Bone 150 (2021) 116011

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Missing and unerupted teeth in osteogenesis imperfecta

Doaa Taqi [a], Hanan Moussa [a,e], Timothy Schwinghamer [a], Alexandre Rezende Vieira [c], Didem Dagdeviren [a], Jean-Marc Retrouvey [a,f], Frank Rauch [b], Faleh Tamimi [a,d,*], Members of the BBDC[1]

[a] Faculty of Dentistry, McGill University, Montreal, Quebec, Canada
[b] Shriners Hospital for Children, Montreal, Quebec, Canada
[c] Department of Oral Biology, School of Dental Medicine, University of Pittsburgh, USA
[d] College of Dental Medicine, QU Health, Qatar University, Doha, Qatar
[e] Faculty of Dentistry, Benghazi university, Libya
[f] School of Dentistry, University of Missouri, Kansas City, USA

ARTICLE INFO

Keywords:
Osteogenesis imperfecta
Rare disease
Missing teeth
Agenesis
Unerupted
Retained teeth
Tooth development
Tooth eruption
Bisphosphonate

ABSTRACT

Introduction: Osteogenesis imperfecta (OI) is a genetic disorder characterized by bone fragility and craniofacial and dental abnormalities such as congenitally missing teeth and teeth that failed to erupt which are believed to be doubled in OI patients than normal populations and were associated with low oral health quality of life. However, the etiology of these abnormalities remains unclear. To understand the factors influencing missing and unerupted teeth, we investigated their prevalence in a cohort of OI patients as a function of the clinical phenotype (OI type), the genetic variant type, the tooth type and the onset of bisphosphonate treatment.
Method: A total of 144 OI patients were recruited from The Shriners Hospital, Montreal, Canada, between 2016 and 2017. Patients were evaluated using intraoral photographs and panoramic radiographs. Missing teeth were evaluated in all patients, and unerupted teeth were assessed only in patients ≥15 years old ($n = 82$).
Results: On average, each OI patient had 2.4 missing teeth and 0.8 unerupted teeth, and the most common missing and unerupted teeth were the premolars and the upper second molars, respectively. These phenomena were more prominent in OI type III and IV than in OI type I, and were not sex or age-related. Missing teeth were significantly more common in patients with C-propeptide variants than all other variants (p-value <0.05). Unerupted teeth were significantly more common in patients with α1 and α2 glycine variants or substitutions than in those with haploinsufficiency variants. Early-onset of bisphosphonate treatment would significantly increase the risk of unerupted teeth in patients with OI types III and IV (OR = 1.68, 95% CI (1.15–1.53)).
Conclusion: The prevalence of missing and unerupted teeth at the tooth type level in OI patients varies according to the nature of the collagen variants and the OI type. These findings highlight the role of collagen in tooth development and eruption.

1. Introduction

Osteogenesis imperfecta (OI) is a genetically and clinically heterogeneous heritable connective tissue disorder with an incidence of approximately 1 in 15,000–20,000 births [1–4]. OI patients were classified based on Sillance classification into four groups OI type I, II, III and IV [1,5,6]. OI type I is mild, type II is pre-or perinatally lethal, type III is the severe type and progressively deteriorating, and type IV is typically of moderate severity (Table 1) [5]. OI is caused by alterations in type I collagen, the most abundant fibrillar form of collagen, which

Abbreviations: OI, osteogenesis imperfecta; Gly, glycine; Sub, substitution.

* Corresponding author at: Faculty of Dentistry, McGill University, Montreal, Quebec, Canada.
E-mail addresses: doaa.taqi@mail.mcgill.ca (D. Taqi), hanan.moussa@mail.mcgill.ca (H. Moussa), timothy.schwinghamer@mail.mcgill.ca (T. Schwinghamer), arv11@pitt.edu (A.R. Vieira), didem.dagdeviren@mcgill.ca (D. Dagdeviren), jean-marc.retrouvey@mcgill.ca (J.-M. Retrouvey), frank.rauch@mcgill.ca (F. Rauch), faleh.tamimimarino@mcgill.ca (F. Tamimi).

[1] The "Members of the BBDC" include Brendan Lee, V. Reid Sutton, Sandesh CS Nagamani, Francis Glorieux, Janice Lee, Paul Esposito, Maegen Wallace, Michael Bober, David Eyre, Danielle Gomez, Gerald Harris, Tracy Hart, Mahim Jain, Deborah Krakow, Jeffrey Krischer, Eric Orwoll, Lindsey Nicol, Cathleen Raggio, Peter Smith, Laura Tosi.

https://doi.org/10.1016/j.bone.2021.116011
Received 14 January 2021; Received in revised form 2 May 2021; Accepted 14 May 2021
Available online 18 May 2021

Table 1
Clinical manifestation of different OI types associated with collagen type 1 mutation.

OI type	Severity	General features	DI[a]	BS[a]	MT[a]	M[a]
I	Mild	Mild fragility, normal height average, minimum deformity.	P/A	P	P/A	Mild
II	Lethal	Multiple rib and long bone intrauterine fractures, severe bone deformity.		P		
III	Severe	Frequent fractures before birth, severe bone deformity, very short stature, severe scoliosis, limited mobility, triangular face.	P/A	A	P/A	Severe
IV	Intermediate	Moderate bone fragility, moderate scoliosis and bone deformity, thin ribs, short stature.	P/A	A	P/A	Moderat to severe

Modified from references [10,26,27].
P; present, A; absent.
[a] DI; dentinogenesis imperfecta, BS; blue sclara, MT; missing teeth, M; maloclussion.

accounts for about 80% of the extracellular matrix of bone and dentin [7,8]. OI is mainly caused by quantitative and/or qualitative alterations in type 1 collagen synthesis due to mutations in the genes encoding proα-1 and proα-2 of type 1 procollagen (*COL1A1* and *COL1A2*) [7]. Most of the severe OI cases (II, III, and IV) were associated with glycine substitution mutations, which results in unstable collagen fibril. However, mild OI type (Type I) is often attributed to mutations that create a premature stop codon within *COL1A1* or *COL1A2*, which decrease the amount of normal collagen formation [9,10].

This disease is characterized by decreased bone mineral density, increased bone fragility, and extra-skeletal manifestations like blue sclera, hearing loss, skin hyperelasticity, craniofacial, and dental alterations [9,10]. Craniofacial alterations include underdeveloped naso-maxillary complex, known as hypoplastic maxilla. These discrepancies are more severe in OI types III and IV, and are manifested as class III dental malocclusion, anterior crossbite, anterior and posterior open bites, as well as posterior crossbite [11–16]. The most well-known oral finding in OI is dentinogenesis imperfecta, which is described clinically as a tooth discoloration [17,18], and is highly associated with the severity of OI and the type of genetic mutation [19]. Another OI and oral health-related challenges are a high incidence of impacted second molars, and twice as many missing teeth as the general population [11,14,20,21]; however, the effect of the genetic variants on missing and unerupted teeth in OI patients remains unclear.

The most widely used treatment for OI is intravenous bisphosphonate therapy [22]. Bisphosphonates are a class of drugs able to inhibit bone-resorbing osteoclasts and to decrease osteoblast and osteocyte apoptosis, thereby improving bone density and contrasting the bone fragility. However, bone resorption is essential for the process of tooth eruption, which could inhibit or delay the tooth eruption in OI patients [23–25].

