questionnaire, thus there is a possibility results were influenced by the parents' point of view. Upon reflection, including questions targeted at parents or guardians would have added insightful information and allowed for both patient and parent perspectives.

## Conclusion

In summary, although XLH is a relatively rare chronic disorder, it has been widely documented in the literature. It demonstrated a significant burden in many aspects, including medical, dental, and financial. For medical management, a paediatric endocrinologist would confirm

diagnosis and provide the appropriate treatment plan. Such management would require a multidisciplinary approach, thus including dentists in the team is essential to determine dental health and address any complications associated with XLH. From the current medical review, concluding one treatment is superior to the other in the management of dental manifestations is unobtainable due to the lack of high-quality evidence. However, when dental implications worsen, recommendations to the medical team to explore novel measures is suggested. Thus, ensuring an open and constant communication between members of the multidisciplinary team would stabilise and improve the patient's overall health.

Furthermore, the dental scoping review emphasised the importance of recognising clinical and radiographic features commonly associated with XLH. Such knowledge of dental tissue alterations would aid in diagnosing and managing manifestations promptly. Generally, the management focuses on preventive care including optimal oral hygiene, application of fluoride varnish, monitor enamel cracks, and placement of fissure sealants. Nevertheless, since recurrent spontaneous abscesses is the most significant complications, treatment options were discussed in detail, including root canal treatment or dental extraction. The final decision remains subjective, depending on the treating clinician's justification, with the consideration of patient's input during the decision-making process. Patients and their parents have the right to be aware of the risks and benefits of both treatment options, and the possible alternative treatments before obtaining a valid informed consent. Although endodontic treatment would allow to maintain the tooth, this might not prevent the development of dental abscesses in the future, ultimately resulting in re-treatment or dental extractions.

Currently, there is no available clinical guideline on dental management. Thus, additional research is essential to provide appropriate guidance for dental professionals when managing children with XLH especially if access to specialised centres is not possible. Additionally, the service evaluation highlighted the range of challenges patients face, with some complaining of recurrent dental abscesses. This confirms the complexity of management and supports the timely referral to a specialised care centre to avoid further deterioration in terms of their dental health. It is also important to continue using the questionnaire at different dental developmental stages to monitor their concerns and observe any improvements in dental manifestations after certain treatments. Overtime, the PROM questionnaire would produce more significant results, which may determine if one dental treatment is superior in managing symptoms. Finally, long-term observational and randomised controlled trials are anticipated to confirm any promising results in the dental aspect of this rare disease.

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# 7. Appendices



## Appendix 1: Data Extraction of Medical Management

<b>Study Number 1</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/31104833/">https://pubmed.ncbi.nlm.nih.gov/31104833/</a>
<b>Article Title</b>	Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2019
<b>Country</b>	USA, Japan, UK, Sweden, South Korea and Australia
<b>Authors</b>	Erik A Imel, Francis H Glorieux, Michael P Whyte, Craig F Munns, Leanne M Ward, Ola Nilsson, Jill H Simmons, Raja Padidela, Noriyuki Namba, Hae Il Cheong, Pisit Pitukcheewanont, Etienne Sochett, Wolfgang Högler, Koji Muroya, Hiroyuki Tanaka, Gary S Gottesman, Andrew Biggin, Farzana Perwad, Meng Mao, Chao-Yin Chen, Alison Skrinar, Javier San Martin, Anthony A Portale
<b>Aims and Methods</b>	
<b>Aims</b>	To compare the efficacy and safety of switching to burosumab versus continuing conventional therapy among 1–12-year-old children with XLH
<b>Study Design</b>	Randomised Controlled Trial
<b>Methods</b>	Randomised, active-controlled, open-label, phase 3 trial
<b>The PCC framework</b>	
<b>Population</b>	61 children with X-linked hypophosphataemia aged 1–12 years. 32 (18 girls, 14 boys) were randomly assigned to continue receiving conventional therapy and 29 (16 girls, 13 boys) were randomly assigned to receive burosumab.
<b>Concept</b>	The primary endpoint was change in rickets severity at week 40, assessed by the Radiographic Global Impression of Change global score and compared between treatment groups.
<b>Context</b>	Recruitment took place between Aug 3, 2016, and May 8, 2017 at 16 clinical sites: five in the USA, three in Japan, three in Canada, two in the UK, one in Sweden, one in South Korea, and one in Australia.
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	Total adverse events with conventional therapy included dental caries (6%) and tooth abscess (9%) of 32 patients in this group
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	Total adverse events with Burosumab therapy included dental caries (31%) and tooth abscess (28%) of 29 patients in this group.
<b>Conventional vs novel therapy</b>	Dental treatment-emergent adverse event (TEAE) were also more frequent in the burosumab group than in the conventional therapy group. The higher frequency of dental abscess in the burosumab group might be due to patient variability, or a direct dental benefit of conventional therapy.
<b>Recommendations</b>	Previous publications suggest that conventional therapy improves dentin mineralisation and decreases the risk of dental abscesses and severe periodontal disease over years. However, correction of hypophosphataemia might not fully address or quickly reverse the components contributing to dental complications; larger numbers of patients over a longer period will be required to assess the clinical significance of this observation.

<b>Study Number 2</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/30638856/">https://pubmed.ncbi.nlm.nih.gov/30638856/</a>
<b>Article Title</b>	Efficacy and safety of burosumab in children aged 1–4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2019
<b>Country</b>	USA
<b>Authors (list as presented on paper)</b>	Michael P Whyte, Thomas O Carpenter, Gary S Gottesman, Meng Mao, Alison Skrinar, Javier San Martin, Erik A Imel
<b>Aims and Methods</b>	
<b>Aims</b>	We aimed to assess the safety and efficacy of burosumab in younger children with X-linked hypophosphataemia.
<b>Study Design</b>	Open-Label clinical trial
<b>Methods</b>	Multicentre, open-label, phase 2 trial
<b>The PCC framework</b>	
<b>Population</b>	Enrolled 13 children (aged 1-4 years) with X-linked hypophosphataemia (9 male and 4 female)
<b>Concept</b>	The coprimary endpoints were safety and change from baseline to week 40 in fasting serum phosphorus concentrations.
<b>Context</b>	Recruitment took place between May 16, 2016, and June 10, 2016 at three hospitals in USA
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	Before enrolment, child (aged 4 years) had a history of tooth abscess and extraction, and had received conventional therapy for 17 months up until a month before baseline.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	One child had a serious adverse event, a tooth abscess (right maxillary buccal and deciduous canine space abscess) that was considered unrelated to burosumab treatment, in the 35th week of treatment that resolved within 3 days with the use of antibiotics and tooth extraction. Furthermore, 15% of patients complained of toothache.
<b>Conventional vs novel therapy</b>	Burosumab had a favourable safety profile, increased serum phosphorus, and improved rickets and prevented early declines in growth in children aged 1–4 years with X-linked hypophosphataemia. These findings could substantially alter the treatment of young children with X-linked hypophosphataemia.
<b>Recommendations</b>	Long-term follow-up and future research are necessary to understand burosumab's effect on growth and to assess the need for, and to evaluate the effect of, treatment in infants younger than 1 year who have begun to show signs and symptoms of the disease.

<b>Study Number 3</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/33112809/">https://pubmed.ncbi.nlm.nih.gov/33112809/</a>
<b>Article Title</b>	Clinical guidelines for burosumab in the treatment of XLH in children and adolescents: British paediatric and adolescent bone group recommendations
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	British Paediatric and Adolescent Bone Group (BPABG) clinical guidelines
<b>Year of publication</b>	2020
<b>Country</b>	UK
<b>Authors (list as presented on paper)</b>	Raja Padidela, Moira S Cheung, Vrinda Saraff and Poonam Dharmaraj
<b>Aims and Methods</b>	
<b>Aims</b>	BPABG reviewed current evidence and provide expert recommendations for care pathway and management of XLH with burosumab
<b>Study Design</b>	Clinical guidance
<b>Methods</b>	The recommendations set via an advisory board meeting for management of XLH using burosumab following NICE authorisation for use within the NHS. The advisory board reviewed data from phase 2 and 3 clinical trials.
<b>The PCC framework</b>	
<b>Population</b>	Children and adolescents with XLH
<b>Concept</b>	We propose recommendations for the clinical management of XLH with burosumab
<b>Context</b>	Review current evidence and provide expert recommendations for care pathway and management of XLH with burosumab
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	<i>Not mentioned</i>
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	In clinical trials with burosumab the most common adverse drug reactions (ADR) reported in paediatric patients up to 64 weeks were tooth abscess (14%).
<b>Conventional vs novel therapy</b>	These recommendations from BPABG support the standardised introduction of the novel FGF23 inhibitor, burosumab, following NICE approval into clinical practice for treatment naïve paediatric and adolescent XLH patients and those who have previously been on conventional therapy.
<b>Recommendations</b>	Twice yearly dental assessment by a suitable professional is recommended in order to screen and manage dental infections and periodontitis.

<b>Study Number 4</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://www.frontiersin.org/articles/10.3389/fendo.2020.00338/full">https://www.frontiersin.org/articles/10.3389/fendo.2020.00338/full</a>
<b>Article Title</b>	Clinical Evidence for the Benefits of Burosumab Therapy for X-Linked Hypophosphatemia (XLH) and Other Conditions in Adults and Children
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2020
<b>Country</b>	Australia
<b>Authors (list as presented on paper)</b>	Aaron Schindeler, Andrew Biggin and Craig F. Munns
<b>Aims and Methods</b>	
<b>Aims</b>	Summarise the clinical trial data with respect to burosumab treatment in adults and children as well as noting several clinical trials currently underway
<b>Study Design</b>	Review
<b>Methods</b>	Review both adult and pediatric cohorts
<b>The PCC framework</b>	
<b>Population</b>	Adults and children with XLH
<b>Concept</b>	Include trials that have demonstrated efficacy and safety concerns of Burosumab
<b>Context</b>	Pediatric clinical trials involving burosumab for XLH
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	With conventional therapy for XLH there remains a major challenge around dental and periodontal complications, and a proactive approach to oral health is recommended.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	Although the benefits of burosumab have been widely described, its impact on some of the other phenotypic features of XLH (e.g., dental abscess, craniosynostosis, Chiari malformation, arthropathy, enthesopathy, etc.) remain unanswered. One notable adverse event (AE) that may be particularly important for pediatric care is the increased rate of dental abscess with burosumab treatment (31% burosumab vs. 6% placebo).
<b>Conventional vs novel therapy</b>	Overall the number of AE seen with burosumab therapy are believed to be more numerous than with conventional therapy, however the number of severe AEs that have been linked to treatment remain rare.  Low dentin mineralisation and periodontitis are common in XLH, and it remains unclear whether this is due to patient variation or a specific relative risk of burosumab vs. conventional therapy.
<b>Recommendations</b>	The development of burosumab as a therapeutic agent has been transformative for the treatment of XLH and is superior to conventional management of the condition in both adults and children.

<b>Study Number 5</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.3389/fped.2020.00048">https://doi.org/10.3389/fped.2020.00048</a>
<b>Article Title</b>	Positive Response to One-Year Treatment With Burosumab in Pediatric Patients With X-Linked Hypophosphatemia
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2020
<b>Country</b>	Spain
<b>Authors (list as presented on paper)</b>	Silvia Martín Ramos, Marta Gil-Calvo, Virginia Roldán, Ana Castellano Martínez and Fernando Santos
<b>Aims and Methods</b>	
<b>Aims</b>	To know the efficacy and safety of burosumab treatment in the everyday clinical setting
<b>Study Design</b>	Case series
<b>Methods</b>	The following data were collected from the basal visit, immediately before starting burosumab, and, when available, from each of the outpatient clinic visits during the period of burosumab treatment: height, weight, and clinical manifestations including adverse effects potentially related with the administration of burosumab as well as the presence of dental impairment
<b>The PCC framework</b>	
<b>Population</b>	Five children (three females) aged from 6 to 16 years, with genetically confirmed XLH
<b>Concept</b>	All patients received burosumab subcutaneously at a dose of 0.8 mg/kg every 2 weeks, after an initial dose of 0.4 mg/kg. Phosphate supplements and 1-hydroxy derivatives of vitamin D administration were withdrawn 2 weeks before the beginning of burosumab.
<b>Context</b>	Three Spanish hospitals
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	2 patients out of 5 experienced dental abscesses prior to the initiation of burosumab
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	As for the unsuitable effects of burosumab, no patient developed new radiological lesions, nephrocalcinosis or dental problems during the period of burosumab treatment.
<b>Conventional vs novel therapy</b>	In summary, this study shows the efficacy and safety of burosumab administered for 1 year in the clinical management and follow-up of pediatric patients with XLH.
<b>Recommendations</b>	Additional studies are necessary to assess the influence of burosumab on the long- term outcome of these patients and to define the criteria for its use.

