Dental alterations on panoramic radiographs of patients with osteogenesis imperfecta in relation to clinical diagnosis, severity, and bisphosphonate regimen aspects: a STROBE-compliant case-control study

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Objective. This study aimed to assess the prevalence of dental findings on panoramic radiographs (PRs) of patients with osteogenesis imperfecta (OI) and correlate these results with epidemiologic and medical data.

Study Design. A case-control study was conducted with 24 patients with OI and 48 sex- and age-matched controls. Demographic, clinical, and bisphosphonate regimen-related data were recorded. The outcome variables were the presence or absence of dental alterations in PRs. Mann-Whitney U test, Pearson's χ^2 test, and multinomial logistic regression analysis (95% confidence interval) were used (significance level of 5%).

Results. OI type 4 demonstrated a high prevalence (62.5%), followed by type 1 (37.5%). With regard to prevalence associated with severity, the moderate form was the most prevalent ($P = .028$). The mean time of intravenous pamidronate regimen was 6.6 ± 4.4 years. Dentinogenesis imperfecta was observed in 75% of patients with OI, and this group showed a high prevalence of dental abnormalities in comparison with controls ($P < .05$). Bisphosphonate therapy was associated with ectopic teeth ($P = .007$) and tooth impaction ($P = .033$). Pulp obliteration was significant with bisphosphonate treatment over a period of 7 years ($P = .026$).

Conclusions. This study found a significant prevalence of dental alterations in patients with OI, and certain alterations were associated with bisphosphonate therapy, indicating its influence on the dentin-related physiopathology. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:621−630)

Osteogenesis imperfecta (OI) is characterized as a heterogenic group of rare genetic disorders showing alterations in the conjunctiva[1] and having an overall estimated incidence of 1 per 15,000 to 20,000 newborns.[2,3] The OI genetic database has been continuously updated, with 18 gene mutations listed in a recent perspective review.[4] This condition has been usually associated with dominant mutations found in genes linked to collagen types I and II (*COL1 A1* in chromosome 17 and *COL1 A2* in chromosome 7, respectively). These are mainly implicated in bone-related qualitative and quantitative repercussions in individuals with OI types 1 to 4.[5] Its classification has been continuously updated since David Sillence first defined, based on their clinical findings in 1979, the 4 types of OI.[6,7] Recent molecular studies have newly identified a fifth type of OI related to the pathogenic variant in the 5′UTR of the interferon-induced transmembrane protein 5 encoding gene (*IFITM5*: C.−14 C>T variant),[8] which is associated with hyperplasic callus, in addition to the classic bone fragility.[5] Moreover, a new phenotypic information obtained on this particular OI type has shown the occurrence of heterotopic ossification of muscle origins and insertions.[9]

Clinically, individuals with OI commonly exhibit some craniofacial morphologic features, including a triangular face, increased head circumference, skeletal class III deformity, and malocclusions, such as open bite and crossbite.[10] A recent study report described bimaxillary retrusive malocclusion associated with a reduced lower face height, as well as multiple absent

Statement of Clinical Relevance

This investigation highlighted the importance of systematic oral examination in medically compromised patients, such as those with osteogenesis imperfecta, and discussed the impact of bisphosphonate therapy on the occurrence of orodental disorders.

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teeth, in OI type 5.[11] Among the dental abnormalities described in OI, dentinogenesis imperfecta is the most reported alteration.[3] It is indicated by brownish, amber, or even opalescent teeth observed on intraoral inspection.[1,12] In fact, it is a relevant clinical and radiographic finding that has been reported as a significant independent predictive factor of increased prevalence of dental caries among patients with OI.[13] Also, with regard to OI severity, dentinogenesis imperfecta has been found to a significant degree in cases clinically categorized as moderate or severe.[14]

Additionally, panoramic radiograph (PR), complementary to the clinical examination, is a suitable imaging modality that has been considered an important clinical tool for the diagnosis of orofacial alterations in OI.[15] It is an accessible and low-cost tool that allows a comprehensive evaluation of the maxillomandibular complex.[16] On radiographic examination, affected teeth may show crowns with a bulbous structure, accentuated constriction in the cementoenamel junction, thin and narrowed roots, large root canals caused by defective dentin formation, and enlarged pulp chambers that may attain a total or partial obliteration pattern.[12,17-19] Also, pulp stones[14] and tooth eruption disorders[20] have been found in the OI spectrum.

The study of rare diseases (i.e., skeletal disorders such as OI) may be improved by using well-designed case-control methodologies, mainly when the aim is to study the association of determined exposures to the disease conditions of interest. Furthermore, the efficiencies of a case-control study design related to low cost and the ability to obtain fast results and to evaluate rare diseases may surpass its limitations.[21] Only 2 studies with a case-control design evaluated the dental aspects in patients with OI.[22,23] However, there are limited data from case-control studies[23] on the prevalence of dental alterations in OI, according to Sillence's classification.

