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Cone Beam Computed Tomography Evaluation of Socket Healing After Third Molar Germ Extraction: A Case Series Study Including Adolescents with Osteogenesis Imperfecta Type I Treated with Bisphosphonates and Healthy Age-Matched Subjects

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Abstract: Bisphophonates (BPs) are widely used in Osteogenesis imperfecta (OI). Cone Beam Computed Tomography (CBCT) shows clinical usefulness in evaluating impacted teeth and adjacent structure relationships, extraction socket healing, bone mineral density (BMD) and BP-related jaw osteonecrosis (BRONJ). The aim of the study was to compare alveolar sockets and the adjacent bone area before and after third molar extraction in OI type I (OI-I) adolescents treated with BPs and age-matched healthy subjects (HSs) by CBCT. **Methods:** Five adolescents with genetically proven OI-I treated with BPs (three males and two females, mean age: 15.2 ± 1.78 years) and four age-matched healthy subjects (two males and two females, mean age: 15.5 ± 1.29 years) were included in this study. Eight Regions of Interest (ROIs) were evaluated: between 3.7 and 3.8 (ROI-1) and 4.7 and 4.8 (ROI-2); after 3.8 (ROI-3) and 4.8 (ROI-4); alveolar sockets 3.8 (ROI-5) and 4.8 (ROI-6); left (ROI-7) and right (ROI-8) cortical bone. **Results:** ROIs were evaluated on both sides of the mandible for all the subjects except one OI patient in which CBCTs were performed pre- and-post third molar extraction only on the right side. CBCT was performed 12.8 ± 4.60 and 11.5 ± 2.51 days before and 8.0 ± 1.41 and 7.7 ± 0.5 months after extraction in OI-I and HSs, respectively. BPs were discontinued 62.0 ± 36.5 months before extraction. None of the OI-I adolescents developed BRONJ. Statistically significant greater values were observed in OI-I for ROI-1 and -2 (p = 0.0464), ROI-3 and -4 (p = 0.0037) and ROI-7 and -8 (p = 0.0079) after extraction. **Conclusions:** This descriptive study confirms that, in OI-I adolescents treated with BPs, third molar extraction is safe, and socket healing occurs properly. In addition, it demonstrates that, if the same device and imaging conditions are used and comparisons to predetermined standard values are avoided, CBCT can be used to monitor BMD changes. The significant greater BMD observed for different ROIs in OI-I could reflect the increased secondary mineralization related to the BP-dependent reduction in bone turnover.

Keywords: osteogenesis imperfecta; cone beam computed tomography; region of interest; bone mineral density; pediatric dentistry; bisphosphonates; third molar extraction; socket healing

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1. Introduction

Osteogenesis imperfecta (OI) is a spectrum of inherited skeletal disorders characterized by reduced bone quality and highly increased risk of fractures. Based on the severity of the clinical phenotype, four main subtypes were distinguished by Sillence and colleagues [1]. Even though OI is more commonly caused by mutations of COL1A1 and COL1A2, other genes have been related to its development [2,3]. Bisphosphonates (BPs) are the most-used drugs in OI [3]. Even though studies have demonstrated a significant contribution of these drugs to the increase in bone mineral density (BMD), data on quality of life and functional status and fracture rate failed to show an unequivocal benefit [3]. In addition, as a side effect, treatment with BPs may be associated with the development of osteonecrosis of the jaw (BP-related osteonecrosis of the jaw, BRONJ). Indeed, BPs are the most common drug implicated in the development of medication-related ONJ (MRONJ), a condition defined by the concomitance of current or previous treatment with antiresorptive drugs (alone or in combination with immune modulators or antiangiogenic medications), the evidence of exposed bone or bone that can be probed through intra- or extra-oral fistula that persists for more than 8 weeks and the absence of a history of radiotherapy or metastasis to the jaws [4]. MRONJ has been more frequently reported in oncologic that in osteoporotic patients [4–7]. Moreover, in patients treated with BPs, the risk of developing BRONJ has been reported to increase significantly when a dental extraction is performed [4,7]. Over the years, different studies have evaluated the effects of BPs and other antiresorptive drugs on the healing of alveolar sockets and the development of MRONJ in pediatric patients [8–12]. Impacted mandibular third molars may be associated with different complications including dental crowding, pericoronitis, caries, root resorption and periodontal problems that can be avoided through teeth removal [13]. However, when this prophylactic procedure is planned, a detailed definition of the relationships between the impacted teeth and adjacent anatomical structure (e.g., inferior alveolar nerve) is required. Especially in cases in which the roots of the molar are in close contact with the mandibular canal, Cone Beam Computed Tomography (CBCT), providing images in three dimensions, may be more accurate compared to panoramic radiography in the definition of the relationships between the impacted teeth and adjacent anatomical structure and in the prediction of inferior alveolar nerve exposure during surgery [14–16]. In addition, CBCT has been reported to show clinical relevance for the diagnosis before bone exposure and treatment planning of MRONJ [17–20]. In contrast, there are no consensus data regarding the accuracy of CBCT in the evaluation of BMD because the intensity values of CBCT are influenced by both the scanned object and the characteristics of the system, especially when they are compared to predetermined standard values [21–25].