<b>Study Number 6</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/34102329/">https://pubmed.ncbi.nlm.nih.gov/34102329/</a>
<b>Article Title</b>	X-linked hypophosphatemia and burosumab: Practical clinical points from the French experience
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2021
<b>Country</b>	France
<b>Authors (list as presented on paper)</b>	Justine Bacchettaa, Anya Rothenbuhler, Iva Gueorguieva, Peter Kamenicky, Jean-Pierre Salles, Karine Briotc, Agnès Linglart
<b>Aims and Methods</b>	
<b>Aims</b>	Discuss the specific management of burosumab in children and adolescents in daily practice.
<b>Study Design</b>	Review of the literature
<b>Methods</b>	Include clinical evidence and guidelines to determine the guidance for diagnosis, treatment, and monitoring of children affected by XLH on burosumab treatment. A consensus was reached when all panel members and authors reviewed and unanimously approved these recommendations.
<b>The PCC framework</b>	
<b>Population</b>	Children and adolescents with XLH (0 to 19 years)
<b>Concept</b>	Discuss the specific management of burosumab in children and adolescents in daily practice.
<b>Context</b>	All physicians involved in the panel discussions are experienced in the management of XLH. The group comprised pediatric and adult specialists from endocrinology, nephrology, and rheumatology.
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	One of the key treatment goals of conventional therapy is to improve dental health. Several limitations associated with conventional treatment observed were dental complications in adulthood.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	<p>Safety results showed that most adverse events (AEs) were mild and related to injection site reactions that resolved within a few days.</p> <p>Burosumab indication in children as first line of treatment include dental abscess. However, Burosumab treatment studies did not comprehensively investigate dental complications, and no reduction in dental AEs has been observed to date.</p> <p>Most common side effects in XLH patients treated with burosumab tooth abscess 35% and tooth decay 11%.</p>
<b>Conventional vs novel therapy</b>	Medically, Burosumab has been more effective than conventional therapy in children. Continuation of burosumab treatment depends on disease severity criteria, one criteria dental abscesses during the last 12 months.
<b>Recommendations</b>	<p>Many parameters, including early diagnosis, disease severity, morbidity, treatment decision, and misdiagnosis, may affect treatment outcomes and disease severity during adulthood. Patient and family awareness and education are critical for treatment outcomes. It is essential to educate parents and children about the specific conditions of treatment administration and prescription.</p> <p>Regular follow-up and monitoring are required to evaluate and ensure adherence and provide information on patient associations and centres.</p>

<b>Study Number 7</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/33970403/">https://pubmed.ncbi.nlm.nih.gov/33970403/</a>
<b>Article Title</b>	Burosumab for Pediatric X-Linked Hypophosphatemia
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2021
<b>Country</b>	USA
<b>Authors (list as presented on paper)</b>	Erik A. Imel
<b>Aims and Methods</b>	
<b>Aims</b>	This review describes advances in the management of XLH using burosumab which was FDA approved for treating children with XLH in 2018.
<b>Study Design</b>	Review of literature
<b>Methods</b>	<i>Not detailed</i>
<b>The PCC framework</b>	
<b>Population</b>	Children with XLH
<b>Concept</b>	Describes advances in the management of XLH using burosumab
<b>Context</b>	Clinical trial evidence of burosumab for XLH
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	Dental abscesses and periodontal disease remain common in children or adults with XLH even on conventional therapy.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	Dental abscesses remained common during treatment with burosumab and were actually more frequent in the burosumab-treated group than with conventional therapy in children over 64 weeks. The long-term influence of burosumab on the morbidities of XLH during adulthood also is not yet known.
<b>Conventional vs novel therapy</b>	<p>Burosumab led to greater improvement in rickets and growth than conventional therapy. However, many questions remain regarding the impact of burosumab on several outcomes, including dental disease. Both treatment options improved dentin-cementum volumes but did not improve mineral density.</p> <p>Furthermore, the annual cost of treating burosumab is many times more expensive than treating with conventional therapy.</p>
<b>Recommendations</b>	The cost-benefit ratio likely varies between those with milder and more severe musculoskeletal disease manifestations, and further studies are needed. Thus, some authors have proposed to initiate patients on conventional therapy and use burosumab when the response is inadequate.

<b>Study Number 8</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/36051396/">https://pubmed.ncbi.nlm.nih.gov/36051396/</a>
<b>Article Title</b>	Dental health of pediatric patients with X-linked hypophosphatemia (XLH) after three years of burosumab therapy
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2022
<b>Country</b>	Israel
<b>Authors (list as presented on paper)</b>	Rafi Brener, Leonid Zeitlin, Yael Lebenthal and Avivit Brener
<b>Aims and Methods</b>	
<b>Aims</b>	Explored the effect of burosumab, an anti-FGF23 antibody, on dental health of children with XLH We aimed to explore the effect of burosumab treatment on dental health, dentition and tooth morphology in pediatric patients with XLH.
<b>Study Design</b>	Prospective case- control observational study
<b>Methods</b>	The study protocol consisted of multidiscipline clinic visits at different time points during burosumab therapy (at baseline and throughout one and three years of treatment). Each visit included anthropometric measurements, physical examination, laboratory evaluation and imaging (left hand, wrists, knees and OPT). Also, orthopantomographic examinations of ten healthy sex- and age-matched controls were selected for comparison.
<b>The PCC framework</b>	
<b>Population</b>	Ten children (age 4.3-15 years) with XLH
<b>Concept</b>	Assessment of their dental status at treatment initiation and after 1 and 3 years of treatment included clinical, laboratory and radiographic evaluation of rickets and dentition.
<b>Context</b>	Patients currently being treated with burosumab in the Pediatric Bone Clinic, Dana-Dwek Children's Hospital, Tel-Aviv Sourasky Medical Centre
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	<i>Not mentioned</i>
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	The frequency of dental abscesses decreased significantly throughout the three years of burosumab treatment, with only one exception. One patient experienced recurrent dental abscesses until the tooth was extracted, suggesting that the abnormal enamel and primary dentin structure that had already been formed could not be counteracted by an increase in serum phosphate intake.  Dental abscesses and persistent periodontal disease have been commonly reported in children during the first 64 weeks of burosumab treatment.
<b>Conventional vs novel therapy</b>	Conventional therapy was found to be inadequate for improving biochemical and radiological features of the disease, while burosumab was reported as being successful in normalizing and stabilizing phosphate levels in most of the patients. Treatment aimed at increasing the serum phosphate levels and thereby improving dentin mineralisation and decreasing the rate of endodontic infections was reportedly a beneficial therapeutic strategy.
<b>Recommendation</b>	In conclusion, burosumab treatment normalized phosphate levels, healed rickets and improved linear growth. Regrettably, the dental morphology of XLH patients as evidenced by excessively larger pulp dimensions did not exhibit the desired decrease in the pulp dimensions expected with age. Our findings suggest that PHEX-related local mineralisation inhibitors, such as osteopontin, play a critical role in dental morbidity. Future therapeutic modalities should target the local hypomineralisation defects.



<b>Study Number 9</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/36398111/">https://pubmed.ncbi.nlm.nih.gov/36398111/</a>
<b>Article Title</b>	Burosumab and Dental Abscesses in Children With X-Linked Hypophosphatemia
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2022
<b>Country</b>	France
<b>Authors (list as presented on paper)</b>	Margaux Gadion, Agathe Hervé, Julia Herrou, Anya Rothenbuhler, Violaine Smail-Faugeron, Frédéric Courson, Agnès Linglart, Catherine Chaussain and Martin Biosse Duplan
<b>Aims and Methods</b>	
<b>Aims</b>	The main objective of our study was to compare the incidence of dental abscesses with XLH treated with either CT or burosumab
<b>Study Design</b>	Monocentric retrospective study
<b>Methods</b>	Measured and compared the incidence of dental abscess in children with XLH treated with either CT or burosumab, followed at our dental centre for at least 1 year. The primary endpoint was the number of dental abscesses per month of dental follow-up.
<b>The PCC framework</b>	
<b>Population</b>	A total of 71 children with XLH were included in the study, with a mean $\pm$ standard deviation (SD) age at the start of dental follow-up of $7.86 \pm 3.76$ . 38 children were treated with CT (53.5%) and 33 with burosumab (46.5%).
<b>Concept</b>	The primary objective of our research was to compare the incidence of dental abscesses in children and adolescents with XLH treated with either CT or burosumab. The secondary objective was to compare the incidence of cellulitis of odontogenic origin.
<b>Context</b>	Referred to and followed in our centre for oral health care from 2019 to 2022.
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	Hypomineralised and hypoplastic dentin is the main driver of spontaneous dental abscesses. Conventional treatment (CT) of XLH improves this tissue defect and reduces the occurrence of dental abscesses. CT also improves dentin formation and mineralisation during tooth formation.(17) This translates into a reduced prevalence of dental abscesses and reduced premature tooth loss in XLH patients treated with CT.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	The impact of burosumab on the mineralisation of dental tissues and on oral complications is unknown. Here, for the first time, we report a possible beneficial effect of burosumab on the occurrence of endodontic infections (dental abscesses) in children. In the study population, the incidence of a dental abscess during the dental follow-up was very high, with 40.8% of the children presenting with at least one abscess, comparable with other studies.
<b>Conventional vs novel therapy</b>	All children treated with burosumab had previously been treated with CT. The mean number of dental abscesses per month of dental follow-up was significantly reduced in the burosumab group compared with the CT group (0.01 versus 0.04; $p = 0.04$ ). Burosumab treatment appears to be associated with a reduction in the number of dental abscesses in XLH children, compared with CT.  We compared the evolution of the size of the pulp chambers on successive radiographs, but we could not conclude on differences between treatments.
<b>Recommendation</b>	Although these results are encouraging, they show that dental follow-up is particularly important regardless of the treatment of XLH. They must be con- firmed in other centres and in controlled prospective studies.

<b>Study Number 10</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1007/s00467-022-05484-7">https://doi.org/10.1007/s00467-022-05484-7</a>
<b>Article Title</b>	Real-world effectiveness of burosumab in children with X-linked hypophosphatemic rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2022
<b>Country</b>	USA
<b>Authors (list as presented on paper)</b>	Neil J. Paloian, Blaise Nemeth, Mark Sharafinski, Peggy Modaff, and Robert D. Steiner
<b>Aims and Methods</b>	
<b>Aims</b>	We aimed to assess the effectiveness of burosumab in a real-world clinical pediatric practice.
<b>Study Design</b>	Retrospective single-centre study
<b>Methods</b>	Study identified and retroactively studied twelve patients aged 1–18 years old with XLH previously treated with conventional therapy and transitioned to burosumab. Laboratory studies and radiographs were obtained routinely as standard of care during two treatment periods: (1) conventional therapy and (2) burosumab treatment. Laboratory values and radiologic rickets severity scores were compared between periods.
<b>The PCC framework</b>	
<b>Population</b>	Twelve patients aged 1–18 years old with XLH previously treated with conventional therapy and transitioned to burosumab
<b>Concept</b>	We compared laboratory and radiographic changes observed following transition from conventional therapy to burosumab in pediatric XLH patients as part of routine care.
<b>Context</b>	Patients receiving care at the University of Wisconsin Hospitals and Clinics, treated with burosumab between April 1, 2018, and May 31, 2020.
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	Conventional treatment of XLH continues to be recommended by some specialists due to lack of published experience with burosumab in the clinical setting. History of dental abscesses in 2 out of 12 (17%) at baseline prior to initiation of Burosumab.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	One patient developed a dental abscess while on burosumab that was successfully treated with antibiotics and oral surgery; no adjustments were made to the burosumab dosing.
<b>Conventional vs novel therapy</b>	Our study demonstrates that burosumab is safe and more effective than conventional therapy in treating real-world pediatric XLH patients and supports the use of burosumab as the first-line therapy for children with XLH.
<b>Recommendation</b>	Further longitudinal, long-term, multicentre studies are needed to assess real-world long-term safety and effectiveness of burosumab in larger cohorts.