Intravenous (IV) bisphosphonate therapy has long been adopted for OI management. This explains the interest in investigating the occurrence of long-term adverse events, such as fractures of long bones and osteonecrosis of the jaws.[24] The effect of bisphosphonate therapy on the dental tissues of individuals with OI receiving the treatment with bisphosphonate is still unclear. Although animal models have shown teeth alterations associated with sodium alendronate administration[25] and systemic bisphosphonate-related post-eruptive dental pulp changes, such as elevated levels of promineralization cytokines and apoptotic markers,[26] data about their clinical impact on dental development are conflicting.[22,23]

Thus, the present case-control study aimed to evaluate the prevalence of dental findings on digital PRs of patients diagnosed with OI and correlate these findings with epidemiologic and medical data.

MATERIALS AND METHODS

Study design

This research was performed in accordance with the ethical standards of the Federal University of Ceará's Ethics Committee (protocol number 1.520.366) and in compliance with the tenets of the Helsinki Declaration of 1975 (updated in 2008). A case-control study was conducted following 'Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statements' (https://www.strobe-statement.org/). The included subjects were patients diagnosed with OI who were under medical follow-up, and the controls were individuals without OI matched by sex and age. Informed consent was obtained from all participants.

Setting

This study included patients with OI admitted for dental evaluation at the School of Dentistry of the Federal University of Ceará, which is a Brazilian Northeast reference service for "special needs patients." The patients were mainly referred from the Albert Sabin Children's Hospital in Fortaleza city, which is a Brazilian reference medical service for OI diagnosis and treatment. Other sources of patients were the Fortaleza General Hospital and the Dr. José Frota Institute. Additionally, control individuals matched by sex and age were recruited from the School of Dentistry, Federal University of Ceará.

Participants

Participants were recruited from February 2017 to July 2018. The inclusion criteria for the OI group were (1) being Brazilian citizens, without restrictions regarding sex or age, and (2) having a confirmed diagnosis of OI provided by a geneticist. Moreover, patients with the ability to comprehend and sign the informed consent form or, if necessary, those with their guardians' consent, were included in the study.

The control group comprised individuals who complied with the following inclusion criteria: (1) citizens of Brazil, matched by sex; (2) being nonsyndromic; and having the ability to comprehend and sign the informed consent form or, if necessary, having the guardian's consent.

Volunteers from both groups (case and control) were excluded if they met at least 1 of the following criteria: (1) initiated or completed malocclusion treatment, (2) previous history of trauma or surgical procedure in the craniofacial region, (3) presence of any systemic disorder except OI, and (4) pregnancy.

Variables

Demographic (sex and age), clinical, and bisphosphonate regimen–related (route of administration and therapy duration) data were obtained. Clinically, patients with OI were evaluated by using 2 classifications based on the studies performed by Sillence et al.[1,6,7] The initial classification proposed by Sillence et al. was updated in the 9th edition of the *Nosology of Skeletal Dysplasia* as follows: type 1 (normal growth, blue sclera, possibility of hearing loss, and mild bone alterations); type 2 (severe generalized bone alterations causing neonatal death); type 3 (severe bone fragility not leading to neonatal death, wheelchair-bound at a very early age, variable blue sclera, and presence of dentinogenesis imperfecta); type 4 (variable bone fragility, short stature, and occurrence of dentinogenesis imperfecta); and type 5 (moderate to severe bone fragility, with calcification of the interosseous membranes and/or hypertrophic callus).[27] Furthermore, the patients were classified as having mild, moderate, severe, and extremely severe OI, according to the OI severity grading scale proposed by Van Dijk and Sillence.[1]

Data from the digital PRs were obtained by systematic analysis. The following variables were investigated: dentinogenesis imperfecta, tooth loss pattern (anodontia, hypodontia, and oligodontia), apically extended pulp chambers (taurodontism), ectopic teeth, microdontia, bulbous crowns, periradicular radiolucency, residual roots, external radicular resorption, internal radicular resorption, narrow and thin roots, tooth retention, pulp obliteration, tooth impaction, radicular dilaceration, and mandibular condyle-altered morphology.

Data source and measurements

Data were obtained from the hospital records of the patients. All the variables were carefully examined by a team of medical professionals led by a geneticist experienced in the treatment of OI. A list of the variables was created, and after carefully reading the medical records, the variables were appropriately categorized as "presence," "absence," or "not reported," depending on the prevalence of dental alterations. Age and bisphosphonate therapy duration were measured in years.

Digital PRs were used to evaluate the presence or absence of specific dental abnormalities. Images were obtained by using Kodak K9000 3-D (Kodak Dental Systems, Carestream Health, Toronto, Canada) with a gray scale of 14 bits (16384 shades), time of exposition of 13.9 seconds, and kilovoltage/milliamperage adjusted according to the size of each individual. The images were exported in Tagged Image File Format without compression and were evaluated by using the software Adobe Photoshop CS5 (Adobe Systems Inc., San Jose, CA).

Bias

To avoid/minimize the occurrence of bias in the study, a few aspects were considered.[28] Sample size calculation was performed to avoid selection bias and to estimate a reasonable sample size considering that OI is a rare condition. Following the gold standard in the literature for rare syndromes, a case-control proportion of 1:2 was adopted to reduce variability in findings.[29] All medical variables were carefully examined by a medical team headed by a geneticist to avoid the possibility of information bias originating from patients' records. When analyzing the medical parameters, the use of bisphosphonates and duration of administration were considered as possible confounding factors. To avoid measurement errors in this study, the images were evaluated by a researcher experienced in the field of oral and maxillofacial radiology, and the reliability of the evaluations was assessed.