In pediatric patients, the assessment of impacted teeth and orthodontic follow-up have been reported to be among the main reasons for CBCT [26] and for repeated CBCTs [27,28], respectively. Notably, very few CBCT-based studies have been conducted on children (and adults as well) with OI. These studies focused on the characterization of the anatomical features of the lower third molar and its adjacent structures [29], on the natural history of craniofacial deformities, on the impact of three- compared to two-dimensional analysis on diagnosis and treatment planning in orthodontics and orthognathic surgery [30] and on the identification of imaging parameters that can assist the dentist in making diagnostic decisions and orthodontic treatments [31]. The aim of our study is to evaluate third molar alveolar socket healing and adjacent bone regions before and after the extraction of third molar germs in adolescents with genetically proven OI type I (OI-I) treated with BPs and in age-matched healthy subjects (HSs) using CBCT.

2. Materials and Methods

2.1. Study Design and Case Selection

The study was conducted in accordance with the Declaration of Helsinki and its later amendments and approved by the ethics review board of the Azienda Ospedaliera Universitaria Policlinico Umberto I of Rome (Ref. C26H15LTC7, 5 October 2021). Five consecutive adolescents with genetically proven OI-I treated with BPs and four consecutive HSs were included in this study. The OI-I patients were clinically followed at the Center for Rare Diseases and Skeletal Dysplasias of the Azienda Ospedaliera Universitaria Policlinico Umberto I of Rome. All CBCTs and third molar extractions were performed at the Pediatric Dentistry Unit of the Azienda Ospedaliera Universitaria Policlinico Umberto I of Rome between 2021 and 2022. OI-I patients and age-matched HSs and their parents/legal guardians were informed in advance that scans might be anonymously used for clinical research reasons later. OI patients and HSs were included in the study according to the following criteria: age between 13 and 17 years; at least one impacted germ of the mandibular third molar; evidence of orthodontic indications for its extraction; availability of signed consent by the parents/legal guardians; two CBCTs performed before and after third molar extraction, the former for pre-operative assessment (relationship of the third molar with adjacent structures, difficulty for tooth extraction regarding the amount of bone sacrifice, prediction of inferior alveolar nerve at surgery), and the latter for orthodontic reasons to design a customized surgical template for the insertion of buccal shelf mini-screw implantation to distalize the mandibular dentition; for OI-I patients, genetically proven diagnosis of OI-I (OMIM #166200) and treatment with BPs. None of the adolescents included in the study were lost to follow-up and all were followed for at least one year with regular oral check-up after the extraction.

2.2. CBCT Evaluation

Keeping into account the pediatric age of the patients, the CBCT was set up as described previously [29]. Briefly, imaging was executed with NewTom V Gi Dental X-ray Machine (QR, Verona, Italia) by one of the authors (DM). Device settings were at 8 mA and 90 kV. Additional technical data included the following: exposure time 0.25 s, total mA 10 mA and delivered dose 0.125 mGy. Each field of view (FOV) mode was 5×5 cm, with an isotropic voxel size of 0.4 mm, and all acquisitions were elaborated for the study of the dental arch to evaluate all parameters needed as described previously [29,31–33]. In addition, to facilitate a more meaningful comparison of BMD changes, the value 0 was assigned to dental papilla area in all the evaluated Regions of Interest (ROIs) before extraction. Image analysis was performed using Infinitt Health Care software (Infinitt, Seoul, Republic of Korea) through multiplane reconstruction. The following ROIs were considered: between 3.7 and 3.8 (ROI-1) and between 4.7 and 4.8 (ROI-2); after 3.8 (ROI-3) and after 4.8 (ROI-4); the alveolar sockets 3.8 (ROI-5) and 4.8 (ROI-6); the left (ROI-7) and right (ROI-8) cortical bone. ROI-5 and ROI-6 were evaluated only after the molar extraction. All ROIs were standardized, taking 1 mm^2 on the sagittal cut of each CBCT with a width of 1 mm (Figure 1).

To evaluate bone mineral density (BMD), the light intensity within each ROI was measured in Hounsfield Units (HUs). This method was selected due to its strong correlation with actual bone density, as confirmed in studies comparing HU in CBCT and fan-beam CT, demonstrating a 90% accuracy correlation in both soft and hard tissues ($R^2 = 0.91$, $p < 0.001$). The measurements were performed pre- and post-extraction, allowing for intra- and inter-group bone healing and mineralization comparisons.