In this context, we hypothesize that the prevalence of missing or unerupted teeth in OI patients depends on the type of OI, the genetic variants, tooth type and the treatment received by the patient. Accordingly, we studied the patterns of these two conditions in OI patients at the tooth level, concerning OI type and mutation type. Missing or impacted teeth can result in psychosocial, esthetic, and functional complications, thus understanding the risk factors involved could help improve the dental care of OI patients.

2. Materials and methods

A total of 171 individuals diagnosed with OI were evaluated in the context of the Brittle Bone Disease study, a longitudinal observational study that collects information from a consortium of specialized OI centers in North America. The consortium is part of the Rare Disease Clinical Research Network, funded by the US National Institutes of Health [28–30].

All study participants described here were diagnosed with OI associated with collagen type I defect at the Montreal Shriners hospital, Canada. Patients were subsequently grouped according to the diagnosis as OI type I, OI type III, or OI type IV. A dental evaluation was performed for participants three years of age or older at the Faculty of Dentistry, McGill University (Montreal, Canada) in the years 2016–2017. Patients who agreed to participate in the dental descriptive study were included, excluding patients younger than seven years of age or patient's refusal to participate. A total of 144 OI patients were included and evaluated using intraoral photographs and panoramic radiographs. Missing teeth were evaluated in all patients, and unerupted teeth were assessed only in patients ≥15 years old ($n = 82$) (Table 2). Ethical approval was obtained from the McGill ethics committee, number A09-M47-15B, and all study participants or their legal guardians provided a written informed consent. The association between tooth eruption and bisphosphonate treatment was evaluated by comparing patients that started treatment before the age of 6 years (the time at which the first permanent tooth erupts) to those receiving the treatment later in their lives. We also evaluated the association between tooth discoloration and the prevalence of missing and unerupted teeth.

2.1. Dental evaluations

Intraoral photographs were taken in a standardized setting by one specialist using a Canon D70 intraoral camera equipped with a 100 mm Canon lens (1:3 magnification) and a ring flash (Canon model Macro Ring Lite MAR 14 Ex II). Five photographs were taken from five different angles (facial view, lateral right view, lateral left view, upper occlusal view, and lower occlusal view) for every participant. Panoramic radiographs were attained for all participants and were used to evaluate the missing teeth, and intraoral photographs were used to confirm the unerupted teeth [31]. A tooth was defined as "missing" when the tooth itself or its bud could not be seen in the radiograph, and it was defined as "unerupted" when it was found in the X-ray but not in the patient's mouth. (Fig. 1).

The tooth types were presented using the "Federation Dentaire Internationale" (FDI) Numbering System (see Sup. Fig. 1). Tooth discoloration was evaluated as described by Taqi et al. [19].

Table 2
Demographical information for OI individuals from different OI type, and the percentage of affected individual pet OI type.

Patients evaluated				
OI type	N	Female/male (%)	Age[b] mean (range)	% affected (CI)
Missing teeth				
OI I	70	38/31 (55%)	22 (7–55)	11% (4,19)[a]
OI III	20	11/9 (55%)	16 (7–30)	62% (39,81)
OI IV	54	29/25 (54%)	18 (7–43)	52% (39,66)
Unerupted teeth				
OI I	40	25/15 (63%)	30 (15–55)	3% (0.73, 0.95)[a]
OI III	10	4/6 (40%)	18 (15–30)	70% (0.06, 0.65)
OI IV	32	16/16 (50%)	30 (15–55)	40% (0.40, 0.72)

N the number of patients.
[a] OI type I is statistically significantly different from OI type III and IV.
[b] Age in years.

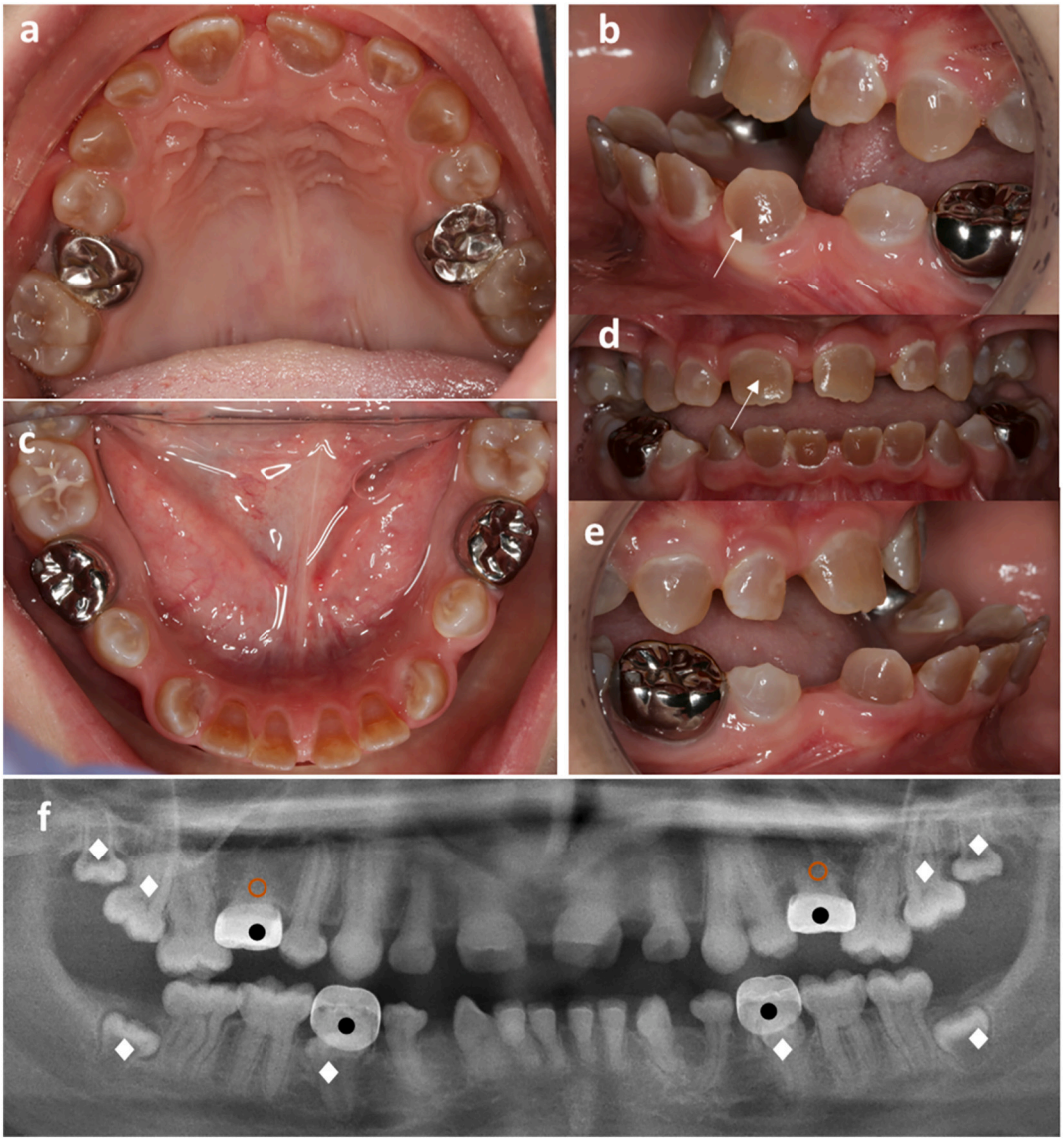

Fig. 1. Intraoral photographs (a–e) and panoramic radiograph (f) of a 17 years old male with OI type IV. The intraoral photos were taken from different directions: (a) upper occlusal (b) lateral left (c) lower occlusal, (d) facial, (e) lateral right. The photos reveal tooth discoloration (arrowed), as well as class III malocclusion, open bite, and posterior crossbite. The radiograph (f) shows missing upper second premolars (○), unerupted teeth (◊), and retained deciduous molars (●).