Sample size

The sample size was calculated on the basis of the study by Waltimo-Sirén et al.[30] Those authors evaluated the cephalometric parameters in patients with OI matched with those in controls (case-control proportion of 1:2). They observed that the individuals with OI showed a statistically significant reduction in the value of the anterior nasal spine-menton (62.1 ± 7.8 mm) cephalometric variable in comparison with the controls (68.9 ± 7.9 mm). Thus, 24 cases and 48 controls were required to conduct this observational study, statistically rejecting the null hypothesis with 90% power and a 95% confidence interval (CI). The Student *t* test was used to evaluate the null hypothesis. For sample size calculation, the type 1 error of rejecting the null hypothesis associated with the test was 0.05.

Quantitative variables

Binary quantitative variables were sex (coded 0 and 1 for males and females, respectively), route of bisphosphonate administration (coded 0 and 1 for non-IV and IV, respectively), and PR-related variables (coded 0 and 1 for absence and presence, respectively). Categorized variables were OI classifications and bisphosphonate therapy duration.

Statistical methods

The data collected were captured in a Microsoft Excel database and exported to SPSS program version 20.0 (SPSS, Inc., Chicago, IL) for analysis. The data were expressed as mean and standard deviation and subjected to the Kolmogorov-Smirnov normality test before further analysis with the Mann-Whitney U test (nonparametric data), or Fisher's exact test/Pearson's χ^2 test (categorical data). Categorical data were expressed as absolute and relative frequencies. Furthermore, a

multinomial logistic regression model was adopted for the analysis of bisphosphonate use, and we adjusted the odds ratio (95% CI) for each variable. The statistical significance level of the results was set as $P < .05$.

To verify the reliability of the analyses, 10 digital PRs were analyzed after a 3-week interval, aiming to assess the level of intrarater reliability with a 95% CI. Cohen's Kappa statistical test[31] was applied to establish uniformity in the imaging evaluation criteria regarding the presence or absence of the studied variables, considering values ≤ 0 (no agreement); 0.01−0.20 (none to slight); 0.21−0.40 (fair); 0.41− 0.60 (moderate); 0.61−0.80 (substantial); and 0.81−1.00 (almost perfect agreement).

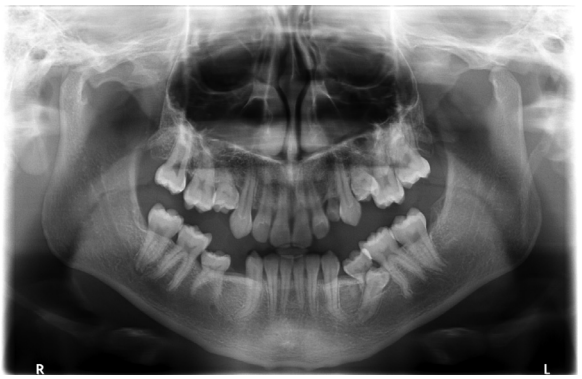

Fig. 1. Panoramic radiograph of a 17-year-old male classified as a case of severe OI.

RESULTS

Reliability and statistical power

The intrarater kappa coefficient was 0.81 (agreement almost perfect). On the basis of the prevalence of dentinogenesis imperfecta in patients with OI in comparison with controls (75% vs 0%), the null hypothesis was rejected (99.8% CI).

General characteristics

In total, 57 patients diagnosed with OI were screened for the study (Figure 1). Of these, 33 were excluded because they met at least 1 of the following exclusion criteria: (1) refusal to participate in the study (n = 25); (2) age less than 2 years and presenting shortness of neck (n = 6); (3) failure to return to undergo panoramic radiography even after consenting to participate in the study (n = 2); and (4) refusal to cooperate adequately during image acquisition (n = 2). The final sample comprised 24 participants with OI matched by age and sex with 48 individuals without OI.

Demographic and medical data

The distribution of OI cases (Table I) in terms of sex was similar (males n = 12; females n = 12) and patient age ranged from 2 to 45 years (15.83 ± 11.90 years). The age of male and female individuals with OI ranged from 7 to 39 years (17.2 ± 10.8) and 2 to 45 years (14.5 ± 12.3), respectively.

On the basis of the updated version of Sillence's classification (see Table I), we estimated a high prevalence of OI type 4 (62.5%), followed by type 1 (37.5%). Types 2, 3, and 5 were not seen in the OI group. With regard to sex, 83.3% of the female patients showed a high prevalence of OI type 4, whereas 41.7% of male patients showed a high prevalence for OI type 1. OI types 1 (58.3%) and 4 (83.3%) were more prevalent among patients 10 years of age or older.