<b>Study Number 11</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://onlinelibrary.wiley.com/doi/full/10.1111/jpc.15976">https://onlinelibrary.wiley.com/doi/full/10.1111/jpc.15976</a>
<b>Article Title</b>	Clinical practice guidelines for paediatric X-linked hypophosphataemia in the era of burosumab
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2022
<b>Country</b>	Australia
<b>Authors (list as presented on paper)</b>	Jessica L Sandy, Peter J Simm, Andrew Biggin, Christine P Rodda, Christie-Lee Wall, Aris Siafarikas and Craig F Munns
<b>Aims and Methods</b>	
<b>Aims</b>	The aim is to outline a clinical practice guideline for burosumab use in children with XLH to assist local clinicians, encourage consistency of management across Australasia and suggest some future directions for management and research.
<b>Study Design</b>	Clinical guideline
<b>Methods</b>	Recommendations were evaluated using the Grading of Recommendations, Assessment, Development and Evaluation system (GRADE) as recommended by the National Health and Medical Research Council (NHMRC).
<b>The PCC framework</b>	
<b>Population</b>	Children with XLH
<b>Concept</b>	Guideline and Recommendations for the Use of Burosumab Therapy
<b>Context</b>	All available research
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	Conventional treatment is onerous; frequent monitoring is required to prevent complications; phosphate is taken multiple times per day, has an unpleasant taste and can cause gastrointestinal side effects. These factors contribute to the burden of disease in XLH and poor adherence. No mention to impact on dental manifestations.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	The effect of burosumab on dental manifestations in XLH is unclear. The phase 3 RCT of burosumab versus conventional therapy in children with XLH noted a numerical increase in frequency of dental complications in the burosumab group, but the clinical relevance of this has not been determined. This has not been seen in other studies and further research is needed.
<b>Conventional vs novel therapy</b>	Burosumab has transformed management of XLH and been shown to result in significant improvements in burden of disease.
<b>Recommendation</b>	<p>Patients should have a dental review prior to commencing therapy and maintain good oral hygiene and dental reviews throughout therapy.</p> <p>Abnormal tooth development in XLH results in increased risk of periodontal disease, dental caries and abscess, so dental hygiene and frequent dental reviews are important, with 6 monthly review recommended in childhood.</p> <p>A coordinated multidisciplinary team is integral to the management of all individuals with rare bone diseases, yet there is variable access to this across Australasia and the world.</p>

<b>Study Number 12</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/35484227/">https://pubmed.ncbi.nlm.nih.gov/35484227/</a>
<b>Article Title</b>	Interdisciplinary management of FGF23-related phosphate wasting syndromes: a Consensus Statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2022
<b>Country</b>	Switzerland, Saudi Arabia, Italy, Spain, Belgium, Singapore, France, UK, Germany, Canada, Australia, Austria, Portugal, Bulgaria and Argentina
<b>Authors (list as presented on paper)</b>	Andrea Trombetti, Nasser Al-Daghri, Maria Luisa Brandi, Jorge B. Cannata-Andía, Etienne Cavalier, Manju Chandran, Catherine Chaussain, Lucia Cipullo, Cyrus Cooper, Dieter Haffner, Pol Harvengt, Nicholas C. Harvey, Muhammad Kassim Javaid, Famida Jiwa, John A. Kanis, Andrea Laslop, Michaël R. Laurent, Agnès Linglart, Andréa Marques, Gabriel T. Mindler, Salvatore Minisola, María Concepción Prieto Yerro, Mario Miguel Rosa, Lothar Seefried, Mila Vlaskovska, María Belén Zanchetta and René Rizzoli
<b>Aims and Methods</b>	
<b>Aims</b>	This Consensus Statement presents the outcomes of a working group of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, and provides robust clinical evidence on management in XLH, with an emphasis on patients' experiences and needs.
<b>Study Design</b>	Narrative literature review
<b>Methods</b>	This Consensus Statement provides the consensus of an expert working group, comprised a diverse panel of 25 expert clinicians from 14 countries chosen for their expertise and publication record in XLH and related disorders. The group also included two patients with XLH and one relative.
<b>The PCC framework</b>	
<b>Population</b>	Patients with XLH
<b>Concept</b>	Topics considered by the group included: pathophysiology of phosphate wasting syndromes; laboratory assessment; burden of XLH disease; management of phosphate wasting syndromes in children and adolescents; management of phosphate wasting syndromes in adults and the role of dentists and orthopaedic surgeons in the management of patients with phosphate wasting syndromes.
<b>Context</b>	All research available
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	In children, the clinical efficacy of conventional treatment is well established, in terms of decreased occurrence of dental complications and pain control. The earlier that conventional treatment is started in individuals with XLH during the growth period and in adulthood, the lower the incidence of dental abscesses and periodontitis. This effect occurs through an improvement in dentin and cementum mineralisation as shown in observational studies.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	The effects of burosumab on dental abnormalities are rather disappointing, with a phase III comparative study in children with XLH showing more events such as spontaneous dental necrosis in the burosumab arm than with conventional treatment.
<b>Conventional vs novel therapy</b>	Such an instrument was used in a phase III clinical study of children with XLH and showed that burosumab improved patient-reported outcome (PRO) measures as compared with conventional treatment. However it only focused on measuring pain, fatigue and physical function, etc.
<b>Recommendation</b>	Long-term studies are also needed to evaluate the effect of this therapy on the clinical burden of XLH, such as bone deformities, dental complications and the number of surgical interventions. Thus, in children with mild disease who are easily managed with conventional therapy, treatment with burosumab is probably not warranted because of the large annual cost of the drug (around US \$200,000).

<b>Study Number 13</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1210/clinem/dgac296">https://doi.org/10.1210/clinem/dgac296</a>
<b>Article Title</b>	Effect of Burosumab Compared With Conventional Therapy on Younger vs Older Children With X-linked Hypophosphatemia
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2022
<b>Country</b>	Canada, USA, Australia, Austria, UK, Japan, Sweden
<b>Authors (list as presented on paper)</b>	Leanne M. Ward, Francis H. Glorieux, Michael P. Whyte, Craig F. Munns, Anthony A. Portale, Wolfgang Högl, Jill H. Simmons, Gary S. Gottesman, Raja Padidela, Noriyuki Namba, Hae Il Cheong, Ola Nilsson, Meng Mao, Angel Chen, Alison Skrinar, Mary Scott Roberts, and Erik A. Imel.
<b>Aims and Methods</b>	
<b>Aims</b>	This work aimed to explore the efficacy and safety of burosumab vs Pi/D in younger (< 5 years) and older (5-12 years) children with XLH.
<b>Study Design</b>	Randomized, active-controlled, open-label, phase 3 study
<b>Methods</b>	The main outcome measure included the least squares means difference (LSMD) in Radiographic Global Impression of Change (RGI-C) rickets total score from baseline to week 64.
<b>The PCC framework</b>	
<b>Population</b>	Sixty-one children aged 1 to 12 years with XLH (younger, n = 26; older, n = 35)
<b>Concept</b>	Explore the efficacy and safety of burosumab vs Pi/D in younger (< 5 years) and older (5-12 years) children with XLH.
<b>Context</b>	The study was conducted at 16 academic health centres in the United States (n = 5), Japan (n = 3), Canada (n = 3), the United Kingdom (n = 2), Sweden (n = 1), South Korea (n = 1), and Australia (n = 1).
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	Dental abscesses occurred in 3 of 12 (25%) younger children who received Pi/D compared with 0 of 20 (0%) of the younger children who received burosumab, whereas 8 of 15 (53%) older children who received burosumab had dental abscesses compared with 0 of 20 (0%) who received Pi/D.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	In this study, none of the younger children who received burosumab experienced dental abscesses, whereas dental abscesses occurred in 53% of the older children who received burosumab.
<b>Conventional vs novel therapy</b>	Dental caries, which were reported more frequently with burosumab than Pi/D (9/29 [31%] vs 2/32 [6%]), occurred slightly more often in older than younger children who received Pi/D (2/20 [10%] vs 0/12 [0%]) and slightly more often in younger than older children who received burosumab (5/14 [36%] vs 4/15 [27%]).  Improvements in phosphate homeostasis, rickets, and lower limb deformities were greater switching to burosumab than continuing Pi/D both in younger and older children with XLH.
<b>Recommendation</b>	Further clinical studies that are sufficiently powered are needed to specifically address whether initiating burosumab at an earlier (rather than later) age ameliorates growth, lower limb deformity, and the risk of dental abscesses.  The XLH Disease Monitoring Program (ClinicalTrials.gov No. NCT03651505) will provide long-term (10 years) longitudinal evaluation of patients with XLH with or without treatment with burosumab.

<b>Study Number 14</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1016/j.bone.2023.116791">https://doi.org/10.1016/j.bone.2023.116791</a>
<b>Article Title</b>	Prevalence and characteristics of paediatric X-linked hypophosphataemia in Australia and New Zealand (NZ): Results from the Australian and the New Zealand Paediatric Surveillance Units survey
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2023
<b>Country</b>	Australia and New Zealand
<b>Authors (list as presented on paper)</b>	Jessica L. Sandy, Carlos Nunez, Benjamin J. Wheeler, Craig Jefferies, Anne Morris, Aris Sifarikas, Christine P. Roddaj, Peter Simm, Andrew Biggin, Sonya Aum, Elizabeth J. Elliot, Craig F. Munns
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of this study is to investigate the prevalence of XLH rickets in Australia and NZ and to describe the associated demographic and clinical characteristics of paediatric XLH.
<b>Study Design</b>	Surveillance Units survey
<b>Methods</b>	Australian and New Zealand Paediatric Surveillance Units collected cross-sectional data from paediatricians on existing cases to estimate prevalence and characteristics of paediatric XLH in Australia and New Zealand.
<b>The PCC framework</b>	
<b>Population</b>	91 paediatric patients with XLH (75 in Australia and 16 in New Zealand)
<b>Concept</b>	Data including demographic, clinical characteristics (including dental manifestations) and overall management of XLH
<b>Context</b>	Investigators from Australia and New Zealand worked collaboratively to determine the prevalence of XLH and collect the same data on children in Australia and New Zealand with XLH
<b>Themes / Outcomes</b>	
<b>Impact of conventional therapy on dental manifestations</b>	100% of patients in New Zealand received conventional therapy, whereas 44% of patients in Australia received it. Out of the 16 patients in NZ, 6% experienced tooth abscess during the study.
<b>Effect of Burosumab (novel therapy) on dental manifestations</b>	In Australia, 56% were on burosumab and none of the children from NZ were on it. This study was not designed to assess the effect of burosumab. The etiology of dental disease is poorly understood and the impact of burosumab on dental abnormalities is unclear
<b>Conventional vs novel therapy</b>	There were no other statistically significant differences between those on burosumab and those not on burosumab when comparing clinical features and biochemistry.
<b>Recommendation</b>	<p>More research is also needed to better elicit the mechanism of dental disease in XLH to help improve oral health for individuals with XLH, and an emphasis on improving communication and coordination of care between health professionals has the potential to improve quality of management.</p> <p>Burosumab is a promising new therapy and these data support clinical trial and real world data of improving biochemistry and subsequently burden of disease. Further research is needed to assess the long term effect of burosumab therapy within a modern management framework of XLH in Australia and NZ.</p>

## Appendix 2: Data Extraction Tool of Dental Management

<b>Study Number 1</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/10982952/">https://pubmed.ncbi.nlm.nih.gov/10982952/</a>
<b>Article Title</b>	Familial hypophosphatemic vitamin D-resistant rickets: Dental findings and histologic study of teeth
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2000
<b>Country</b>	Japan
<b>Authors</b>	Takafumi Murayama, Reiko Iwatsubo, Shigehisa Akiyama, Atsuo Amano, and Ichijiro Morisaki
<b>Aims and Methods</b>	
<b>Aims</b>	Report the dental findings of familial XLH in a 15-year-old Japanese boy, as well as the histologic findings of his extracted mandibular right third molar. Discuss the treatment provided in this case
<b>Study Design</b>	Case report
<b>Methods</b>	A 15-year-old boy with XLH visited our facility complaining of a toothache in the left lower canine region
<b>The PCC framework</b>	
<b>Population</b>	15 years old male with XLH
<b>Concept</b>	Dental findings, histologic study of teeth and discussion of treatment
<b>Context</b>	Department of Oral and Maxillofacial Surgery at Kyoto First Red Cross Hospital
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Spontaneous Dental Abscess and non-vital pulp. No clinically detectable changes such as caries, tooth fractures, or periodontal pockets that could induce pulp necrosis were found. Also, no enamel defects or hypoplasia noted. However, dentition is highly susceptible to dental caries or attrition.
<b>Key radiographic features</b>	Short roots and large pulp chambers. Also, perapical radiolucencies observed. Root dysplasia and absence of lamina dura in incisors and premolars.
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- For periodontal abscess: incision and drainage to relieve pain followed by endodontic treatment.</li> <li>- Early treatment and preventive care for caries and attrition including professional dental care consisting of periodical examinations, topical fluoride application, and the maintenance of good oral hygiene should be performed</li> <li>- Application of prefabricated metal crowns for primary teeth without caries is effective in preventing attrition and enamel microfracture</li> </ul>
<b>Special clinical consideration</b>	Aggressive preventive method cannot be adopted in all patients, because not all pulp tissue is infected and iatrogenic pulp infection may occur during crown prep.