2.2. Reliability evaluation

D.T. and H.M, who were blinded to the OI type, evaluated the photographs and X-rays, and a third party, JM.R., was consulted in case of disagreement. Six months after the first evaluation, D.T. randomly repeated the assessment of 70 patients for interexaminer validity. The kappa analysis was performed and showed a >0.8 agreement proportion for the inter and intraexaminer reliability.

2.3. Statistical analysis

The participants' demographical characteristics were summarized using descriptive analysis and the frequency of unerupted and missing teeth. Chi-square test and odds ratio were used to analyze the association between the binomial variables, while the Kruskal-Wallis test was used to compare the nonparametric categorical variables such as mutation types. Generalized linear models (GLIMMIX) and the binary distribution were used to compare the dental findings in every tooth type for each OI types. A p-value of <0.05 was considered statistically significant after Bonferroni's adjustment for multiple comparisons. All statistical analyses were performed using SPSS (IBM 22.0., Armonk, NY, USA.2013) except for the GLIMMIX procedure in which SAS (SAS 9.4 by SAS Institute Inc., Cary, NC, USA) was used.

3. Results

Descriptive statistics on the population demography and the statistical analyses for the distribution of missing and unerupted teeth in every OI type are summarized in Table 2.

Overall, each patient had on average 2.4 missing teeth and 0.8 unerupted teeth, and both variables were not sex or age-related (p-value >0.05) (Supplementary Tables 1 & 2). The prevalence of missing or unerupted teeth was the highest in OI type III patients, followed by OI type IV and OI type I, which had a significantly lower prevalence ($p <$ 0.05). The descriptive statistics are summarized in Table 2, and in Fig. 2.

3.1. Missing teeth

A total of 175 teeth were missing in the 114 OI patients evaluated. The most frequently missing teeth were the premolars, particularly the

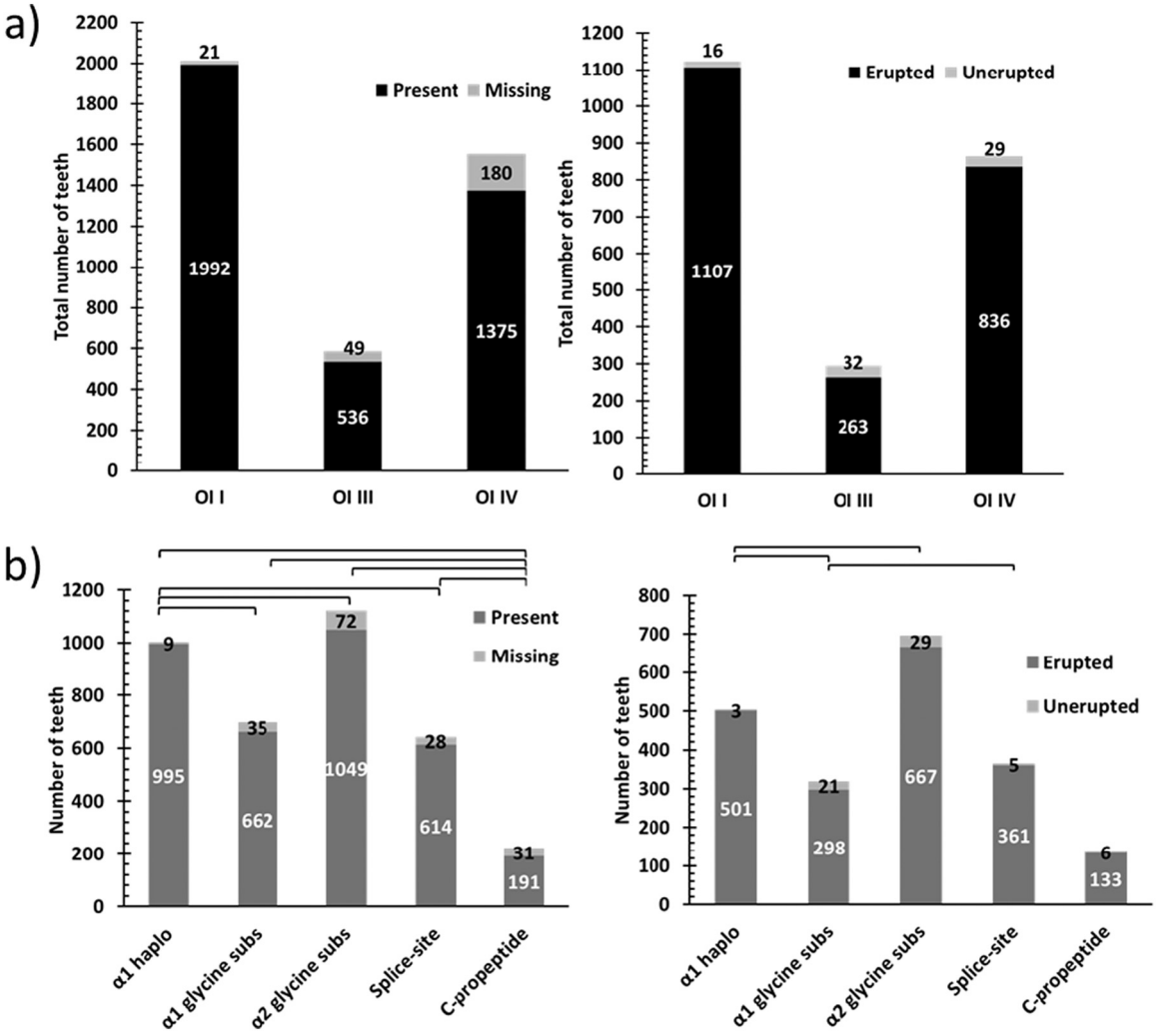

Fig. 2. Bar charts representing the number of missing/present and unerupted/erupted teeth in the study population as a function of the type of OI (a) and genetic variants (b). The brackets indicate significant differences in the prevalence of missing and unerupted teeth as a function of the genetic variants (p-value<0.05). The prevalence of missing teeth was significantly higher among teeth with C-propeptide variants than in those with other variants, and significantly lower among teeth with the α1 haploinsufficiency variant (p-value<0.05). The prevalence of unerupted teeth was significantly lower in the haploinsufficiency variant than in those with the glycine substitution variant (p-value<0.05).

second premolars in OI type III and IV. Upper right first molars and canines were also frequently missing in OI type I and OI type III patients, respectively (Fig. 3). Lower incisors and upper left first molars were not missing in any patient regardless of OI type. Also, there were not any missing upper central incisors in OI type I and IV patients.

Interestingly, the upper and lower jaws had different phenotypes of missing teeth that varied according to OI type. For example, upper anteriors and molars in OI type III patients and upper posteriors in OI type I, were more likely to be missing than their opposing lower teeth. Also, in OI type IV patients, upper premolars and lower molars were more likely to be missing than their opposing teeth (Fig. 4).

The prevalence of missing teeth was also significantly associated with the type of variant (OR 61.7; $p < 0.05$, and adjusted OR = 22, $p < 0.05$). Also, in OI IV patients, C-propeptide variant was associated with significantly more missing teeth than haploinsufficiency variant or α1 and α2 glycine substitution, while α2 glycine substitution and splice site showed significantly more missing teeth than α1 glycine substitution (Supplementary Table 10). When the Kruskal Wallis test was used to compare the effect of different variants on missing teeth in all individuals, haploinsufficiency variants affected missing teeth significantly less than all the other mutations, while C-propeptide variants showed a significantly higher effect than all other variants (Supplementary Table 8).