There was a statistically significant difference among patients with OI with regard to severity of OI ($P = .028$). The moderate form was the most prevalent (58.3%), followed by the mild (37.5%) and severe (4.2%) forms

Table I. Sample characterization in relation to medical classifications and bisphosphonate variables

	Parameters	*Total*	*Sex*			*Age (years)*		*Mean ± SD*
			Female	*Male*	*F:M ratio*	*Up to 10*	*>10*	
OI types	1	9 (37.5%)	2 (16.7%)	7 (58.3%)	0.29	7 (58.3%)	2 (16.7%)	11.9 ± 10.4
	4	15 (62.5%)	10 (83.3%)	5 (41.7%)	2	4 (41.7%)	10 (83.3%)	18.2 ± 12.5
	P value*	.382†	.089†			.089†		.216‡
OI severity forms	Moderate	9 (37.5%)	2 (16.7%)	7 (58.3%)*	0.29	7 (58.3%)	2 (16.7%)	11.9 ± 10.4
	Mild	14 (58.3%)*	10 (83.3%)*	4 (33.3%)	2.5	5 (41.7%)	9 (75.0%)	18.3 ± 12.9
	Severe	1 (4.2%)	0 (0%)	1 (8.3%)*	0	0 (0%)	0 (0%)	17.0 ± 0.0
	P value*	**.028**†	**.042**†			.085†		.471‡
Bisphosphonate use	No	9 (37.5%)	4 (33.3%)	5 (41.7%)	0.8	3 (25%)	6 (50%)	25.4 ± 14.1*
	Yes	15 (62.5%)	8 (66.7%)	7 (58.3%)	1.14	9 (75%)	6 (50%)	10.1 ± 4.9
	P value*	.382†	1.000†			.400†		**.001**‡
Bisphosphonate therapy period (years)	Up to 7	7 (46.7%)	5 (62.5%)	2 (28.6%)	2.5	6 (66.7%)	1 (16.7%)	6.4 ± 3.2
	>7	8 (53.3%)	3 (37.5%)	5 (71.4%)	0.6	3 (33.3%)	5 (83.3%)	13.2 ± 3.7*
	P value*	1.000†	.315†			.119†		.002‡

*$P < .05$.
†Fisher's or Pearson's χ^2 test (n, %).
‡Mann-Whitney U test.
OI, osteogenesis imperfecta; *SD,* standard deviation.

(see Table I). There were no cases with a diagnosis of the extremely severe form of OI. Female patients were associated with the moderate form of OI, whereas male individuals showed mild and severe forms ($P = .042$). There was a high prevalence of the mild form (58.3%) among patients age up to 10 years, whereas a high prevalence for the moderate form (75%) was seen among those aged greater than 10 years.

The bisphosphonate agent administered to all patients (age range 1.5−16 years) was IV pamidronate, and the mean duration of its use was 6.6 ± 4.4 years. With regard to age, there was no statistically significant difference between male (8.4 ± 5.9 years; range 1.5−16 years) and female (5.6 ± 2.76; range 1.8−10 years) patients with OI ($P = .233$). Table I shows a predominance of IV bisphosphonate therapy among individuals age up to 10 years (75%). The group of patients with a bisphosphonate regimen duration greater than 7 years showed a mean time of 13.2 ± 3.7 years, which was statistically significant ($P = .002$).

Dental alterations on PRs

The PRs of the study patients showed a diversity of dental alterations, according to the medical classifications of OI as illustrated in Figures 1−5. The OI group demonstrated a high prevalence of dental abnormalities compared with the control group, summarized as follows: missing teeth in maxilla ($P = .003$) and mandible ($P = .046$), dentinogenesis imperfecta ($P < .001$), apically extended pulp chambers ($P = .034$), ectopic tooth ($P = .049$), microdontia ($P = .001$), bulbous crowns ($P < .001$), periradicular radiolucency ($P = .014$), residual roots ($P = .034$), narrow and thin roots ($P < .001$), pulp obliteration ($P < .001$), tooth impaction ($P = .041$), radicular dilaceration ($P = .002$), and mandibular condyle altered morphology ($P < .001$) (Table II). The number of missing teeth in the OI group was statistically significant with respect to the posterior mandible ($P = .002$) and the posterior maxilla ($P = .009$). Furthermore, the multinomial logistic regression analysis results adjusted for bisphosphonate therapy in the OI group showed missing teeth in maxilla ($P = .023$; OR = 7.0), periradicular radiolucency ($P = .016$; OR = 11.5), residual roots ($P = .002$; OR = 13.75), narrow and thin roots ($P < .001$; OR = 80.5), pulp obliteration ($P = .001$; OR = 58.75), radicular dilaceration ($P = .003$; OR = 18.4), and mandibular condyle altered morphology ($P = .001$; OR = 58.75) as independent parameters in relation to bisphosphonate use.

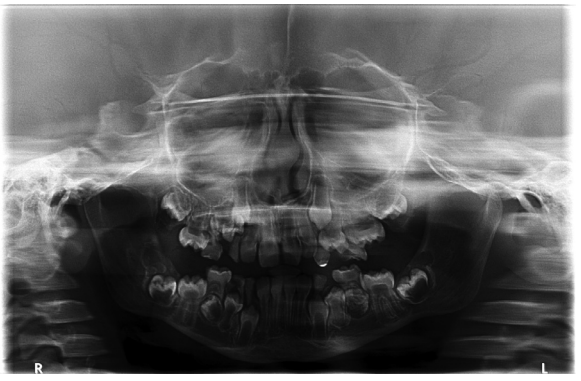

Fig. 2. Panoramic radiograph of a 7-year-old male classified as a case of mild OI.