<b>Study Number 2</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1111/j.1747-4477.2001.tb00340.x">https://doi.org/10.1111/j.1747-4477.2001.tb00340.x</a>
<b>Article Title</b>	Endodontic Management Of a Patient With X-linked Hypophosphataemic Rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Clinical Review and Case report
<b>Year of publication</b>	2001
<b>Country</b>	Australia
<b>Authors</b>	S. Alexander, L. Moloney, and N. Kilpatrick
<b>Aims and Methods</b>	
<b>Aims</b>	Report of a 16-year-old male with history of XLH and unusual root configuration of lower anterior teeth which posed an endodontic challenge
<b>Study Design</b>	Case report
<b>Methods</b>	Patient presented to the Department of Dentistry at the Royal Children's Hospital, Melbourne for dental treatment of multiple dental abscesses in the lower anterior teeth.
<b>The PCC framework</b>	
<b>Population</b>	16-year-old male, with a history of XLH since the age of 2
<b>Concept</b>	Dental finding and management of XLH
<b>Context</b>	Department of Dentistry at the Royal Children's Hospital, Melbourne for dental treatment of multiple dental abscesses in the lower anterior teeth.
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Most primary dentition extracted due to spontaneous abscess, incisal wear on lower anterior with necrotic pulp.
<b>Key radiographic features</b>	Large pulp spaces with high pulp horns. Upper right permanent lateral incisors and all four lower incisors had curvatures with periapical lesions. Taurodontism of permanent molars.
<b>Dental management of XLH</b>	Endodontic treatment of affected teeth was indicated as appropriate therapy. Nevertheless, patient will require regular reviews as his history would suggest spontaneous recurrent abscesses involving other teeth in the future is very likely.
<b>Special clinical consideration</b>	<ul style="list-style-type: none"> <li>- Limit crown preparation as this may further compromise pulp</li> <li>- Pulp therapy can be successful in XLH patients</li> <li>- Use of sealants was not encouraged as acid may penetrate into pulp chamber via enamel cracks</li> <li>- Alternatively, use glass ionomer cement over occlusal/incisal surfaces</li> <li>- PMC for primary teeth and full veneer gold crowns for permanent teeth</li> <li>- Nightguard acrylic splint to reduce attrition which may subsequently lead to abscess formation</li> </ul>



<b>Study Number 3</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/12212880/">https://pubmed.ncbi.nlm.nih.gov/12212880/</a>
<b>Article Title</b>	Evaluation of aggressive pulp therapy in a population of vitamin D-resistant rickets patients: a follow-up of 4 cases
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2002
<b>Country</b>	USA
<b>Authors</b>	Deven V. Shroff, DMD, Alton G. McWhorter, DDS, MS, N. Sue Seale, DDS, MSD
<b>Aims and Methods</b>	
<b>Aims</b>	The purpose of this investigation was to examine the records of patients who have received the aggressive pulp treatment to determine its effectiveness in saving primary teeth from extraction.
<b>Study Design</b>	Case report
<b>Methods</b>	This investigation collected clinical and radiographic data from a retrospective chart review of patients diagnosed with VDRR and treated dentally since the pulp therapy recommendation was made in 1991.
<b>The PCC framework</b>	
<b>Population</b>	4 patients (3 to 7 years old), previously received aggressive prophylactic pulp treatment of primary teeth
<b>Concept</b>	Clinical and radiographic data of patients with at least one posterior primary tooth treated with a standard 5-minute formocresol pulpotomy
<b>Context</b>	Texas Scottish Rite Hospital for Children in Dallas, Texas
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	The first clinical abscess occurs prior to age 3 years, 9 months All patients presented with spontaneous abscesses
<b>Key radiographic features</b>	Enlarged pulp chamber / Periapical radiolucency / Furcation involvement / External and internal resorption
<b>Dental management of XLH</b>	In an attempt to preserve the primary dentition, all patients received prophylactic pulpotomy and stainless steel crown – which reported to clinically fail
<b>Special clinical consideration</b>	The results reported from these 4 cases indicate that prophylactic pulpotomy therapy does not appear to be successful and cannot be recommended

<b>Study Number 4</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://www.sciencedirect.com/science/article/abs/pii/S0022347602403691">https://www.sciencedirect.com/science/article/abs/pii/S0022347602403691</a>
<b>Article Title</b>	Dental Abnormalities In Patients With Familial Hypophosphatemic Vitamin D–Resistant Rickets: Prevention By Early Treatment With 1-Hydroxyvitamin D
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2003
<b>Country</b>	France
<b>Authors</b>	Catherine Chaussain-Miller, MD, Christiane Sinding, Md, Maryse Wolikow, Md, Phd, Jean-Jacques Lasfargues, Md, Phd, Gaston Godeau, Phd, And Michèle Garabédian, Md, Phd
<b>Aims and Methods</b>	
<b>Aims</b>	To evaluate the dental effects of 1-hydroxylated vitamin D3 treatment in patients with familial hypophosphatemic vitamin D–resistant rickets.
<b>Study Design</b>	Clinical trial
<b>Methods</b>	All patients were clinically examined, and panoramic and periapical radiographs were made. Evaluations of decayed, missing, or filled teeth and decayed or filled teeth indexes and of pulp ratios allowed comparison with healthy age- matched control patients.
<b>The PCC framework</b>	
<b>Population</b>	Forty-eight children and adult patients were included in the study, 32 patients (age range 3-25) were the younger group
<b>Concept</b>	Evaluate the effect of medical treatment on dental status
<b>Context</b>	Outpatients in the Saint Vincent de Paul Hospital, Paris
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	White or brown enamel spots (enamel defects) observed more frequently on permanent teeth than on primary teeth (35% vs 8%).  Only 3 of the 32 patients, all boys, had dental abscesses on primary molars not related to trauma or caries.
<b>Key radiographic features</b>	Normal dentine aspect of the primary and permanent teeth and all had normal radiodensity of the alveolar bone.  Abnormal persistence of prominent pulp horns of primary molars extending up to or beyond the dentino-enamel junction. The pulp horn enlargement was less frequently observed in permanent teeth  Taurodontism, short dental crowns, and long roots are shown
<b>Dental management of XLH</b>	10 out of 32 patients previously received endodontic treatment
<b>Special clinical consideration</b>	Local prophylactic measures have therefore been proposed to prevent the occurrence of multiple dental abscesses

<b>Study Number 5</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1111/j.1834-7819.2003.tb00026.x">https://doi.org/10.1111/j.1834-7819.2003.tb00026.x</a>
<b>Article Title</b>	Diagnosis and management of unusual dental abscesses in children
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2003
<b>Country</b>	Australia
<b>Authors</b>	WK Seow
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of this paper is to review these unusual conditions which are commonly associated with pulpal abscesses in children, in order to update the dental practitioner in the diagnosis and management of these entities.
<b>Study Design</b>	Review
<b>Methods</b>	In the present paper, these relatively unknown entities which cause unusual abscesses in children are reviewed with the aim of updating the general practitioner in their diagnosis and management
<b>The PCC framework</b>	
<b>Population</b>	Available research on paediatric patients
<b>Concept</b>	Literature available of unusual conditions associated with pulpal abscesses
<b>Context</b>	All available research
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	'Spontaneous' dental abscesses in the absence of caries or trauma
<b>Key radiographic features</b>	The pulps of the teeth are large and the radiodensity of dentine is reduced. Periapical and furcation radiolucencies of primary teeth. Taurodontism is also reported.
<b>Dental management of XLH</b>	The main management strategy is prevention of pulpal abscesses. Primary: <ul style="list-style-type: none"> <li>- Incisor teeth: Composite resins</li> <li>- Molar teeth: Prophylactic coverage of teeth with steel crowns (Hall technique) to reduce risk of pulp exposure with conventional techniques</li> </ul> Permanent: <ul style="list-style-type: none"> <li>- Partially erupted molars: protect the occlusal surfaces with composite resin</li> <li>- Fully erupted molars: stainless steel crowns</li> </ul>
<b>Special clinical consideration</b>	<ul style="list-style-type: none"> <li>- Dentists should be alerted to this condition as the systemic features may be mild, and dental abscesses may be the first presenting signs</li> <li>- Usually, the younger the patient when the first abscesses occur, the more severe the dental manifestation.</li> </ul>

<b>Study Number 6</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/16842025/">https://pubmed.ncbi.nlm.nih.gov/16842025/</a>
<b>Article Title</b>	Prevalence and pathogenesis of dental and periodontal lesions in children with X-linked hypophosphatemic rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2006
<b>Country</b>	Italy
<b>Authors and affiliations</b>	G.I. Baroncelli, M. Angiolini, E. Ninni, V. Galli, R. Saggese, and M.R. Giuca
<b>Aims and Methods</b>	
<b>Aims</b>	To assess the prevalence and to investigate the pathogenetic mechanisms of dental and periodontal lesions in children with X-linked hypophosphatemic rickets (XLH) examined at diagnosis or during treatment.
<b>Study Design</b>	Quasi-experiment
<b>Methods</b>	Oral examination was performed according to the evidence of carious and gingival lesions. Decayed or filled teeth (dft) index for primary teeth, and the decayed, missing, or filled teeth (DMFT) index for permanent teeth was assessed. All patients with a history of spontaneous dental abscesses underwent orthopantomography examination.
<b>The PCC framework</b>	
<b>Population</b>	Nine children with XLH (2.0 to 13.3 years)
<b>Concept</b>	Clinical and biochemical data of patients at entry into the study. Dental and periodontal lesions examined.
<b>Context</b>	Department of Neuroscience, Division of Dentistry, University of Pisa, Italy
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Six out of nine patients (67%) had a history of spontaneous fistulae as a consequence of periapical abscesses occurring in the absence of dental decay or history of injury.  One patient had enamel hypoplasia and two had enamel dyschromic alterations.
<b>Key radiographic features</b>	Enlarged pulp chambers associated with prominent pulp horns extending up to the dentino-enamel junction in both primary and permanent dentition.
<b>Dental management of XLH</b>	One patient underwent endodontic treatment.  Regular dental care with periodic examinations by specialists, topical applications and systemic fluoride administration, pit and fissure sealants, and maintenance of good oral hygiene are strongly indicated in order to reduce the risk of spontaneous abscesses and fistulae caused by the penetration of microorganisms through dentinal clefts
<b>Special clinical consideration</b>	Not mentioned

<b>Study Number 7</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.5395/rde.2017.42.2.146">https://doi.org/10.5395/rde.2017.42.2.146</a>
<b>Article Title</b>	X-Linked Hypophosphatemia: Dental and Histologic Findings
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2006
<b>Country</b>	UK
<b>Authors and affiliations</b>	Puneet Batra, Zahra Tejani and Michael Mars
<b>Aims and Methods</b>	
<b>Aims</b>	To review the features of this disorder and to discuss the risks and benefits of the treatment options suggested in the literature.
<b>Study Design</b>	Case report
<b>Methods</b>	Patient was referred to the department for dental evaluation and reviewed until the age of 11.
<b>The PCC framework</b>	
<b>Population</b>	A 3-year-old boy with XLH
<b>Concept</b>	Dental and histological findings
<b>Context</b>	The maxillofacial and dental department at Great Ormond Street Hospital for Children
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscesses at regular intervals between the age of 4 and 10 years, teeth were sound, caries-free and no history of trauma.  Deep fissures of permanent molars
<b>Key radiographic features</b>	Spontaneous root resorption / Turodontism / Severley malpositioned canine
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Extraction under local anesthetic of primary teeth with history of abscess to prevent further abscess formation.</li> <li>- Remaining primary molars required preventive stainless steel crowns</li> <li>- Permanent molars required fissure sealants</li> <li>- Surgical removal of ectopic canine</li> </ul>
<b>Special clinical consideration</b>	<p>Fissure sealants to prevent ingress of bacteria into the enamel microfractures.</p> <p>Caution during crown preparation, minimal to avoid inadvertent pulp exposure</p> <p>Occurrence of spontaneous abscesses following a shallow cavity preparation necessitates aggressive preventive dental procedures.</p> <p>Extraction of teeth at presentation of abscess is controversial, and the success of endodontic treatment is questionable</p>

<b>Study Number 8</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/17825183/">https://pubmed.ncbi.nlm.nih.gov/17825183/</a>
<b>Article Title</b>	Oral findings of hypophosphatemic vitamin D-resistant rickets: report of two cases
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2007
<b>Country</b>	China
<b>Authors and affiliations</b>	SU Ji-mei, LI Yun, YE Xiao-wei and WU Zhi-fang
<b>Aims and Methods</b>	
<b>Aims</b>	Present oral findings in two cases in one family, mother and her daughter
<b>Study Design</b>	Case report
<b>Methods</b>	Dental history, general physical examination, oral examination and laborartoy examination gathered
<b>The PCC framework</b>	
<b>Population</b>	3 years and 1 month old Chinese girl
<b>Concept</b>	Oral findings of XLH
<b>Context</b>	Children's Hospital, School of Medicine, Zhejiang University, China
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	<p>Premature exfoliation of primary maxillary central incisors at the age of 2, teeth were intact, caries-free and no history of trauma.</p> <p>Teeth were loose, increased mobility</p>
<b>Key radiographic features</b>	Enlarged pulp chambers, radioclar canals and open apices in all primary teeth. Large pulp horns in all second primary molars, the horns extended to the dentino-enamel junctions. Short roots in mandibular incisors and hypoplastic alveolar ridge was observed.
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Topical fluoride varnish to anterior primary teeth</li> <li>- Pit and fissure sealants to primary molar teeth</li> </ul>
<b>Special clinical consideration</b>	To prevent multiple dental abscesses, both early treatment and preventive care for caries and attrition are necessary