Assessment at the tooth level showed that all the variants investigated were associated with cases of missing lower premolars and first molars. However, only C-propeptide variants, α1 Gly substitutions and α2 Gly substitutions, were associated with missing anteriors. In addition, C-propeptide variants often resulted in missing upper premolars and first molars, splice site mutations were associated with missing second molars and upper premolars, α1 haploinsufficiency was associated with missing upper second molars, α 2 glycine substitutions often resulted in missing upper premolars, and α1 glycine resulted in missing upper teeth and lower second molars. (Figs. 2 & 3 Supplementary Table 9). No association of tooth discoloration and the prevalence of missing teeth was observed.

3.2. Unerupted teeth

Out of 2100 evaluated teeth, only 63 (3%) were unerupted. The only unerupted teeth were the canines, premolars, and second molars. Interestingly, apart from the upper second molars, the lower jaw presented with more unerupted teeth than the upper jaw.

Patients with OI type I only presented unerupted premolars, while those with OI type IV presented unerupted upper second molars, and OI

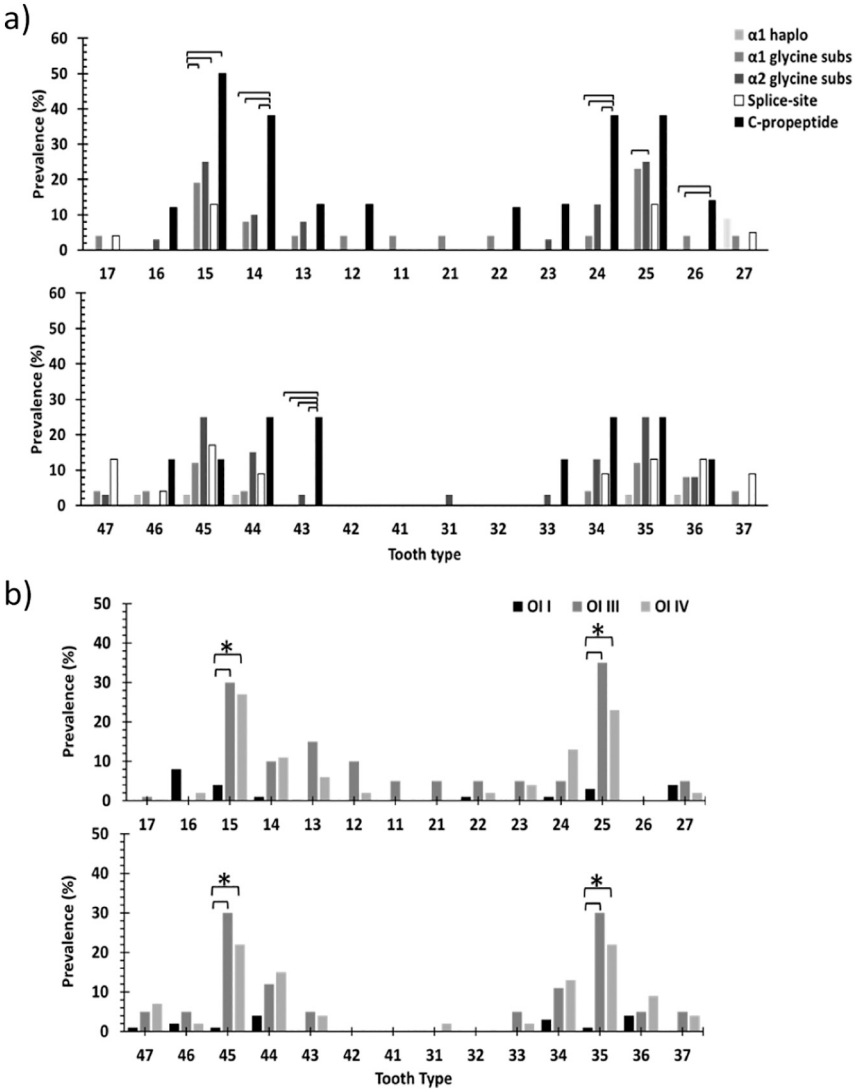

Fig. 3. The prevalence of missing teeth at the tooth level. a) The prevalence of missing teeth evaluated in every type of genetic mutations, b) the prevalence of missing teeth in different types of OI.

type III showed unerupted premolars, the lower canines, and upper second molars. Also, only OI type III patients presented unerupted upper first premolars (Fig. 4). Unerupted upper second molars were more common in OI type III (60%–70%) and IV (34%–37%) than in OI type I (2%–3%) ($p < 0.05$). Also, we observed unerupted lower second premolars in 20%–50% of patients OI type III and 3% of those with OI type IV, but not in patients with OI type I, and we found unerupted lower first premolars in 3% of patients with OI type I and IV, and in 30% of those with OI type III.

Unerupted canines were very rare; only one individual with OI type IV had unerupted upper canines and one unerupted lower canine, and one patient with OI type III had unerupted lower canines (Fig. 4).

Assessment of genetic variants revealed that glycine substitute variants affected tooth eruption differently than haploinsufficiency and splice site variants (p-value <0.05) (Fig. 2, Supplementary Table 8). For instance, patients with α1 glycine substitutions presented significantly more cases of unerupted teeth than those with haploinsufficiency and splice-site variants, and among OI I patients, this mutation was significantly associated with more unerupted teeth than all other variants (Supplementary Table 10).

Tooth level analysis revealed that all variants presented cases of unerupted upper second molars except for α1 haploinsufficiency, which only presented cases of unerupted second premolars. On the other hand, only patients with glycine substitution variants presented unerupted premolars and canines. Unerupted lower premolars and upper second molars were significantly more common among patients with α1 glycine substitution than those with α2 glycine substitutions. (Fig. 4 & Supplementary Table 9). Our results also revealed that the presence of DI was not associated with the prevalence of unerupted teeth.

3.3. Early exposure to bisphosphonate treatment

The data on the onset of bisphosphonate treatment was available only for 105 patients (this data was missing in 43 patients with OI type I, 2 patients with OI type III and 4 patients with OI type IV). The average age when bisphosphonate treatment was first started was presented in Fig. 5. The Kruskal Wallis test was used to evaluate the age difference between OI types when bisphosphonate was first started and showed that patients with OI type I were significantly older than those with OI types III and IV (p-value <0.05) at the onset of bisphosphonate treatment.