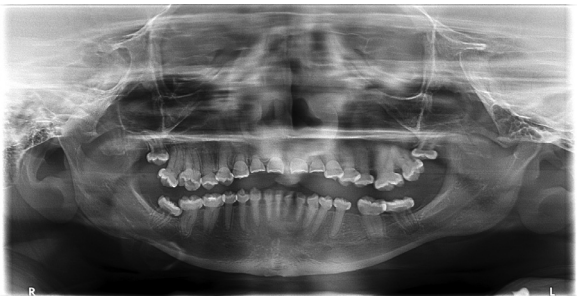

Fig. 3. Panoramic radiograph of a 15-year-old female classified as a case of moderate OI.

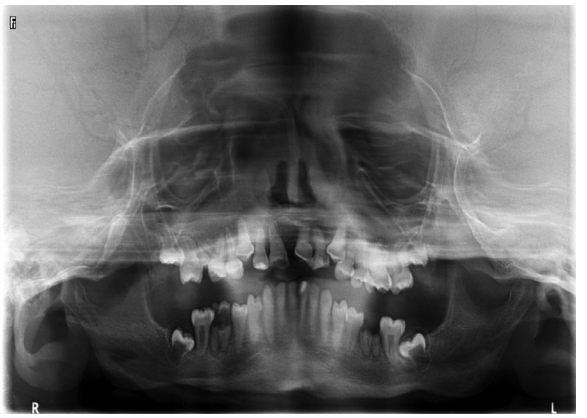

Fig. 4. Panoramic radiograph of a 15-year-old male classified as a case of OI type 4.

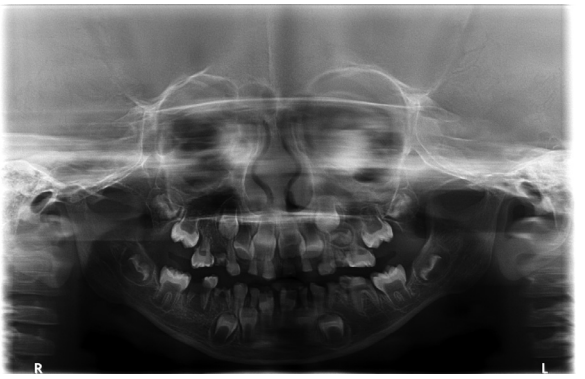

Fig. 5. Panoramic radiograph of a 5-year-old female classified as a case of OI type 1.

Table II. Bivariate and multivariate analyses of dental aspects in control and OI groups

	Control	*OI*	*P value**	*P value†*	*Adjusted OR*
Maxillary missing teeth	16 (33.3%)	17 (70.8%)	**.003**	**.023**	**7 (1.3−37.64)**
Mandibular missing teeth	20 (41.7%)	16 (66.7%)	**.046**	.179	2.8 (0.62−12.59)
Dentinogenesis imperfecta	0 (0%)	18 (75%)‡	**<.001**	1.000	1.62 (0.16−16.28)
Apically extended pulp chambers	0 (0%)	3 (12.5%)‡	**.034**	1.000	1.23 (0.12−12.37)
Ectopic tooth	8 (16.7%)	9 (37.5%)‡	**.049**	.995	3.45 (0.34−34.5)
Microdontia	0 (0%)	6 (25%)‡	**.001**	1.000	6.32 (0.63−63.28)
Bulbous crowns	0 (0%)	9 (37.5%)‡	**<.001**	1.000	1.87 (0.18−18.72)
Periradicular radiolucency	2 (4.2%)	6 (25%)‡	**.014**	**.016**	**11.5 (1.59−83.9)**
Residual roots	4 (8.3%)	7 (29.2%)‡	**.034**	**.002**	**13.75 (2.59−72.77)**
External radicular resorption	1 (2.1%)	1 (4.2%)	1.000	.227	5.87 (0.33−103.76)
Internal radicular resorption	0 (0%)	1 (4.2%)	.333	1.000	2.29 (0.22−29.2)
Narrow and thin roots	2 (4.2%)	16 (66.7%)‡	**<.001**	**<.001**	**80.5 (9.71−667.39)**
Tooth retention	4 (8.3%)	3 (12.5%)	.679	.788	1.37 (0.13−13.95)
Pulp obliteration	1 (2.1%)	10 (41.7%)‡	**<.001**	**.001**	**58.75 (5.45−633.11)**
Tooth impaction	8 (16.7%)	10 (41.7%)‡	**.041**	.677	1.6 (0.17−14.63)
Radicular dilaceration	2 (4.2%)	8 (33.3%)‡	**.002**	**.003**	**18.4 (2.66−127.03)**
Mandibular condyle altered morphology	1 (2.1%)	11 (45.8%)‡	**<.001**	**.001**	**58.75 (5.42−633.11)**

*Fisher's or Pearson's χ^2 test.
†Multinomial logistic regression model adjusted for bisphosphonate therapy.
‡$P < .05$.
OI, osteogenesis imperfecta; *OR,* odds ratio.