<b>Study Number 9</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1016/j.tripleo.2008.12.003">https://doi.org/10.1016/j.tripleo.2008.12.003</a>
<b>Article Title</b>	Familial hypophosphatemic vitamin D-resistant rickets—prevention of spontaneous dental abscesses on primary teeth: A case report
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2009
<b>Country</b>	France
<b>Authors</b>	Diane Douyere, Clara Joseph, Céline Gaucher, Catherine Chaussain, and Frederic Courson
<b>Aims and Methods</b>	
<b>Aims</b>	This report describes the case of a young hypophosphatemic boy with abscesses.
<b>Study Design</b>	Case report
<b>Methods</b>	Patient referred by Saint Vincent de Paul Hospital for an abscess
<b>The PCC framework</b>	
<b>Population</b>	A 4-year-old boy with XLH inherited from his mother
<b>Concept</b>	Prevention of spontaneous dental abscesses
<b>Context</b>	Referred to the Dentistry Department of the Bretonneau Hospital in November 2005
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscesses with severe mobility
<b>Key radiographic features</b>	Severe alveolar bone loss
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Prophylactic cleaning every 3-6 months</li> <li>- Application of fluoride varnish</li> <li>- 5 extractions of primary teeth</li> <li>- 2 endodontic treatment of primary teeth</li> <li>- As a preventative measure all occlusal surfaces were covered with fluid resin composite with a self-etching bonding system. Reapplied 10 months after first application</li> <li>- Prophylactic sealing of FPMs</li> </ul>
<b>Special clinical consideration</b>	<p>This report proposes replacement of the systematic crowning of primary teeth by resin composite sealing to prevent spontaneous necrosis of primary teeth</p> <p>Self-etching bonding system has low viscosity, offers easy application (absence of rinsing, decreased operative time) and optimally fills the cracks without damage. Moreover, its mechanical resistance confers a lifespan comparable with that of usual wear and tear by bruxism of primary teeth seen in any child of the same age</p>

<b>Study Number 10</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1590/S1807-59322010001000017">https://doi.org/10.1590/S1807-59322010001000017</a>
<b>Article Title</b>	Dental abnormalities and oral health in patients with Hypophosphatemic rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2010
<b>Country</b>	Brazil
<b>Authors</b>	Melissa Almeida Souza, Luiz Alberto Valente Soares Junior, Marcela Alves dos Santos, Maria Helena Vaisbich
<b>Aims and Methods</b>	
<b>Aims</b>	To verify the dental abnormalities and the oral health condition in XLH patients
<b>Study Design</b>	Prospective study
<b>Methods</b>	This report employed a simple method to be easily reproducible: oral clinical exam and radiographic evaluation.
<b>The PCC framework</b>	
<b>Population</b>	14 patients, median age of 11 year (range 4 to 26) – 5 males and 9 females
<b>Concept</b>	Oral conditions in patients with Hypophosphatemic rickets
<b>Context</b>	Pediatric Nephrology Unit of Instituto da Crianca – Hospital das Clinicas da Faculdade de Medicina da Universidade de Sa˜o Paulo (HCFMUSP)
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Enamel hypoplasia in 8 patients (57.1%), occlusal defects (such as open bite and crossbite) in 12 patients (85.7%) and dental abscess only in 1 patient (7.1%).
<b>Key radiographic features</b>	Enlarged pulp chambers in 6 patients (42.8%), Hypoplasia in 2 patients (14.3%) and dentine alterations in 2 patients (14.3%)
<b>Dental management of XLH</b>	Periodic oral examinations; topical fluoride applications, pit and fissure sealants and maintenance of good oral hygiene.
<b>Special clinical consideration</b>	Permanent teeth form after birth, and their development could potentially be improved by the initiation of medication soon after birth. Early medical treatment could probably avoid dental abscess formation. Also, pit and fissure sealants are useful when the teeth are erupting



<b>Study Number 11</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://www.ijcpd.com/doi/pdf/10.5005/jp-journals-10005-1046">https://www.ijcpd.com/doi/pdf/10.5005/jp-journals-10005-1046</a>
<b>Article Title</b>	Dental Development in Patients with Hypophosphatemic Rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2010
<b>Country</b>	Jordan
<b>Authors</b>	Al-Jundi SH and Hazza'a AM
<b>Aims and Methods</b>	
<b>Aims</b>	To assess dental development of a group of children with (HR) and to compare that to healthy matched controls, and to assess relationship between delayed medical treatment and dental development.
<b>Study Design</b>	Controlled cross-sectional study
<b>Methods</b>	Study carried out on a sample of 21 children with HR and healthy age and sex matched controls. Assessed dental ages using Demirjian et al method. Other statistical methods used to test relationship between age of commencement of treatment and dental development delay.
<b>The PCC framework</b>	
<b>Population</b>	21 HR patients with an age range of 4 to 16 years (7 males and 14 females) with a control group consisting of the same number of age and sex matched healthy children.
<b>Concept</b>	Relationship between age of medical treatment and dental development delay
<b>Context</b>	Orthodontic department at the dental teaching centre of Jordan University of Science and Technology
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Of the 21 HR patients, 14 demonstrated dental delay ranging from 0.2 to 2.5 years which was significant
<b>Key radiographic features</b>	Deficiency in the anterior cranial base, class III skeletal relationship, and reduction in maxillary arch dimensions
<b>Dental management of XLH</b>	Early intervention to prevent permanent deficit in development
<b>Special clinical consideration</b>	Delay in commencement of treatment may lead to a permanent deficit in dental development. In the present study, more than half of the patients were diagnosed at or after age 2 years, which may leave a deficit that will not be corrected later

<b>Study Number 12</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://link.springer.com/article/10.1007/BF03262779">https://link.springer.com/article/10.1007/BF03262779</a>
<b>Article Title</b>	Hypophosphatemic rickets and aggressive periodontitis: a review of the role of dentine matrix protein 1 (DMP1) in the pathogenesis
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2011
<b>Country</b>	Jordan
<b>Authors</b>	S.H. Al-Jundi, M.M. Hammad, and I. Dabous
<b>Aims and Methods</b>	
<b>Aims</b>	We report a case of a child diagnosed with HR who showed excessive periodontal breakdown, which may indicate a possible association with mutation of DMP1.
<b>Study Design</b>	Case report
<b>Methods</b>	The case is discussed in the context of relevant literature; the possible role of dentine matrix protein 1 in the aetiology of such periodontal defects in patients with HR is also discussed.
<b>The PCC framework</b>	
<b>Population</b>	15 year-old male patient diagnosed with HR
<b>Concept</b>	Clinical, periodontal, radiographic and laboratory examinations with treatment and follow up
<b>Context</b>	Dental teaching centre in Jordan University of Science and Technology (JUST)
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Spontaneous loss of maxillary and mandibular permanent incisors after becoming excessively mobile. Patient had poor oral hygiene, gingival inflammation, and caries. Patient also had premature exfoliation of primary teeth.  Periodontal examination revealed increased pocket depths with attachment loss
<b>Key radiographic features</b>	Widened periodontal ligament space, loss of crestal bone height, reduced radiopacity of lamina dura and abscess formation.
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Referral to periodontal department for scaling, polishing, and maintaining good oral hygiene</li> <li>- Chlorhexidine gel 0.2% prescribed</li> <li>- Extraction for carious FPMs</li> <li>- Removable prosthesis</li> </ul>
<b>Special clinical consideration</b>	Aggressive periodontitis is a well-known entity that affects a small percentage of otherwise healthy children. However, when aggressive periodontitis is detected in a child, it is recommended to consult with a paediatrician to rule out systemic disease

<b>Study Number 13</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3533156/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3533156/</a>
<b>Article Title</b>	Dental Problems in Hypophosphatemic Rickets, a Cross Sectional Study
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2012
<b>Country</b>	Iran
<b>Authors</b>	Ali Rabbani, Parisa Rahmani, Vahid Ziaee and Sharareh Ghodoosi
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of this study was evaluation of the dental problems in XLHR patients.
<b>Study Design</b>	Cross sectional study
<b>Methods</b>	The investigation was conducted in a referral pediatrics endocrinology clinic in Iran during 3 years (2008- 2010). All cases of suspected hypophosphatemic rickets were enrolled in this study. After taking dental history, all subjects had dental examination and OPG was performed if necessary.
<b>The PCC framework</b>	
<b>Population</b>	19 patients, age range 3-17 years old (11 were female, 8 were male)
<b>Concept</b>	Dental problems associated with HR in children
<b>Context</b>	Pediatrics endocrinology clinic in Iran from 2008 to 2010
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	<ul style="list-style-type: none"> <li>- Dental caries (6 females and 3 males reported caries)</li> <li>- Delay in eruption of dentition in 9 patients (47.7%)</li> <li>- Enamel hypoplasia in 8 patients (42.1%)</li> <li>- Dental abscess in 2 patients (10.5%)</li> <li>- Gingivitis in 2 patients (10.5%)</li> </ul>
<b>Key radiographic features</b>	3 patients (15.8%) had taurodontism
<b>Dental management of XLH</b>	<p>Dental care of these patients should consist of periodic examination, topical fluoride application, pit and fissure sealants and maintenance of good oral hygiene.</p> <p>Prophylactic pulpotomy therapy may have been no benefit in preserving the primary dentition in XLHR patients.</p>
<b>Special clinical consideration</b>	This supplement therapy (Vitamin D) can prevent dental anomalies by good dental mineralisation and development

<b>Study Number 14</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://www.jendodon.com/article/S0099-2399(11)01243-X/fulltext">https://www.jendodon.com/article/S0099-2399(11)01243-X/fulltext</a>
<b>Article Title</b>	Endodontic Management in a Patient with Vitamin D-resistant Rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2012
<b>Country</b>	Greece
<b>Authors</b>	Charalampos Beltes, and Evanthia Zachou
<b>Aims and Methods</b>	
<b>Aims</b>	The present case report refers to a young white boy with the sporadic form of VDRRs who showed recurrent periapical pathology and underlines the importance of the overall knowledge for the correct diagnosis and treatment of such individuals.
<b>Study Design</b>	Case report
<b>Methods</b>	A 15-year-old boy was referred to the private clinic for endodontic treatment. Dental and radiographic examinations carried out. Conservative endodontic treatment completed in all teeth with pulp necrosis.
<b>The PCC framework</b>	
<b>Population</b>	15 year old boy diagnosed with VDRR disease
<b>Concept</b>	Endodontic management of paediatric patient with recurrent periapical pathology
<b>Context</b>	Private clinic in Greece
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, lack of response to electric pulp test
<b>Key radiographic features</b>	Enlarged pulp horn extending to DEJ, radiolucent band between enamel and dentine, lack of or poorly defined lamina dura in some areas, and periapical radiolucencies.
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- History of preentively covered primary posterior teeth with metal crowns</li> <li>- Root canal therapy of non-vital teeth, good quality obturation advised</li> </ul>
<b>Special clinical consideration</b>	<p>6-month radiographic follow-up is necessary to assess if endodontic treatment was successful.</p> <p>One abscess is a predictor of future abscesses, as patient returned after 4 months with more necrotic pulp that didn't exist 4 months prior.</p> <p>Endodontic treatment instead of extraction, esp for permanent teeth to maintain a functional dentition.</p>

<b>Study Number 15</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1111/j.1365-2842.2011.02250.x">https://doi.org/10.1111/j.1365-2842.2011.02250.x</a>
<b>Article Title</b>	Periapical and endodontic status of permanent teeth in patients with hypophosphatemic rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2012
<b>Country</b>	Denmark
<b>Authors</b>	M. G. Andersen, S. S. Beck-Nielsen†‡, D. Haubek, H. Hintze, H. Gjørup and S. Poulsen
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of the present study was to describe the periapical and endodontic status of permanent teeth in patients with genetically and/or biochemically confirmed HR.
<b>Study Design</b>	Cross-sectional study
<b>Methods</b>	The patients were recruited from a medical study on HR patients. The patients underwent a dental examination including a digital panoramic radiograph, which was scored for endodontically affected teeth (i.e. teeth with periapical radiolucencies and/or endodontically treated teeth).
<b>The PCC framework</b>	
<b>Population</b>	A total of 52 patients including 16 children (age range: 5.7 – 18) 11 females and 5 males
<b>Concept</b>	Periapical and endodontic status of permanent teeth
<b>Context</b>	School of Dentistry, Aarhus University, Denmark
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	High number of endodontically affected teeth, the number of affected teeth rose significantly with age. No statistical significance gender difference.  In youngest group age, only incisors and canines were affected.
<b>Key radiographic features</b>	The radiographs were examined for endodontically treated permanent teeth and periapical radiolucencies (apical periodontitis).  A total of 5 endodontically affected teeth were found, one with periapical radiolucency but no endodontic treatment and the remaining 4 were endodontically treated teeth without periapical radiolucency.
<b>Dental management of XLH</b>	Need for endodontic treatment is comprehensive
<b>Special clinical consideration</b>	The high level of dental care received by these patients reflects the maintenance of a high number of teeth, but it also represents a considerable economic burden carried by the patients themselves.