To study the association between early bisphosphonate treatment (starting before the age of 6 years) and the prevalence of missing or unerupted teeth generalized linear model was used after adjustment for OI type, and sex. Our results showed no significant association between early bisphosphonate intervention and the prevalence of missing teeth

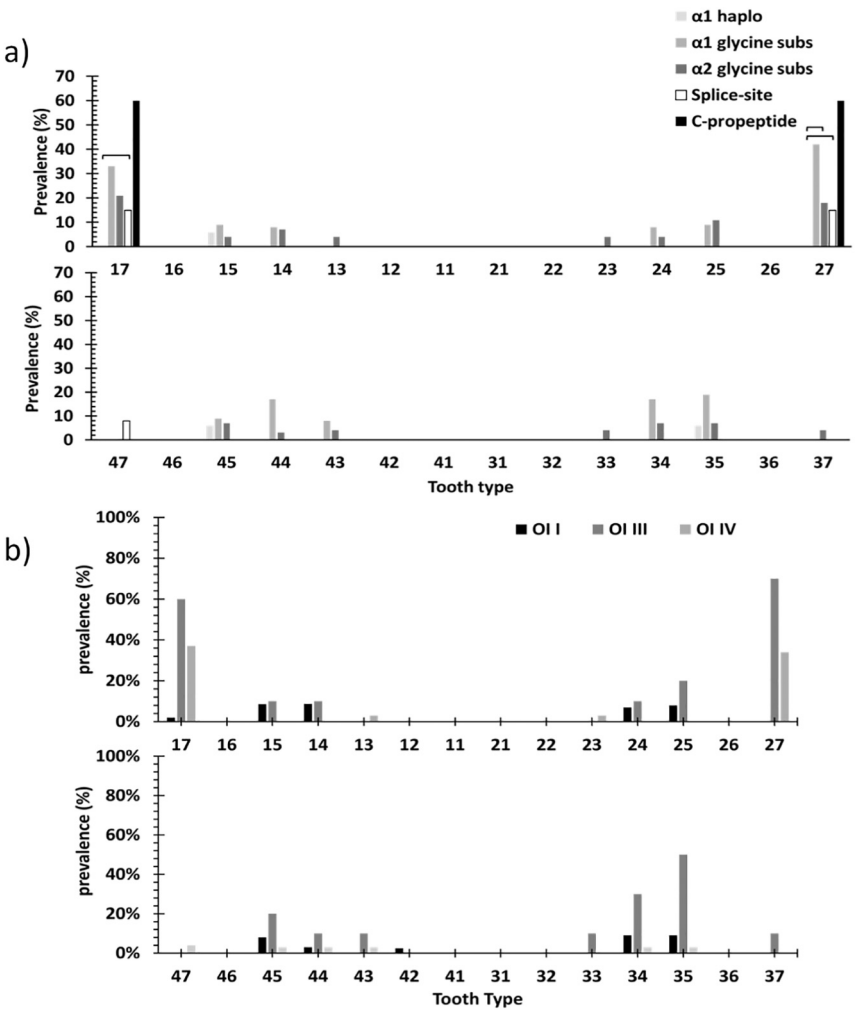

Fig. 4. The prevalence of unerupted teeth at the tooth level. a) the prevalence of unerupted teeth in every type of genetic mutations. b) The prevalence of unerupted teeth in different types of OI.

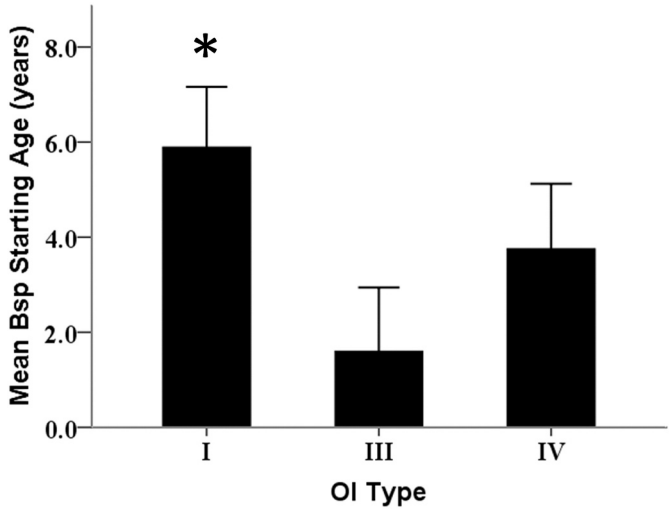

Fig. 5. The mean of age when Bisphosphonate treatment was first started in patients with different OI types. *Patients with OI type I were significantly older than those with OI types III and IV in the age when bisphosphonate was first started ($p < 0.05$).

but it was associated with higher prevalence of unerupted teeth in OI types III (OR = 2.4, 95% CI = 1.39–4.15) and IV (OR = 1.76, 95%CI = 1.61–5.03). In our cohort, 90% of patients that started bisphosphonate treatment before the age of 6 years presented at least one unerupted tooth, with an odds ratio of 1.68, 95% CI (1.15–1.53) compared to those who started treatment at a later age.

4. Discussion

Our study revealed that the prevalence of missing or unerupted teeth varied according to the type of tooth, OI type and variant. Prevalence of missing or unerupted teeth is higher in patients with severe conditions (OI types III and IV), and it affected predominantly missing premolars and unerupted upper second molars. We also found that bisphosphonate treatment at an early age was associated with an increased prevalence of unerupted teeth.

4.1. Missing teeth

In our study, the prevalence of missing teeth in OI patients was much higher than that observed in the general population (6.4%) [32], and it was associated with the severity of the disease. Indeed, patients with moderate to severe OI presented a much higher prevalence of missing teeth (OI type IV 52%, OI type III 61%) than patients with OI type I (11%).

Interestingly, the pattern of missing teeth among our OI patients was

also different from that observed in the general population. Besides third molars, the most commonly missing teeth in the general population are the mandibular second premolars (1–6%), the upper lateral incisors (1–4%) [33], and to a lesser extent, the upper second premolars [32]. However, OI patients in our cohort were also missing teeth that are rarely missing in the general population, such as first premolars, canines, first molars and central upper incisors. Although collagen is expressed in all types of teeth, the consequences of their inactivation may be different in different tooth types. It has been reported that the high prevalence of missing teeth in OI patients could be due to the deleterious effects of structurally abnormal type I collagen on tooth germ development and mineralization during the initiation of tooth formation [20].

A large body of recent work has employed mouse models of OI to help in understanding the pathophysiology of the disease and potential treatment. Several current mouse models of OI [34,35] report post-cranial phenotypes similar to those seen in human patients with OI. However, a limited number of studies also reporting human-like alterations to cranial and dental integrity [36–38], but missing and unerupted teeth were not reported in such models.

However, many human and animal studies found that dental anomalies, mainly missing teeth, and craniofacial alterations, could share common genetic factors [39–42], such as mutations in MSX1, PAX9, TGF-α and FGF family genes [42,43]. Interestingly, some of these genetic mutations were associated with missing specific tooth types. For example, MSX1 mutations were associated with preferentially missing premolars causing oligodontia [43], while PAX9 mutations were associated with preferentially missing molars [44]. In our study, an association was found between certain collagen mutations and specific teeth agenesis. For example, C-propeptide variants were associated with the highest number of missing teeth and resulted in a significantly higher number of missing premolars and first molars than all the other variants. Also, splice site variants affected only posterior teeth, with more missing teeth in the lower jaw than the upper jaw. These observations indicate that the type of variant is an important predictor for missing teeth patterns in OI patients and could be playing a part in teeth formation and development.

Different patterns of missing teeth between the upper and lower jaw were seen in our study. The maxilla was associated with more missing teeth, and while anterior teeth were missing more often in the maxilla, molars were more often missing in the mandible. These observations could be due to the maxilla's under development and the closing mandibular growth rotation observed in OI patients (especially OI III and IV) [13,36]. These alterations in craniofacial development reduce the space for tooth development in the anterior maxilla and posterior mandible and could play a key role in the pattern of missing teeth observed in OI patients. This is further confirmed by the fact that premolars are among the last teeth to be initiated and mineralized, and are the most commonly missing teeth, probably due to the lack of remaining space by the time they form. Indeed, tooth and craniofacial development are two processes controlled by common genetic mechanisms [13,45,46], and tooth agenesis has also been associated with Class III malocclusion and hypodivergent skeletal patterns with decreased angular prognathism [47], which were consistently found in moderate to severe OI [36]. These observations would suggest that craniofacial developmental defects in OI are key to the prevalence of missing teeth. Future studies on the association between genetic mutations in OI and craniofacial phenotypes will help understand the mechanism behind the dental phenotypes.