With regard to the influence of tooth loss in individuals with OI on the prevalence of the studied variables (Table III), a high prevalence of dentinogenesis imperfecta in hypodontia and oligodontia ($P < .001$), pulp obliteration in hypodontia ($P = .009$), and mandibular condyle altered morphology in anodontia and hypodontia ($P = .008$) were observed.

As illustrated in Table IV, in patients who had received IV bisphosphonate therapy, a high prevalence of ectopic teeth ($P = .007$) and tooth impaction ($P = .033$) was seen. Moreover, there was a statistically significant prevalence of pulp obliteration in individuals who had received bisphosphonate therapy for greater than 7 years ($P = .026$).

Table III. Bivariate analyses of demographic variables and missing teeth types in individuals with OI

	Oligodontia	*Hypodontia*	*P value**
Total	12 (75%)	4 (25%)	.172
Sex			
Female	5 (29.4%)	3 (60%)	.309
Male	12 (70.6%)	2 (40%)	
F:M ratio	0.60	1.50	
Age (years)			
Up to 10	9 (52.9%)	2 (40%)	1.000
>10	8 (47.1%)	3 (60%)	
Mean ± SD	16.5 ± 11.0	27.8 ± 21.0	.119
OI types			
1	4 (41.7%)	1 (25%)	1.000†
4	7 (58.3%)	3 (75%)	
OI severity forms			
Moderate	5 (41.7%)	1 (25%)	0.196†
Mild	7 (58.3%)	2 (50%)	
Severe	0 (0.0%)	1 (25%)	
Bisphosphonate use	8 (27.6%)	2 (22.2%)	1.000†
Bisphosphonate therapy period (years)			
Up to 7	2 (25%)	1 (50%)	1.000†
>7	6 (75%)	1 (50%)	
Mean ± SD	6.8 ± 3.4	8.9 ± 10.1	0.592‡

*$P < .05$.
†Fisher's or Pearson's χ^2 test.
‡Mann-Whitney U test.
OI, osteogenesis imperfecta; *SD,* standard deviation.

DISCUSSION

According to the World Health Organization, the incidence of rare syndromes is approximately 65 per 100,000 newborns. Because OI has shown incidence rates such as 5 per 100,000[32] and 7.4 per 100,000 newborns,[33] it is considered a rare syndrome. Thus, this study adopted a case-control design, with the aim to perform a reasonable evaluation of patients with OI, based on a statistically estimated sample size, contrary to all previous oral features−related studies that included convenience samples.[18,22,23,34-37]

OI is an uncommon skeletal disorder with a heterogeneous genetic mutation pattern that results in different clinical phenotypes and associated orofacial changes, as observed in the present investigation. These changes are critical findings, contributing to the understanding of the etiopathogenic context in OI. Historically, OI diagnosis has been based on its clinical and radiographic aspects, and the present data highlight the importance of orofacial manifestations in a semiologic context. In fact, the orofacial aspects of OI were not described at first in 1849, in that patients were characterized by the presence of bone fragility, blue sclera,

Table IV. Bivariate analyses of dental and medical parameters in patients with OI