<b>Study Number 16</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1016/j.bone.2012.01.010">https://doi.org/10.1016/j.bone.2012.01.010</a>
<b>Article Title</b>	Tooth dentin defects reflect genetic disorders affecting bone mineralisation
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2012
<b>Country</b>	France and USA
<b>Authors</b>	S. Opsahl Vital, C. Gaucher, C. Bardet, P.S. Rowe, A. George, A. Linglart, and C. Chaussain
<b>Aims and Methods</b>	
<b>Aims</b>	In this review, we focus on two genetic diseases (XLH and OI) that disrupt both bone and dentin mineralisation.
<b>Study Design</b>	Review
<b>Methods</b>	Literature available for the two diseases exploring clinical features, systemic treatment, principles of dental management
<b>The PCC framework</b>	
<b>Population</b>	Paediatric and adult patients with XLH and OI
<b>Concept</b>	Bone and dentine mineralisation
<b>Context</b>	Available research on both diseases
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Severe dental anomalies. Occurrence of spontaneous abscesses (on both primary and permanent teeth) without trauma or decay. DMFT of XLH patients is significantly higher than healthy age-matched controls.
<b>Key radiographic features</b>	Enlarged pulp chamber with prominent horns extending up to DEJ
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Dental examination should be carried out twice a year</li> <li>- Recommended to protect both dentitions from bacterial invasion by early sealing of occlusal surfaces using composite resins</li> <li>- Abscesses on permanent teeth: conventional endodontic treatment</li> <li>- Abscesses on primary teeth: extraction might be best</li> <li>- Orthodontic treatment is not contraindicated</li> </ul>
<b>Special clinical consideration</b>	<p>Patients who received a treatment during the growth period and with good compliance to therapy have less dental abnormalities in their permanent teeth, which as a consequence are less prone to spontaneous abscesses.</p> <p>Extraction of primary teeth with abscesses will depend on stage of root development. Historically, for primary teeth PMCs were recommended to protect molars, however their benefit is not as effective as resin sealing</p>

<b>Study Number 17</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1111/j.1754-4505.2012.00310.x">https://doi.org/10.1111/j.1754-4505.2012.00310.x</a>
<b>Article Title</b>	Clinical approach in familial hypophosphatemic rickets: report of three generations
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2013
<b>Country</b>	Brazil
<b>Authors</b>	Eduardo Costa Studart Soares, Fábio Wildson Gurgel Costa, Thyciana Rodrigues Ribeiro, Ana Paula Negreiros Nunes Alves, Cristiane Sá Roriz Fonteles
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of the present work was to describe the main systemic and oral findings of a family affected by XLHR, and to discuss the elected treatment strategy in these cases.
<b>Study Design</b>	Case report
<b>Methods</b>	Oral exams, laboratorial and histologic evaluations, cone-beam computed tomographies, panoramic and periapical radiographs were performed to properly institute the most adequate treatment strategy.
<b>The PCC framework</b>	
<b>Population</b>	Six-year-old male patient presented with his mother and a 10-year-old sister
<b>Concept</b>	The knowledge of clinical signs and symptoms of XLHR is essential for the correct diagnosis of this disease, and for the establishment of preventive and comprehensive dental care.
<b>Context</b>	Pediatric Dental Clinic (Federal University of Ceara, Brazil)
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent gum abscesses without apparent cause, premature tooth loss, dental color alterations associated with primary dentition
<b>Key radiographic features</b>	Number of absent primary teeth, generalised bone loss, advanced root resorption (primary dentition), taurodontism, close proximity between pulp horns and DEJ, and radiolucency associated with periodontal abscess
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Paediatric patients were treated as part of a high-caries risk category</li> <li>- Dental extraction in the absence of bone support or unfeasible endodontic treatment</li> <li>- Restorative: composite and/or sealants</li> <li>- Space maintenance considered when needed</li> <li>- Short term monitoring (every 3 months) if periodontal involvement noted</li> </ul>
<b>Special clinical consideration</b>	Resin sealants were applied on all caries-free occlusal surfaces, reasons: (1) attempting prevention of future spontaneous abscesses secondary to pulpal infection; (2) dental caries prevention.

<b>Study Number 18</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://shorturl.at/hlmZ2">https://shorturl.at/hlmZ2</a>
<b>Article Title</b>	Dental characteristics of hypophosphatemic rickets. Case report
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2013
<b>Country</b>	Mexico
<b>Authors</b>	Gabriela Godina Hernández, and Francisco Belmont Laguna
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of the present article was to raise awareness on the characteristics of this disorder, as well as its treatment and dental considerations
<b>Study Design</b>	Case report
<b>Methods</b>	Referred due to suspension of XLH, once confirmed patient was then referred to stomatology service to receive dental treatment including extra-oral and intra-oral examination
<b>The PCC framework</b>	
<b>Population</b>	4 year old male patient with XLH, referred from the National Rehabilitation Institute (Instituto Nacional de Rehabilitación)
<b>Concept</b>	Dental characteristics and appropriate dental management of XLH
<b>Context</b>	Stomatology service, National Pediatrics Institute (Instituto Nacional de Pediatría), Mexico City
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Caries-free, incomplete primary dentition (due to extractions), scarring of fistulae, multiple appearance of abscesses, fistulae with pus discharging and fusion of primary teeth.
<b>Key radiographic features</b>	Enlarged pulp chambers with pulp horns extending up to DEJ
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- History of extractions due to abscesses</li> <li>- Pulpectomy on primary molars with presence of a fistula and pus</li> <li>- Preventive treatment with pulpotomy to the remaining teeth which had not presented abscesses</li> <li>- Restore teeth with stainless-steel crowns on molars</li> <li>- GIC or resin restorations on anterior teeth</li> <li>- Upper fixed appliance to replace extracted upper primary central incisors</li> </ul>
<b>Special clinical consideration</b>	An abscess in one tooth indicates that at least one additional tooth will be equally affected. However, patients who are less affected by XLH, may require routine preventive treatments such as sealants and topical application of fluoride only.



## Study Number 19

Bibliographic Information	
Study ID	<a href="https://doi.org/10.1590/1679-775720130249">https://doi.org/10.1590/1679-775720130249</a>
Article Title	Dental manifestations of patient with Vitamin D-resistant rickets
Extracted by	B.Al-Otaibi
Checked by	S.Parekh
Type of publication	Journal article
Year of publication	2013
Country	Brazil
Authors	Andréia Pereira Souza, Tatiana Yuriko Kobayashi, Natalino Lourenço Neto, Salete Moura Bonifácio Silva, Maria Aparecida Andrade Moreira Machado, Thais Marchini Oliveira
Aims and Methods	
Aims	The purpose of this article is to report a case of Vitamin D-resistant rickets in a 5-year old boy, describing the dental findings and the treatment to be performed in these cases.
Study Design	Case report
Methods	Referred to department due to complaint of ‘small ball in the mouth’,
The PCC framework	
Population	5 year-old boy with Vitamin D-resistant rickets
Concept	Dental findings and treatment provided
Context	Paediatric Dentistry Clinic, Bauru School of Dentistry, University of São Paulo, Brazil.
Themes / Outcomes	
Key dental features	Spontaneous gingival abscesses with no trauma or caries, fistula, physiologic wear of incisors, crown alteration (fused primary teeth)
Key radiographic features	Enlarged pulp chambers with horns that extend into DEJ, short roots, poorly defined lamina dura and hypoplastic alveolar ridge.
Dental management of XLH	Treatment options for dental abscesses: <ol style="list-style-type: none"> <li>1) Extraction</li> <li>2) Pulpectomy</li> </ol> Early loss of primary teeth, lead some clinicians to proceed with fixed space maintainers
Special clinical consideration	Prognosis of spontaneously abscessed teeth have been extremely poor.  Patient in the case report was constantly sick and did not attend the consultations.

<b>Study Number 20</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="http://dx.doi.org/10.1136/bcr-2012-008318">http://dx.doi.org/10.1136/bcr-2012-008318</a>
<b>Article Title</b>	Oral manifestations of vitamin D resistant rickets in orthopantomogram (OPG)
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2013
<b>Country</b>	India
<b>Authors</b>	Rajendrasinh Rathore, Triveni M Nalawade, Deepak Pateel, and Rachappa Mallikarjuna
<b>Aims and Methods</b>	
<b>Aims</b>	Report oral manifestations observed on OPG including dental treatment provided
<b>Study Design</b>	Case report
<b>Methods</b>	General, extraoral, intraoral and radiographic examination, followed by dental treatment
<b>The PCC framework</b>	
<b>Population</b>	9 year old girl with XLH complaining of missing teeth
<b>Concept</b>	Determine the oral manifestations
<b>Context</b>	Department of Pedodontics and Preventive Dentistry, K M Shah Dental College and Hospital, Vadodara, Gujarat, India
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Edentulous mandibular arch, carious with mobility of maxillary primary molars
<b>Key radiographic features</b>	Root resorption, hypoplasia, dentine abnormalities, enlarged pulp chambers, all developing permanent teeth (esp FPMs) showed enlarged chambers, short roots, poorly defined lamina dura and hypoplastic alveolar ridge
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Conventional pulpotomies of carious primary molars</li> <li>- Preventive resin restoration on remaining teeth</li> <li>- Close follow up</li> </ul>
<b>Special clinical consideration</b>	Early diagnosis and treatment of these conditions is necessary to prevent major dental abnormalities

<b>Study Number 21</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1530/EC-13-0103">https://doi.org/10.1530/EC-13-0103</a>
<b>Article Title</b>	Therapeutic management of hypophosphatemic rickets from infancy to adulthood
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2014
<b>Country</b>	France
<b>Authors</b>	Agnes Linglart, Martin Biosse-Duplan, Karine Briot, Catherine Chaussain, Laure Esterle, Severine Guillaume-Czitrom, Peter Kamenicky, Jerome Nevoux, Dominique Prie, Anya Rothenbuhler, Philippe Wicart and Pol Harvengt
<b>Aims and Methods</b>	
<b>Aims</b>	Describe the current and future treatments available to counteract phosphate wasting, restore serum phosphate and allow adequate bone and tooth mineralisation.
<b>Study Design</b>	Review
<b>Methods</b>	Included reports available of both children and adults with XLH, reporting therapy in both age groups.
<b>The PCC framework</b>	
<b>Population</b>	Paediatric and adults with XLH
<b>Concept</b>	Management of XLH from infancy to adulthood as reported in the literature
<b>Context</b>	Available literature
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Spontaneous dental abscess affecting both primary and permanent teeth
<b>Key radiographic features</b>	Enamel layer appears thinner while the dentin layer is more radiolucent. Pulp chambers are enlarged, resembling taurodontism and prominent pulp horn extend up to the DEJ
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Treatment of spontaneous dental abscess is by conventional RCT</li> <li>- Prevention of abscesses include sealing tooth surface (primary and permanent) with resin</li> <li>- Orthodontic treatment is not contraindicated if XLH is well-controlled</li> </ul>
<b>Special clinical consideration</b>	<p>Abscess in primary teeth spread rapidly in the jawbone and tooth extraction is often necessary</p> <p>For primary teeth, sealants are non-invasive and painless approach consists in applying an adhesive system (preferably no rinsing step called 'self-etching') and then a light-cured flowable resin. This procedure must be repeated regularly (every year) due to gradual wear of the resin until the natural exfoliation of the tooth.</p>

<b>Study Number 22</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1002/sca.21141">https://doi.org/10.1002/sca.21141</a>
<b>Article Title</b>	X-linked Hypophosphatemic Rickets: Enamel Abnormalities and Oral Clinical Findings
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2014
<b>Country</b>	Italy
<b>Authors</b>	Ilaria Cremonesi, Cesare Nucci, Giovanni D'alessandro, Nadia Alkhamis, Silvia Marchionni, and Gabriela Piana
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of our study was to assess the presence of enamel alterations, such as microclefts and/or structure defects in patients with XLH and give guidelines of prevention of XLH dental complications.
<b>Study Design</b>	Case-control – observational study
<b>Methods</b>	Clinical and medical history taken for each patient and a complete oral examination of teeth, gingival tissues, mucosa, tongue, and palate including radiographs was performed.
<b>The PCC framework</b>	
<b>Population</b>	10 subjects (2 males and 8 females) diagnosed with XLH with age range 4 - 18
<b>Concept</b>	This investigation presents the oral clinical, radiographic and histologic data of 10 subjects affected with XLH.
<b>Context</b>	Dentistry for Special Needs Patients Division at the Department of Oral Sciences (University of Bologna, Italy).
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, fistula, dental caries, enamel hypoplasia
<b>Key radiographic features</b>	Two cases enlarged pulp chambers were radiologically detected, high pulp horns of FPMs, periapical lesions, and root resorption
<b>Dental management of XLH</b>	Extraction of abscessed primary teeth, endodontic treatment of permanent abscessed teeth, restorations where possible
<b>Special clinical consideration</b>	In order to avoid the onset of abscesses, the best prevention are the prophylactic sealing or application of a low viscosity composite resin with a self-etching system on the entire crowns of all the teeth present.  If recurrent lesions appear after endodontic treatment, extraction followed by prosthetic treatment are recommended