4.2. Unerupted teeth

In our study, 33% of OI patients had at least one unerupted tooth, and the prevalence of tooth eruption was associated with the severity of the disease as OI type III patients showed the highest prevalence of unerupted teeth (70%) followed by OI type IV (40%), and lastly, OI type I (30%). Unerupted teeth were also associated with qualitative mutations such as α1 and α2 glycine mutations rather than Haploinsufficiency mutations, which is in agreement with previous studies indicating a high prevalence of unerupted teeth in patients within Col1a1/1a2 qualitative mutations [21]. We also observed that α1 glycine variants were associated with unerupted teeth, even in mild OI cases (OI I). Our results also indicated that patients with mild OI are at higher risk of developing unerupted second premolars when associated with α1 glycine variants. While in moderate to severe OI, different genetic variants seem to have a similar effect on unerupted teeth. Interestingly, splice site and C-propeptide variants (moderate to severe OI) only associated with unerupted second molars and only the upper ones in splice site variants. These genetic phenotypes could be directly linked to craniofacial development. Patients with OI tend to have clockwise rotated maxillae and anteriorly rotated mandible resulting in the retrognathic maxilla and class III malocclusion [21,48]. This could help explain the high prevalence of unerupted maxillary second molars.

Unerupted permanent teeth are common in the general population, and this affects mainly the 3rd molars (91%), canines (5.3%), premolars (1.6%), and second molars 2.3% [49]. However, our study showed that the prevalence of retained teeth is different in OI patients; for example, OI affected eruption of maxillary second molars the most (OI type III (70%), OI IV (35%), and OI I (2%), followed by the second premolars (50%), the lower first premolars (30%) and the upper premolars (up to 20%).

Schwartz et al. [11] found that most impacted teeth in OI patients were in the lower arch associated with class III malocclusion. The low prevalence of unerupted teeth in the Schwartz's study (17%) in comparison to ours (33%) could be related to the small number of participants ($n = 28$) from which only 17 had a panoramic X-ray. In our results, the prevalence of unerupted lower second molar was the highest in OI type III associated with splice-site variants (10%), followed by OI type IV associated with α2 glycine variants (4%).

In our cohort, lower canines were unerupted in 10% of OI type III patients and about 3% of OI type IV and only in patients with glycine substitution variants. Unerupted maxillary canines were found only in OI type IV, and only in patients with α2 glycine substitutions variants (3%). Unerupted canines were not observed in OI type I, probably due to close-to-normal jaws sizes and relations [13].

Tooth eruption is the movement of teeth from their origin within the jaw to their functional position in the oral cavity, and it depends on regulated bone remodelling [50]. Genetic and local environmental factors determine the intra-osseous movement speed. One of the most important local environmental factors is crowding among the developing and erupting teeth. Other local environmental factors that may influence the intra-osseous tooth eruption stage are obstructions in the eruption path (e.g., supernumerary teeth, odontomas, and cysts), trauma, and early extraction or detention of primary teeth [51].

The speed of intra-osseous tooth migration during eruption varies according to tooth type and the distance of migration. Among permanent teeth, the shortest distance of this journey is for the first molar (about 5 mm) and the longest for canines (about 20 mm); thus the eruption process takes 2.5 and 6.5 years, respectively. For the other permanent teeth, the intra-osseous stage duration varies from about 3.5–5 years [52]. This could explain the small prevalence of unerupted first molars but would indicate that canines should have been more often unerupted, which is not the case in patients with OI.

Tooth crowding, which is common in OI patients, could also play a major role in the high prevalence of unerupted teeth in our study population. Indeed, crowding often leads to follicle collisions where one follicle is placed on top of another, leaving both teeth unerupted [50]. The prevalence of unerupted premolars and second molars in the general population is very low (1.6%–2.3%, respectively) [49], while it is relatively high in OI patients. Second premolars, especially in the mandible, are the last teeth to erupt in the oral cavity before the second and third molars, and with lack of space, delaying or failing to erupt is expected.

At the same time, posterior rotation of the maxilla could be a reason to retentive maxillary second molar, especially in severe and moderate OI types [53,54].

In summary, it seems that the prevalence of missing and unerupted teeth is influenced by the clinical and genetic phenotype of OI patients, probably by affecting craniofacial development and the intra-osseous stage of tooth eruption; however, future research is required to confirm these observations further.

4.3. Bisphosphonate treatment

All the individuals assessed in our study were treated with bisphosphonates to increase bone mineral density and reduce the risk of bone fractures [25]. These drugs inhibit osteoclast function and bone resorption, which are both required for tooth eruption. Thus, bisphosphonate treatment could be another possible explanation for the high prevalence of unerupted teeth in our cohort OI patients. Indeed, human and animal studies have shown delayed tooth eruption and impaction associated with bisphosphonates [23–25], as well as interferences with orthodontic treatments [55], and they slow down the fast rate of tooth development found in OI patients [56]. As expected, our results showed that early exposure to bisphosphonate was significantly associated with a high prevalence of unerupted teeth in patients with OI types III and IV, and this is in agreement with a recent study showing that bisphosphonate therapy in OI patients seems to lower the dental age, delay the dental maturity, and tooth eruption when administration before 2 years of age [57]. On the other hand, patients with a milder form of OI (OI type I), started the bisphosphate treatment at an older age and this is probably why they presented fewer incidents of tooth impaction.

The prevalence of missing teeth, on the other hand, did not seem to be associated with the onset of bisphosphonate treatment in our study. This is in disagreement with a recent study reporting higher prevalence of tooth agenesis in children who had begun treatment with bisphosphonate before the age of 2 years [58]. In Malmagren et al. study [58], they did not adjust for the type of OI, and most of the patients that were treated before 2 years of age in their cohort were OI type III (13/22), where nine of them presented missing teeth, while the majority of patients treated after 2 years of age in their cohort where of OI type I (11/20), and the only missing teeth were in OI type III (5/20) patients in that group. While in our study, we adjusted for the type of OI where no significant difference was reported between the two age groups in different OI types.

4.4. Strength and limitations

A major strength of the present study is the relatively large number of patients included. However, the disproportion in the sample size of individual OI groups could be insufficient to characterize all the significant differences among all OI types. This study's cross-sectional design includes the most common OI types and the associated genetic variants, but the missing control group could appear as an obvious limitation. However, previous publications on missing and unerupted teeth prevalence offered a robust source for comparison. Moreover, other populational, genetic, and local factors such as phylogenetic or congenital influence and different ethnicity could affect the results [51].

Overall, we recommend additional investigations to further solidify the association between the genotype and the dental phenotype to offer more predictable and personalized oral health management of patients with OI. As well as studying local dental factors such as ankylosis as a potential cause for lack of eruption. This study's findings provide a snapshot of the dental phenotype of patients with different types of OI, and are of great importance for dental prevention and management for OI patients, especially for orthodontic and pediatric procedures. Also, we need to emphasize the importance of regular radiographical evaluations for OI patients.