	OI types			*OI severity forms*				*Bisphosphonate use*			*Bisphosphonate therapy period (years)*		
	1	*4*	*P value**	*Moderate*	*Mild*	*Severe*	*P value**	*No*	*Yes*	*P value**	*Up to 7*	*> 7*	*P value**
Pulp-extended pulp chamber	1 (11.1%)	2 (13.3%)	.692	2 (11.1%)	2 (14.3%)	0 (0%)	.905	1 (11.1%)	2 (13.3%)	.692	0 (0%)	2 (25%)	.467
Ectopic tooth	4 (44.4%)	5 (33.3%)	.678	4 (44.4%)	4 (28.6%)	1 (100%)	.312	0 (0%)	9* (60%)	**.007**	4 (57.1%)	5 (62.5%)	.678
Microdontia	2 (22.2%)	4 (26.7%)	1	2 (22.2%)	4 (28.6%)	0 (0%)	.792	3 (33.3%)	3 (20%)	.635	0 (0%)	3 (37.5%)	.2
Bulbous crown	2 (22.2%)	7 (46.7%)	.389	2 (22.2%)	7 (50%)	0 (0%)	.297	4 (44.4%)	5 (33.3%)	.678	1 (14.3%)	4 (50%)	.282
Periradicular radiolucency	2 (22.2%)	4 (26.7%)	1	2 (22.2%)	4 (28.6%)	0 (0%)	.792	3 (33.3%)	3 (20%)	.635	0 (0%)	3 (37.5%)	.2
Residual root	1 (11.1%)	6 (40%)	.191	1 (11.1%)	6 (42.9%)	0 (0%)	.212	5 (55.6%)	2 (13.3%)	.061	1 (14.3%)	1 (12.5%)	1.000
External radicular resorption	0 (0%)	1 (6.7%)	1.000	0 (0%)	1 (7.1%)	0 (0%)	.689	1 (11.1%)	0 (0%)	.375	0 (0%)	0 (0%)	1.000
Internal radicular resorption	0 (0)%	1 (6.7%)	1.000	0 (0%)	1 (7.1%)	0 (0%)	.689	1 (11.1%)	0 (0%)	.375	0 (0%)	0 (0%)	1.000
Narrow and thin roots	5 (55.6%)	11 (73.3%)	.412	5 (55.6%)	11 (78.6%)	0 (0%)	.183	7 (77.8%)	9 (60%)	.657	4 (57.1%)	5 (62.5%)	1.000
Tooth retention	2 (22.2%)	1 (6.7%)	.533	2 (22.2%)	1 (7.1%)	0 (0%)	.525	1 (11.1%)	2 (13.3%)	1.000	0 (0%)	2 (25%)	.467
Pulp obliteration	2 (22.2%)	8 (53.3%)	.21	2 (22.2%)	8 (57.1%)	0 (0%)	.174	5 (55.6%)	5 (33.3%)	.403	0 (0%)	5 (62.5%)	**.026**
Tooth impaction	4 (44.4%)	6 (40%)	1.000	4 (44.4%)	5 (35.7%)	1 (100%)	.442	1 (11.1%)	9* (60%)	**.033**	4 (57.1%)	5 (62.5%)	1.000
Radicular dilaceration	4 (44.4%)	4 (26.7%)	.412	4 (44.4%)	3 (21.4%)	1 (100%)	.183	4 (44.4%)	4 (26.7%)	.412	1 (14.3%)	3 (37.5%)	.569
Mandibular condyle altered morphology	3 (33.3%)	8 (53.3%)	.423	3 (33.3%)	8 (57.1%)	0 (0%)	.344	4 (55.6%)	6 (40%)	.675	1(14.3%)	5 (62.5%)	.119

*$P < .05$; Fisher's or Pearson's χ^2 test.
OI, osteogenesis imperfecta.

and deafness.[38] Later, some authors emphasized the importance of careful investigation of dentinogenesis imperfecta, a common oral finding, in connection with this syndrome,[17] which was defined and classified by Sillence et al.[6]

With respect to the demographic aspects (age and sex), the present study design had no age restrictions because of the rarity of OI. Although patient age ranged from 2 to 45 years, a predominance of young individuals, representing 75% of the total sample, was observed. A similar finding was reported in several studies on OI populations with a focus on the orodental aspects.[18,22,23,34-37] In contrast, a few studies that evaluated craniofacial alterations[30,39] included samples that mainly consisted of adults. The main purpose of this study was to analyze abnormalities related to tooth development and other acquired conditions. Alterations in the deciduous and permanent dentitions are more prevalent in young age, as reported in the literature.[22,23] Furthermore, a statistically significant difference was not found between individuals with OI and those without OI in terms of sex, whereas others studies have demonstrated a well-defined prevalence of OI more in males than in females (male/female ratio [M:F]): 24:15,[23] 85:67,[36] 74:54.[37] These reports reinforce the importance of the present data, which reflect the variability in the demographics of patients with OI.

All studies that have previously investigated orodental parameters in OI have used Sillence's classification,[18,22,23,36,37] which was also adopted in the present study. This investigation used the most recent and updated classification of OI types, which considers the existence of an additional clinical form.[40] Type 5 was accepted by the medical community at the 2009 meeting of the International Nomenclature Group for Constitutional Disorders International Congress of Human Genetics of the Skeleton.[37] According to this new classification, types 1 to 4 have the same diagnostic parameters as described in Sillence's classification I to IV. In contrast to previous OI studies,[23,30,36,37] the present study did not find any patient who could be classified as belonging to types 2, 3, and 5. This finding probably reflects the different mutation patterns that have been seen in patients with OI. Moreover, the present study also characterized the participants according to the severity of the clinical presentation, on the basis of a recent classification model proposed by Van Dijk and Sillence[1]; this classification was never reported in previous studies investigating the orodental aspects of OI.

Observational studies are particularly important in the field of epidemiologic investigations.[28] For instance, observational studies evaluating orodental findings in OI have been mainly designed as cohort studies,[36,37] followed by transversal noncontrolled type studies[18] and case-control studies,[22,23] with the present study being a

close example of the last type. In our study, the technique used to perform analyses was digital panoramic radiography, which has been well reported and validated in previous reports.[36,37] One investigation reported the use of dental panoramic tomography to assess root development in patients with OI.[23] In fact, bisphosphonates have been shown to delay tooth development in rats treated with zoledronic acid or alendronate.[41-43]

Dentinogenesis imperfecta was the most reported alteration detected by radiographic examination in individuals with OI, representing 75% of the samples in the present study. As a classic dental manifestation, its incidence was previously estimated, in 1975, as 1 in 6000 to 8000 individuals.[44] It is a condition observed with dentin-associated alterations, classified by Shield as types I, II, and III. Shield's dentinogenesis imperfecta type I has been clearly associated with OI, whereas the type II shows only dentin alterations not associated with OI, and type III presents additional findings, such as pulp exposition and dental crowns with a bell morphology.[45] In the present study, dentinogenesis imperfecta was found to be restricted to OI because it was not observed in the control group. In addition, we observed that OI severity was a risk factor for dentinogenesis imperfecta, as reported previously by other authors.[46]