<b>Study Number 23</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://link.springer.com/article/10.1007/s00784-015-1425-4">https://link.springer.com/article/10.1007/s00784-015-1425-4</a>
<b>Article Title</b>	Review of the dental implications of X-linked hypophosphataemic rickets (XLHR)
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2015
<b>Country</b>	Germany
<b>Authors</b>	Martin M. I. Sabandal, Peter Robotta, Sebastian Bürklein, and Edgar Schäfer
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of this article was to review the dental implications of XLHR and to provide suggestions regarding the dental treatment of these patients
<b>Study Design</b>	Review
<b>Methods</b>	The following search items X-linked hypophosphataemia, hypophosphataemic rickets, vitamin D-resistant rickets were used for literature search. Only full-text articles were analysed and summarized to get an overview of the different treatments and outcomes of hypophosphataemic patients
<b>The PCC framework</b>	
<b>Population</b>	Patients with XLHR
<b>Concept</b>	Dental implication and treatment of XLHR
<b>Context</b>	Full-text articles of different treatments and outcome of hypophosphataemic patients
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, most affected teeth incisors > molars > premolars, delayed tooth eruption
<b>Key radiographic features</b>	Enlarged pulp chambers with an abnormally high pulp, taurodontism, thin enamel layer and dentinal defects, short roots, root resorptions in primary dentition, poorly defined lamina dura, hypoplastic alveolar ridge
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Routine dental care, topical fluoride, fissure sealants (resin)</li> <li>- For abscesses: RCT of permanent teeth followed by definitive crown</li> <li>- Prophylactic PMC of primary molars</li> </ul>
<b>Special clinical consideration</b>	<ul style="list-style-type: none"> <li>• Postpubertary males tend to develop more severe dental symptoms</li> <li>• During RCT, working length should be accurate, by using electronic apex locator. Final obturation with no voids, to prevent reinfection. Therefore the use of thermoplasticised obturation technique using a virtually insoluble sealer is advisable</li> <li>• RCT of incomplete root, require careful copious irrigation and apical plug using mineral trioxide aggregate (MTA)</li> <li>• The bonding strength of adhesive composite restorations, is assumed to be reduced. Therefore, care must be taken to obtain the best retention. Moreover, prolonged etching times or the use of total-etch systems seem to be related with an increased risk of pulp irritation.</li> </ul>

<b>Study Number 24</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://pubmed.ncbi.nlm.nih.gov/27098722/">https://pubmed.ncbi.nlm.nih.gov/27098722/</a>
<b>Article Title</b>	Hypophosphatemic Rickets and Pre-eruptive Spontaneous Dental Abscess
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2016
<b>Country</b>	USA
<b>Authors</b>	Natalie M. Stinton, Karen A. Uston, and Courtney D. Davis
<b>Aims and Methods</b>	
<b>Aims</b>	To describe the diagnosis and dental treatment of a medically complex 14-year-old boy with XLH who presented with a pre-eruptive abscess on a mandibular molar and facial swelling.
<b>Study Design</b>	Case report
<b>Methods</b>	Seen for evaluation of facial cellulitis on the posterior right mandible.
<b>The PCC framework</b>	
<b>Population</b>	14 year old male with complex medical history
<b>Concept</b>	Diagnosis and dental treatment provided for XLH
<b>Context</b>	Dental clinic at the Geisinger Medical Centre (GMC), Danville, Pa., USA
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, delayed dental development, calculus
<b>Key radiographic features</b>	Intracoronaral resorption, large pulp chamber and canals, widened periodontal ligament, unerupted permanent teeth (delayed), thin enamel, taurodontism
<b>Dental management of XLH</b>	Emergency extraction and full-mouth debridement
<b>Special clinical consideration</b>	Due to the patient's complex medical history, and is tube-fed, decision was made not to address any prophylactic treatment of remaining teeth unless symptomatic.

<b>Study Number 25</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.5395/rde.2017.42.2.146">https://doi.org/10.5395/rde.2017.42.2.146</a>
<b>Article Title</b>	Dental management of patients with X-linked hypophosphatemia
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2017
<b>Country</b>	Korea
<b>Authors</b>	Bin-Na Lee, Hye- Yoon Jung, Hoon- Sang Chang, Yun- Chan Hwang, In-Nam Hwang, and Won-Mann Oh
<b>Aims and Methods</b>	
<b>Aims</b>	This article describes the problems and limitations of dental treatment in XLH patients
<b>Study Design</b>	Case report
<b>Methods</b>	Referred from the Department of Pediatric Dentistry for evaluation and treatment of the lower right first molar
<b>The PCC framework</b>	
<b>Population</b>	14 year old boy with XLH
<b>Concept</b>	Dental problems and treatment of XLH patients
<b>Context</b>	Department of Conservative Dentistry at Chonnam National University Dental Hospital
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, sinus tract, dental alterations, delayed eruption in both primary and permanent teeth, hypodontia
<b>Key radiographic features</b>	Complete/partial absence of the lamina dura, short roots, enlarged pulp chamber, prominent pulp horns
<b>Dental management of XLH</b>	Endodontic treatment and definitive crown for permanent molars
<b>Special clinical consideration</b>	Working length established with apex locator and radiograph method  Close monitoring to observe the progress of his teeth

<b>Study Number 26</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	10.4172/2161-1122.1000423
<b>Article Title</b>	Endodontic Management of Patients With X Linked Hypophosphatemic Rickets: Case Series Report
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2017
<b>Country</b>	France
<b>Authors</b>	Tchilalo Boukpepsi, Anne-Laure Charreteur, Agnès Linglart and Catherine Chaussain
<b>Aims and Methods</b>	
<b>Aims</b>	Report endodontic management with clinical and radiographic follow up
<b>Study Design</b>	Case report
<b>Methods</b>	Seen at the endodontic department for history of multiple dental abscesses. Provide clinical and radiographic examination and necessary endodontic treatment in necrotic teeth
<b>The PCC framework</b>	
<b>Population</b>	15-year- old boy with XLH
<b>Concept</b>	Bone healing process after endodontic treatment of XLH patients
<b>Context</b>	Endodontic department of Charles Foix hospital (Ivry sur seine France).
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess (primary and permanent)
<b>Key radiographic features</b>	Enlarged pulp chambers, thin enamel and dentine, internal root resorption
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Antibiotics (Amoxicillin and metronidazole)</li> <li>- Endodontic treatment, GIC used to fill access cavity</li> <li>- Teeth restored with resin composite</li> </ul>
<b>Special clinical consideration</b>	The endodontic therapy of the necrotic tooth was performed under operative microscope. Working length confirmed electronically and radiographically. Patient attended for 6-month review with no clinical symptoms and perioapical lesion was reduced in size, sign of healing



<b>Study Number 27</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	10.4274/jpr.50455
<b>Article Title</b>	Dental Management of Hypophosphatemic Vitamin D Resistant Rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2018
<b>Country</b>	Turkey
<b>Authors</b>	Akif Demirel, Ayşe Tuba Altuğ, Esra Erdemli, and Firdevs Tulga Öz
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of this case report is to summarize the dental clinical, radiographical, histopathological findings and treatment options of VDRR in a 4.5-year-old girl.
<b>Study Design</b>	Case report
<b>Methods</b>	Report the dental clinical, radiographical, histopathological findings and treatment options of a 4.5-year-old girl
<b>The PCC framework</b>	
<b>Population</b>	4.5-year-old female patient with VDRR
<b>Concept</b>	Dental clinical, radiographic and histological features of a VDRR case
<b>Context</b>	Ankara University Faculty of Dentistry, Department of Pediatric Dentistry, Ankara, Turkey
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, fistula, crown colour change, dental caries, deep palatal vault
<b>Key radiographic features</b>	Periapical radiolucency
<b>Dental management of XLH</b>	Extraction, and restoration with resin composite
<b>Special clinical consideration</b>	Prophylactic pulpotomy is not recommended due to lack of sufficient evidence for a good prognosis

<b>Study Number 28</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1007/s12105-017-0872-4">https://doi.org/10.1007/s12105-017-0872-4</a>
<b>Article Title</b>	Dentoalveolar Abscesses Not Associated with Caries or Trauma: A Diagnostic Hallmark of Hypophosphatemic Rickets Initially Misdiagnosed as Hypochondroplasia
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2018
<b>Country</b>	Brazil
<b>Authors</b>	Silvia Elena Yacarini Paredes, Raquel Assed Bezerra Segato, Leila Daher Moreira, Alcides Moreira, Kranya Victoria Díaz Serrano, Clarissa Teles Rodrigues, Luciana Yamamoto Almeida, and Jorge Esquiche León
<b>Aims and Methods</b>	
<b>Aims</b>	This case highlights the importance of early diagnosis of HR and knowledge of their dental implications to provide the best possible treatment options.
<b>Study Design</b>	Case report
<b>Methods</b>	Clinical, radiographic and histological examination, followed by laboratory tests to confirm the HR diagnosis, after which the treatment is initiated
<b>The PCC framework</b>	
<b>Population</b>	7-year-old boy
<b>Concept</b>	Knowledge of HR dental manifestations and appropriate treatment options
<b>Context</b>	Paediatric dentistry clinic of the School of Dentistry of Ribeirão Preto, University of Sao Paulo (FORP/USP)
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Facial asymmetry, multiple fistulas and abscesses (primary teeth) and mobility
<b>Key radiographic features</b>	Enlargement of pulp cavities and irregular dentine, high pulp horns, radicular resorptions
<b>Dental management of XLH</b>	Extraction
<b>Special clinical consideration</b>	Preventive care and early treatment for dental caries and attrition are recommended. Topical fluoride and fissure sealants may prevent endodontic complications.  <u>Primary molars:</u> Prophylactic PMC to prevent attrition and enamel microfracture <u>Permanent teeth:</u> RCT when needed, and the use of thermoplasticised gutta percha obturation using a virtually insoluble sealer is advised

<b>Study Number 29</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.12968/denu.2019.46.11.1067">https://doi.org/10.12968/denu.2019.46.11.1067</a>
<b>Article Title</b>	Spontaneous Dental Abscesses in Hereditary Hypophosphataemic Rickets: a Preventive Restorative Approach in the Primary Dentition
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2019
<b>Country</b>	UK
<b>Authors</b>	Sara L Hughes and Emma J Hingston
<b>Aims and Methods</b>	
<b>Aims</b>	A preventive/restorative approach to protect the unaffected primary teeth is described and demonstrates how early clinical intervention can result in a symptom- and disease-free patient one year following treatment.
<b>Study Design</b>	Case report
<b>Methods</b>	Provide preventive restorative approach and follow up in 1 year clinically and radiographically
<b>The PCC framework</b>	
<b>Population</b>	3-year-old boy
<b>Concept</b>	Preventive restorative approach in primary dentition
<b>Context</b>	Unit of Paediatric Dentistry, at the University Dental Hospital Cardiff
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, delayed eruption, sinus, anterior open bite, generalised spacing, dental caries
<b>Key radiographic features</b>	Periapical radiolucency, thin enamel and dentine, enlarged pulp chambers, pulp horns extending to DEJ
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Antibiotics previously perscribed</li> <li>- Prophylactic PMC on all primary molars (Hall technique)</li> <li>- Impression and laboratory-made full coverage composite crowns for anterior teeth, cemented with opaque Panavia</li> <li>- Extraction of abscessed primary teeth</li> </ul>
<b>Special clinical consideration</b>	<p>Recall on 3 to 6 monthly basis</p> <p>The use of prophylactic pulpotomies to preserve primary teeth after abscess are outdated and show a high failure rate. Extraction of abscessed primary teeth may be preferable. However, abscessed permanent teeth should be managed by endodontic treatment or extraction. If RCT it should be void-free with a good apical and coronal seal, ideally using thermoplastic obturation.</p>

<b>Study Number 30</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1016/j.ortho.2020.06.003">https://doi.org/10.1016/j.ortho.2020.06.003</a>
<b>Article Title</b>	Orthodontic treatment of a nine-year-old patient with hypophosphatemic rickets diagnosed since the age of two: A case report
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2020
<b>Country</b>	Greece, UAE, and Cyprus
<b>Authors</b>	Miltiadis A. Makrygiannakis, Mahmoud Dastoori, and Athanasios E. Athanasiou
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of this case report is to describe the orthodontic treatment of a 9-year old Caucasian female patient suffering from HR.
<b>Study Design</b>	Case report
<b>Methods</b>	Provide orthodontic treatment and provide clinical recommendations
<b>The PCC framework</b>	
<b>Population</b>	A 9-year 3-month old Caucasian female
<b>Concept</b>	Describe the orthodontic treatment of a young female patient suffering from XLH and to propose clinical recommendations
<b>Context</b>	Graduate Orthodontic Clinic of the Hamdan Bin Mohammed College of Dental Medicine (HBMCDM) of Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU), Dubai, UAE
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Mild Class III maxillary skeletal pattern, bilateral posterior crossbite
<b>Key radiographic features</b>	No periapical radiolucencies evident in this case
<b>Dental management of XLH</b>	The findings of this report indicate that XLH does not constitute a contraindication for orthodontic treatment, when the condition is kept under control, good oral hygiene is maintained, dental and periodontal health are regularly monitored, and the clinician collaborates closely with the patient's physician
<b>Special clinical consideration</b>	There is no available data about orthodontically induced root resorption in patients with XLH, thus close monitoring is important