5. Conclusion

The prevalence of missing and unerupted teeth in OI patients depends on the tooth type, OI type and variant type. And the dental phenotypes vary between upper and lower jaw. Also the genetic variant is a better predictor for the dental phenotype than the OI type. Missing premolars showed the highest prevalence in OI patients, especially those with C-propeptide variants. In comparison, Unerupted second molars were seen in high prevalence, especially in patients with C-propeptide and splice site variants followed by premolars which were significantly associated with α1 glycine variants. And Finally, early onset of bisphosphonate treatment seems to increase the risk of developing unerupted teeth.

Declaration of competing interest

Authors declare no conflicts of interest.

Acknowledgments

The Brittle Bone Disease Consortium [1U54AR068069-0] is a part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network (RDCRN) and is funded through a collaboration between the Office of Rare Diseases Research (ORDR), NCATS, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Dental and Craniofacial Research (NIDCR), and the Eunice Kennedy Shriver National Institutes of Child Health and Development (NICHD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We declare no conflict of interest.

Authors contributions

D.T, contributed to conception, design, data acquisition and interpretation, performed some statistical analyses, drafted and critically revised the manuscript. D.T, F.T, JM.R, F.R have contributed to conception designed the study, data acquisition and interpretation, and critically revised the manuscript. D.T, H.M, JM.R collected and validated the data. T.S, performed Generalized linear models analyses and data acquisition and interpretation. AR.V., critically reviewed the manuscript. D.D, prepared the X-ray and trained, D.T on data collection. All the above authors revised the article and Agreed to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors declare no conflict of interests.

Funding

National Institutes of Health. Grant Number: 1U54AR068069-0.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2021.116011.

References

[1] D.O. Sillence, A. Senn, D.M. Danks, Genetic heterogeneity in osteogenesis imperfecta, J. Med. Genet. 16 (2) (1979) 101–116.
[2] F.H. Glorieux, Osteogenesis imperfecta, Best Pract. Res. Clin. Rheumatol. 22 (1) (2008) 85–100.
[3] C. Stoll, B. Dott, M.-P. Roth, Y. Alembik, Birth prevalence rates of skeletal dysplasias, Clin. Genet. 35 (2) (1989) 88–92.
[4] P.E. Andersen Jr., M. Hauge, Osteogenesis imperfecta: a genetic, radiological, and epidemiological study, Clin. Genet. 36 (4) (1989) 250–255.
[5] D.O. Sillence, D.L. Rimoin, Classification of osteogenesis imperfect, Lancet. 1 (8072) (1978) 1041–1042.