The present study did not find types II and III of dentinogenesis imperfecta, and this probably reflects the complex genetic alterations associated with the classic OI mutations related to collagen deficiency (*COL1 A1* and *COL1 A2* genes), as well as the SIBLING (Small Integrin-Binding Ligand N-linked Glycoprotein) family−associated genes.[47] The study by Falk et al. did not find any different dentinogenesis imperfecta phenotypes related to OI genetic mutations.[48] Luder et al. studied the influence of genetic alterations on the dentinogenesis imperfecta phenotype.[49] Although bone tissue presents constitutive modifications resulting from a mutation in the gene for the alpha 2(I) collagen chain, minor effects on dental tissues were observed. According to these authors, the exclusion of the abnormal alpha 2(I) collagen chains by odontoblasts promotes a compensation of this specific genetic defect, and it could depend on the developmental stage and/or the rate of extracellular matrix formation. For instance, it is well reported in the literature that patients with OI usually show collagen abnormalities in dentin, such as a significant increase of acidic amino acids, according to the classic study performed by Gage et al.[50] Recently, dentin abnormalities were also observed at a histologic level in patients without a clinic-radiograph diagnosis of dentinogenesis imperfecta.[36]

Despite dentinogenesis imperfecta being the main dental finding in patients with OI, findings from the present case-control investigation highlight the increased prevalence of other orodental alterations, such as narrow and thin roots and apically extended pulp chambers, which were observed in previous studies[17,36,45] and should be carefully evaluated in these individuals. The presence of bulbous crowns was statistically significant in patients with OI in comparison with the control group. This finding is a common aspect reported in the literature, and we believe that it is noteworthy as an early orofacial finding on PRs And, thus, would help in the diagnosis of OI, when suspected particularly in young patients. There are no published OI-related case-control studies that have evaluated this variable since its first description by Shields.[45] The present study is also relevant because it demonstrated a high prevalence of other conditions (pulp obliteration, radicular dilacerations, microdontia, and mandibular condyle altered morphology) in patients with OI, with statistically significant differences from that in the control group.

Furthermore, a relevant finding among the evaluated individuals in the OI group was a high prevalence of missing teeth (approximately 71%), with a predilection for the posterior regions of the jaws, as previously reported.[37] Lukinmaa et al. had already reported this finding as a common orodental characteristic in this skeletal disorder, drawing special attention to hypodontia.[51] In fact, hypodontia was more prevalent than oligodontia and agenesis in the retrospective cohort-designed study performed by Malmgren et al.[37] In the present study, the occurrence of oligodontia was a more significant finding compared with that of hypodontia in individuals with OI. Caution should be taken during the interpretation of these variables, particularly in observational studies, where the data are obtained exclusively from imaging records and, thus, could be a source of bias. The present methodologic design helped avoid this potential bias.

This study also highlights the role of bisphosphonate therapy as a risk factor for the occurrence of dental abnormalities in individuals with OI. The endovenous use of bisphosphonates is related to delayed tooth eruption in children with OI, probably as a result of a bisphosphonate-related delay (mean 1.67 years[22]) in the deciduous root resorption process.[25] Ectopic teeth and dental impaction were observed in patients treated with IV bisphosphonates. Tooth impaction had already been reported as a common finding in individuals with OI syndrome,[52] mainly in those classified as type III, according to Sillence's classification.[36] It has been suggested that dental alterations related to the use of bisphosphonates may be related to the mechanism of action of these drugs in inhibiting the farnesyl pyrophosphate synthase in the osteoclasts,[53] which may disturb the process of dental eruption.[35,54] The present results also showed a statistically significant

association between pulp obliteration and bisphosphonate administration over a 7-year period. It could be hypothesized that the mechanism of action of bisphosphonate may be associated with an anticipated production of secondary dentin in patients receiving long-term drug therapy. However, additional studies are needed to confirm this hypothesis. In the context of the present results, Moraes et al. aimed to analyze the alterations observed in human teeth extracted from areas of bisphosphonate-induced osteonecrosis. They found a high prevalence of pulp stones attached to dentine and loose pulp stones in the pulp chamber and root canals, in addition to linear calcifications.[55]

CONCLUSIONS

This study found a significant prevalence of tooth alterations in patients with OI, particularly dentinogenesis imperfecta, in comparison with matched controls, thus highlighting the importance of oral investigation in medically compromised patients. Bisphosphonate therapy was associated with tooth impaction and ectopic teeth. Patients who received bisphosphonate therapy for greater than 7 years showed a high prevalence of pulp obliteration. These findings may indicate the influence of bisphosphonate on dentin-related physiopathology. In summary, our findings suggest the need for a systematic examination of OI to establish preventive oral interventions that may help avoid misdiagnosis, particularly in young patients. Furthermore, the role of bisphosphonate therapy on the treatment of the orodental aspects in OI require well-designed observational studies in a similar context as that of the present investigation.

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