<b>Study Number 31</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1016/j.pdj.2020.06.005">https://doi.org/10.1016/j.pdj.2020.06.005</a>
<b>Article Title</b>	X-linked hypophosphatemia diagnosed after identification of dental symptoms
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2020
<b>Country</b>	Japan
<b>Authors</b>	Kaoruko Wato, Rena Okawa, Saaya Matayoshi, Yuko Ogaya, Ryota Nomura, Kazuhiko Nakano
<b>Aims and Methods</b>	
<b>Aims</b>	We encountered a case of XLH diagnosed after appearance of periapical periodontitis without abscess formation and describe the details here.
<b>Study Design</b>	Case report
<b>Methods</b>	Patient followed up clinically and radiographically from age 1 year and 5 months to 5 year and 7 months
<b>The PCC framework</b>	
<b>Population</b>	1Y5M Japanese boy
<b>Concept</b>	Dental features and management of patient with suspected XLH
<b>Context</b>	Pediatric Dentistry Clinic of Osaka University Dental Hospital, Japan
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	History of trauma, colour change, increased mobility, enamel hypoplasia, no history of spontaneous abscess
<b>Key radiographic features</b>	Radiolucency at apex, thin dentine, wide pulp chambers and pulp horns
<b>Dental management of XLH</b>	Root canal treatment of traumatised tooth
<b>Special clinical consideration</b>	At 5Y7M, the tooth was extracted due to disturbed eruption of its permanent successor

<b>Study Number 32</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1007/s00223-021-00841-4">https://doi.org/10.1007/s00223-021-00841-4</a>
<b>Article Title</b>	Characterization of Oral Health Status in Chilean Patients with X-Linked Hypophosphatemia
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2021
<b>Country</b>	Chile and USA
<b>Authors</b>	Alejandro Marin, Pilar Morales, Macarena Jiménez, Eugenia Borja, Danisa Ivanovic-Zivic, Michael T. Collins, and Pablo Florenzano
<b>Aims and Methods</b>	
<b>Aims</b>	The aim of our study is to describe the oral findings in XLH Chilean population in order to promote the importance of a comprehensive management of the disease, in which dental care is of the utmost importance.
<b>Study Design</b>	Cross-sectional observational study
<b>Methods</b>	All patients had an oral clinical exam, radiographic evaluation; clinical and biochemical data were obtained to determine their association with oral features.
<b>The PCC framework</b>	
<b>Population</b>	6 (23%) of patients were children with XLH, age range 5 to 16
<b>Concept</b>	Describe oral health status in a cohort of Chilean patients with XLH and explore its correlation with biochemical presentation and treatment
<b>Context</b>	Centre for Translational Research in Endocrinology of the Endocrinology Department, Pontificia Universidad Católica de Chile
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Abscess and/or fistulae were common (33%), caries was higher than the Chilean national average
<b>Key radiographic features</b>	Pulpal chamber enlargement (94%) and radiolucent apical lesions (74%)
<b>Dental management of XLH</b>	Two cases required endodontic treatment
<b>Special clinical consideration</b>	Early and periodical dental care is important to prevent dental damage and assure a good quality of oral health for XLH patients

<b>Study Number 33</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://www.journalbonefragility.com/wp-content/uploads/journal/2021/1.2/74-79.pdf">https://www.journalbonefragility.com/wp-content/uploads/journal/2021/1.2/74-79.pdf</a>
<b>Article Title</b>	Dental and periodontal features and management in XLH children and adults
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2021
<b>Country</b>	France
<b>Authors</b>	Martin Biosse Duplan, Elvire Le Norcy, Frédéric Courson, and Catherine Chaussain
<b>Aims and Methods</b>	
<b>Aims</b>	To understand the types of defect created by XLH in dental and periodontal tissues, the clinical manifestations of these defects, and how to prevent and manage these manifestations
<b>Study Design</b>	Expert opinion
<b>Methods</b>	Explore dental and periodontal tissue anomalies in XLH, enamel, dentine, cementum and alveolar bone
<b>The PCC framework</b>	
<b>Population</b>	Paediatric and adult patients with XLH
<b>Concept</b>	Discussion on clinical manifestation and management of children with XLH
<b>Context</b>	All available research
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, fistula, enamel hypoplasia, attrition, dental caries, malocclusion
<b>Key radiographic features</b>	Enamel can appear thinner with slightly reduced radiopacity, enlarged pulp chambers with prominent pulp horns extending to EDJ, lamina dura may be absent
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Acute abscess: antibiotics, followed by endodontic treatment or extraction</li> <li>- Prevention of abscess: prophylactic treatment such as sealants using flowable resin composite (permanent and primary teeth)</li> </ul>
<b>Special clinical consideration</b>	<p>In the primary dentition, incisors and canines are most frequently affected by abscesses, followed by the first and second molars</p> <p>Orthodontic treatment is routinely conducted in patients with XLH</p> <p>Interval between appointments 6-12 months</p>

<b>Study Number 34</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	doi:10.1111/iej.13520
<b>Article Title</b>	Presentation and non-surgical endodontic treatment of two patients with X-linked hypophosphatemia: a case report
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2021
<b>Country</b>	UK
<b>Authors</b>	H. Bradley, A. Dutta, and R. Philpott
<b>Aims and Methods</b>	
<b>Aims</b>	To describe two patients with XLH presenting with spontaneous signs of pulpal necrosis in multiple intact teeth.
<b>Study Design</b>	Case report
<b>Methods</b>	The presentation and management are discussed, along with the diagnostic and endodontic treatment challenges
<b>The PCC framework</b>	
<b>Population</b>	16 year old male with XLH
<b>Concept</b>	Management of dental infection
<b>Context</b>	Department of Restorative Dentistry at the Edinburgh Dental Institute, UK
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Buccal swelling, draining buccal sinus, recurrent spontaneous abscess (primary and permanent), mobility
<b>Key radiographic features</b>	Large pulp chambers, wide canals, short roots, open apices, periapical radiolucencies
<b>Dental management of XLH</b>	Endodontic treatment with MTA due to open apex
<b>Special clinical consideration</b>	Perform comprehensive endodontic examination (tenderness to percussion, tenderness to palpation, presence or absence of a sinus, mobility and periodontal pocket probing depth)



<b>Study Number 35</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	<a href="https://doi.org/10.1007/s00774-020-01136-8">https://doi.org/10.1007/s00774-020-01136-8</a>
<b>Article Title</b>	Pulp chamber features, prevalence of abscesses, disease severity, and PHEX mutation in X-linked hypophosphatemic rickets
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2021
<b>Country</b>	Italy
<b>Authors</b>	Giampiero I. Baroncelli, Elisa Zampollo, Mario Manca, Benedetta Toschi, Silvano Bertelloni, Angela Michelucci, Alessandro Isola, Alessandra Bulleri, Diego Peroni, and Maria Rita Giuca
<b>Aims and Methods</b>	
<b>Aims</b>	To assess some features of the pulp chambers, such as size, shape, and morphology, by ortho- pantomography (OPT) examination, and whether they were related to the prevalence of abscesses, biochemical findings, severity of disease, and type of PHEX gene mutation
<b>Study Design</b>	Case control
<b>Methods</b>	Pulp chambers size, shape, and morphology were assessed by OPG in XLH patients and in sex and age-matched healthy controls
<b>The PCC framework</b>	
<b>Population</b>	Twenty-four Caucasian prepubertal XLH patients (nine males and 15 females) aged $5.8 \pm 1.6$ years
<b>Concept</b>	Prevalence of abscesses, pulp chamber features, biochemical findings, disease severity, and PHEX gene mutation were examined
<b>Context</b>	Endocrine Unit of Pediatrics at the University Hospital, Italy
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	16 patients (67%, nine males and seven females) had a history of abscesses, fistulae, incisors were affected more than canines and molars
<b>Key radiographic features</b>	Enlarged pulp chambers with prominent pulp horns, altered shape and morphology
<b>Dental management of XLH</b>	Not mentioned
<b>Special clinical consideration</b>	The patients suffering abscesses had a more severe form of rickets indicating that impaired mineralisation of growth plates and dentine are likely related to similar mechanisms

<b>Study Number 36</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	doi:10.3389/fendo.2021.688309
<b>Article Title</b>	X-Linked Hypophosphatemic Rickets: Multisystemic Disorder in Children Requiring Multidisciplinary Management
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2021
<b>Country</b>	Italy
<b>Authors</b>	Giampiero Igli Baroncelli and Stefano Mora
<b>Aims and Methods</b>	
<b>Aims</b>	XLH is a multisystemic disorder requiring multidisciplinary approaches in specialized subdisciplines
<b>Study Design</b>	Review
<b>Methods</b>	Explore clinical, biochemical, radiological findings, including medical and multidisciplinary management
<b>The PCC framework</b>	
<b>Population</b>	Paediatric patients
<b>Concept</b>	Multidisciplinary management of XLH
<b>Context</b>	All available research
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscesses with gingival fistulae in both primary and permanent teeth, maxillofacial cellulitis
<b>Key radiographic features</b>	Enlarged pulps chambers with altered shape and morphology and prominent pulp horns into the tooth crown in primary and permanent molars
<b>Dental management of XLH</b>	<ul style="list-style-type: none"> <li>- Dental examination twice a year</li> <li>- Prevention: Fissure sealant, topical fluoride and good oral hygiene</li> <li>- Acute abscess: antibiotics if severe, followed extraction or endodontic treatment</li> </ul>
<b>Special clinical consideration</b>	<p><u>Abscessed primary teeth</u>: treatment depends on extent of infection, recurrence and expected time of exfoliation</p> <p><u>Abscessed permanent teeth</u>: Endodontic treatment and re-treatment are preferred</p>

<b>Study Number 37</b>	
<b>Bibliographic Information</b>	
<b>Study ID</b>	DOI:10.1177/14653125211039521
<b>Article Title</b>	X-linked hypophosphatemic rickets: Orthodontic considerations and management. A case report
<b>Extracted by</b>	B.Al-Otaibi
<b>Checked by</b>	S.Parekh
<b>Type of publication</b>	Journal article
<b>Year of publication</b>	2021
<b>Country</b>	UK
<b>Authors</b>	Clara Gibson, Suhaym Mubeen, and Robert Evans
<b>Aims and Methods</b>	
<b>Aims</b>	We present the orthodontic clinical findings from seven patients and outline in detail the management of three patients with XLH undergoing orthodontic and dental treatment
<b>Study Design</b>	Case review
<b>Methods</b>	A total of seven patients with XLH were seen over an eight-year period up to 2019, documenting the orthodontic, skeletal pattern and clinical findings of these patients and the treatment undertaken
<b>The PCC framework</b>	
<b>Population</b>	A total of seven patients with XLH (age range 4-12)
<b>Concept</b>	Outcome of orthodontic treatment
<b>Context</b>	Dental and Maxillofacial Department over an eight-year period up to 2019
<b>Themes / Outcomes</b>	
<b>Key dental features</b>	Recurrent spontaneous abscess, delayed dental development
<b>Key radiographic features</b>	Enlarged pulp chambers extending DEJ, enamel thin, taurodontism, delayed root maturation
<b>Dental management of XLH</b>	Endodontic treatment, Orthodontic treatment, extraction for orthodontic need,
<b>Special clinical consideration</b>	There is no evidence that orthodontic treatment should be avoided in patients with XLH, once medical management of the condition is optimal and there is no active dental pathology

## Appendix 3: Final PROM questionnaire

# X-Linked Hypophosphatemia (XLH) Patient Survey



Thank you for helping us with our survey. We would like to ask you a few questions about how X-Linked Hypophosphatemia (XLH) affects your teeth and gum.

Please turn the page and answer the questions. When you are finished, please give it back to the dentist.

**Circle your answers like the example below:**

1. Do your teeth cause you pain or sensitivity?	Often	<b>Sometimes</b>	Never
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**The dentist will fill out the following information for you**

**Age:** ..... years




**Gender:** M / F / X

**Relevant Medical History:**

**Medications:**

**Dental treatment stage:** Pre-treatment / Mid-treatment / Post-treatment

**Attendance:** Regular / Under review only / Discharged

Please circle ONE answer			
1. Do your teeth cause you pain or sensitivity?	Often	Sometimes	Never
2. Do you find it hard to eat foods you like because of your teeth?	Often	Sometimes	Never
3. Does it hurt when you brush your teeth?	Often	Sometimes	Never
4. Do you ever feel you have bad (bitter) taste in your mouth?	Often	Sometimes	Never
5. Do you often get a bump (swelling) around your teeth or gum?	Often	Sometimes	Never
6. Do you feel scared (sad) about going to the dentist?	Often	Sometimes	Never
7. Did you ever have a bad experience with a dentist?	Often	Sometimes	Never
8. Do you feel happy with your teeth?	No		Yes
9. How many times do you visit the dentist every year?	More than 5 times	2-4 times	1-2 times
10. How many visits this year because you were in pain? (i.e., emergency visit)	More than once	Once	Never
11. What treatments did you get at the dentist?	Extractions	Fillings	Only check-ups
12. Is there anything else you would like to tell us about XLH and how it affects your teeth and smile?			