[6] D.O. Sillence, D.L. Rimoin, D.M. Danks, Clinical variability in osteogenesis imperfecta-variable expressivity or genetic heterogeneity, Birth Defects Orig. Artic Ser. 15 (5B) (1979) 113–129.
[7] P. Fratzl, Collagen: Structure and Mechanics, an Introduction, Springer, Collagen, 2008, pp. 1–13.
[8] G.W. Marshall Jr., Dentin: microstructure and characterization, Quintessence Int. 24 (9) (1993).
[9] F. Rauch, F.H. Glorieux, Osteogenesis imperfecta, Lancet 363 (9418) (2004) 1377–1385.
[10] J.C. Marini, A. Forlino, H.P. Bachinger, N.J. Bishop, P.H. Byers, A. Paepe, et al., Osteogenesis imperfecta, Nature Rev. Dis. Primers 3 (2017) 17052.
[11] S. Schwartz, P. Tsipouras, Oral findings in osteogenesis imperfecta, Oral Surg. Oral Med. Oral Pathol. 57 (2) (1984) 161–167.
[12] P.-C. Chang, S.-Y. Lin, K.-H. Hsu, The craniofacial characteristics of osteogenesis imperfecta patients, Eur. J. Orthod. 29 (3) (2007) 232–237.
[13] J. Rizkallah, S. Schwartz, F. Rauch, F. Glorieux, D.-D. Vu, K. Muller, et al., Evaluation of the severity of malocclusions in children affected by osteogenesis imperfecta with the peer assessment rating and discrepancy indexes, Am. J. Orthod. Dentofac. Orthop. 143 (3) (2013) 336–341.
[14] R. Saeves, L. Lande Wekre, E. Ambjornsen, S. Axelsson, H. Nordgarden, K. Storhaug, Oral findings in adults with osteogenesis imperfecta, Spec. Care Dentist. 29 (2) (2009) 102–108.
[15] K.H. Bendixen, H. Gjørup, L. Baad-Hansen, J. Dahl Hald, T. Harsløf, M.H. Schmidt, et al., Temporomandibular disorders and psychosocial status in osteogenesis imperfecta - a cross-sectional study, BMC Oral Health 18 (1) (2018) 35.
[16] A.C. O'Connell, J.C. Marini, Evaluation of oral problems in an osteogenesis imperfecta population, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 87 (2) (1999) 189–196.
[17] M.J. Barron, S.T. McDonnell, I. Mackie, M.J. Dixon, Hereditary dentine disorders: dentinogenesis imperfecta and dentine dysplasia, Orphanet. J. Rare Dis. 3 (2008) 31.
[18] E.D. Shields, D. Bixler, A.M. el-Kafrawy, A proposed classification for heritable human dentine defects with a description of a new entity, Arch. Oral Biol. 18 (4) (1973) 543–553.
[19] D. Taqi, H. Moussa, T. Schwinghamer, M. Ducret, D. Dagdeviren, J.-M. Retrouvey, et al., Osteogenesis imperfecta tooth level phenotype analysis: cross-sectional study, Bone. 115917 (2021).
[20] B. Malmgren, K. Andersson, K. Lindahl, A. Kindmark, G. Grigelioniene, V. Zachariadis, et al., Tooth agenesis in osteogenesis imperfecta related to mutations in the collagen type I genes, Oral Dis. 23 (1) (2017) 42–49.
[21] K. Andersson, G. Dahllöf, K. Lindahl, A. Kindmark, G. Grigelioniene, E. Åström, et al., Mutations in COL1A1 and COL1A2 and dental aberrations in children and adolescents with osteogenesis imperfecta–a retrospective cohort study, PLoS One 12 (5) (2017), e0176466.
[22] J.T. Tauer, M.E. Robinson, F. Rauch, Osteogenesis imperfecta: new perspectives from clinical and translational research, JBMR Plus (2019) e10174.
[23] A. Kamoun-Goldrat, D. Ginisty, M.L. Merrer, Effects of bisphosphonates on tooth eruption in children with osteogenesis imperfecta, Eur. J. Oral Sci. 116 (3) (2008) 195–198.
[24] T. Hiraga, T. Ninomiya, A. Hosoya, H. Nakamura, Administration of the bisphosphonate zoledronic acid during tooth development inhibits tooth eruption and formation and induces dental abnormalities in rats, Calcif. Tissue Int. 86 (6) (2010) 502–510.
[25] K. Dwan, C.A. Phillipi, R.D. Steiner, D. Basel, Bisphosphonate therapy for osteogenesis imperfecta, Cochrane Database Syst. Rev. 10 (2016).
[26] H.D. Binh, K. Maasalu, V.C. Dung, C.T. Ngoc, T.T. Hung, T.V. Nam, et al., The clinical features of osteogenesis imperfecta in Vietnam, Int. Orthop. 41 (1) (2017) 21–29.
[27] M.J. Wallace, R. Kruse, S. Shah, The spine in patients with osteogenesis imperfecta, J. Am. Acad. Orthop. Surg. 25 (2) (2017) 100–109.
[28] M. Najirad, M.S. Ma, F. Rauch, V.R. Sutton, B. Lee, J.-M. Retrouvey, et al., Oral health-related quality of life in children and adolescents with osteogenesis imperfecta: cross-sectional study, Orphanet. J. Rare Dis. 13 (1) (2018) 187.
[29] J.-M. Retrouvey, D. Taqi, F. Tamimi, D. Dagdeviren, F.H. Glorieux, B. Lee, et al., Oro-dental and cranio-facial characteristics of osteogenesis imperfecta type V, Eur. J. Med. Genet. 62 (12) (2019) 103606.
[30] M.S. Ma, M. Najirad, D. Taqi, J.M. Retrouvey, F. Tamimi, D. Dagdeviren, et al., Caries prevalence and experience in individuals with osteogenesis imperfecta: a cross-sectional multicenter study, Spec. Care Dent. 39 (2) (2019) 214–219.
[31] W. Cholitgul, B. Drummond, Jaw and tooth abnormalities detected on panoramic radiographs in New Zealand children aged 10-15 years, New Zeal. Dental J. 96 (423) (2000) 10–13.
[32] K. Khalaf, J. Miskelly, E. Voge, T.V. Macfarlane, Prevalence of hypodontia and associated factors: a systematic review and meta-analysis, J. Orthod. 41 (4) (2014) 299–316.
[33] A.L. Symons, F. Stritzel, J. Stamation, Anomalies associated with hypodontia of the permanent lateral incisor and second premolar, J. Clin. Pediatr. Dent. 17 (1993) 109.
[34] T.A. Enderli, S.R. Burtch, J.N. Templet, A. Carriero, Animal models of osteogenesis imperfecta: applications in clinical research, Orthop. Res. Rev. 8 (2016) 41–55.
[35] J. Lim, I. Grafe, S. Alexander, B. Lee, Genetic causes and mechanisms of osteogenesis imperfecta, Bone. 102 (2017) 40–49.
[36] H. Eimar, F. Tamimi, J.M. Retrouvey, F. Rauch, J.E. Aubin, M.D. McKee, Craniofacial and dental defects in the Col1a1Jrt/+ mouse model of osteogenesis imperfecta, J. Dent. Res. 95 (7) (2016) 761–768.
[37] H. Xu, S.A. Lenhart, E.Y. Chu, M.B. Chavez, H.F. Wimer, M. Dimori, et al., Dental and craniofacial defects in the Crtap−/− mouse model of osteogenesis imperfecta type VII, Dev. Dyn. 249 (7) (2020) 884–897.
[38] C.L. Phillips, D.A. Bradley, C.L. Schlotzhauer, M. Bergfeld, C. Libreros-Minotta, L. R. Gawenis, et al., Oim mice exhibit altered femur and incisor mineral composition and decreased bone mineral density, Bone. 27 (2) (2000) 219–226.
[39] S. Yüksel, T. Uçem, The effect of tooth agenesis on dentofacial structures, Eur. J. Orthod. 19 (1) (1997) 71–78.
[40] A.Y. Gungor, H. Turkkahraman, Effects of severity and location of nonsyndromic hypodontia on craniofacial morphology, Angle Orthod. 83 (4) (2013) 584–590.
[41] C. Bajraktarova Miševska, L. Kanurkova, E. Bajraktarova Valjakova, S. Georgieva, B. Bajraktarova, Z. Georgiev, et al., Craniofacial morphology in individuals with increasing severity of hypodontia, South Eur. J. Orthod. Dentofac. Res. 3 (1) (2016) 12–17.
[42] A.S. Rodrigues, E.C. Teixeira, L.S. Antunes, P. Nelson-Filho, A.S. Cunha, S.C. Levy, et al., Association between craniofacial morphological patterns and tooth agenesis-related genes, Prog. Orthod. 21 (2020) 1–8.
[43] A.R. Vieira, R. Meira, A. Modesto, J. Murray, MSX1, PAX9, and TGFA contribute to tooth agenesis in humans, J. Dent. Res. 83 (9) (2004) 723–727.
[44] S. Frazier-Bowers, D. Guo, A. Cavender, L. Xue, B. Evans, T. King, et al., A novel mutation in human PAX9 causes molar oligodontia, J. Dent. Res. 81 (2) (2002) 129–133.
[45] J. Retrouvey, S. Schwartz, J. Hartsfield, Oral-facial aspects of osteogenesis imperfecta, in: Osteogenesis Imperfecta: A Translational Approach to Brittle Bone Disease, Academic, London, 2014.
[46] A. Cocos, D.J. Halazonetis, Craniofacial shape differs in patients with tooth agenesis: geometric morphometric analysis, Eur. J. Orthod. 39 (4) (2016) 345–351.
[47] P.N. Acharya, S.P. Jones, D. Moles, D. Gill, N.P. Hunt, A cephalometric study to investigate the skeletal relationships in patients with increasing severity of hypodontia, Angle Orthod. 80 (4) (2010) 699–706.
[48] B. Malmgren, S. Norgren, Dental aberrations in children and adolescents with osteogenesis imperfecta, Acta Odontol. Scand. 60 (2) (2002) 65–71.
[49] L. Bondemark, J. Tsiopa, Prevalence of ectopic eruption, impaction, retention and agenesis of the permanent second molar, Angle Orthod. 77 (5) (2007) 773–778.
[50] G. Kock, S. Kreiborg, J.O. Andreasen, Eruption and shedding of teeth, in: Pediatric Dentistry a Clinical Approach, 3rd ed., Wiley-Blackwell, Oxford, 2017, pp. 40–54.
[51] M. Celikoglu, O. Miloglu, F. Kazanci, Frequency of agenesis, impaction, angulation, and related pathologic changes of third molar teeth in orthodontic patients, J. Oral Maxillofac. Surg. 68 (5) (2010) 990–995.
[52] S. Kreiborg, B.L. Jensen, Tooth formation and eruption–lessons learnt from cleidocranial dysplasia, Eur. J. Oral Sci. 126 (2018) 72–80.
[53] B.L. Jensen, A.M. Lund, Osteogenesis imperfecta: clinical, cephalometric, and biochemical investigations of OI types I, III, and IV, J. Craniofac. Genet. Dev. Biol. 17 (3) (1997) 121–132.
[54] J. Waltimo-Sirén, M. Kolkka, S. Pynnönen, K. Kuurila, I. Kaitila, O. Kovero, Craniofacial features in osteogenesis imperfecta: a cephalometric study, Am. J. Med. Genet. A 133 (2) (2005) 142–150.
[55] V.F. Zymperdikas, M.P. Yavropoulou, E.G. Kaklamanos, M.A. Papadopoulos, Effects of systematic bisphosphonate use in patients under orthodontic treatment: a systematic review, Eur. J. Orthod. 42 (1) (2020) 60–71.
[56] I. Vuorimies, H. Arponen, H. Valta, O. Tiesalo, M. Ekholm, H. Ranta, et al., Timing of dental development in osteogenesis imperfecta patients with and without bisphosphonate treatment, Bone. 94 (2017) 29–33.
[57] B. Malmgren, G. Tsilingaridis, N. Monsef-Johansson, Z.H.A. Qahtani, G. Dahllöf, E. Åström, Bisphosphonate therapy and tooth development in children and adolescents with osteogenesis imperfecta, Calcif. Tissue Int. 107 (2) (2020) 143–150.
[58] B. Malmgren, I. Thesleff, G. Dahllöf, E. Åström, G. Tsilingaridis, Abnormalities in tooth formation after early bisphosphonate treatment in children with osteogenesis imperfecta, Calcif. Tissue Int. (2021), https://doi.org/10.1007/s00223-021-00835-2. Epub ahead of print. PMID: 3374302.