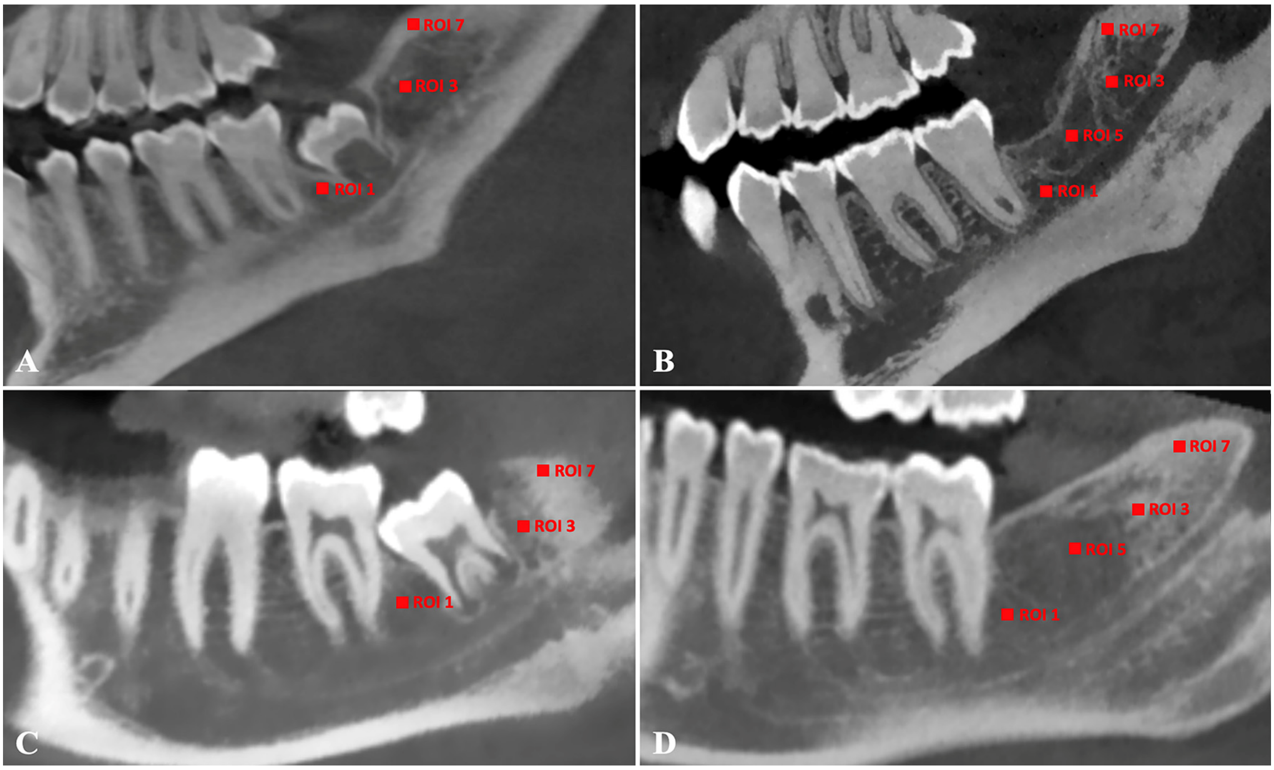

Figure 1. Representative CBCT images from one OI-I patient (patient one in Table 1 (**A**,**B**)) and from an age-matched HS (male, 17 years (**C**,**D**)). CBCTs before and after surgery are shown in (**A**) and (**C**) and in (**B**) and (**D**), respectively. ROIs from the left side are shown. ROI 2, 4, 6 and 8 were the same for ROI 1, 3, 5 and 7 on the right side.

Table 1. Clinical synopsis of the OI-I patients and age-matched healthy subjects included in this study.

Id	Gender/Age	Ethnicity (Geographic Area)	Gene (Mutation) *	DI	Blu Sclerae	Fractures	Type of BP (Time of Treatment)	Discontinuation of BP Before Extraction
OI-I-1	male/14 ys	Hispanic/Latino (Latin America, Chile)	*COL1A1* (c.3235G>A)	+	-	+	alendronate (24 ms), then neridronate (15 ms)	4 ms
OI-I-2	male/17 ys	White/Caucasian (Europe, Italy)	*COL1A1* (c.769G>A)	-	-	+	neridronate for 78 ms	60 ms
OI-I-3	female/17 ys	White/Caucasian (Europe, Italy)	*COL1A1* (c.757C>T)	-	+	+	neridronate for 81 ms	60 ms
OI-I-4	female/13 ys	White/Caucasian (Europe, Italy)	*COL1A1* (c.471+1G>C)	-	+	+	neridronate for 21ms	66 ms
OI-I-5	male/15 ys	White/Caucasian (Europe, Italy)	*COL1A1* (c.1719_1720 insAC)	-	-	+	neridronate for 12 ms	120 ms
Ctr-1	female/16 ys	White/Caucasian (Europe, Italy)	No clinical indication for molecular analysis.	Negative personal and family clinical history.				
Ctr-2	male/14 ys	White/Caucasian (Europe, Italy)						
Ctr-3	male/15 ys	White/Caucasian (Europe, Italy)						
Ctr-4	female/17 ys	White/Caucasian (Europe, Italy)						

* All mutations have been previously reported [34]. DI: Dentinogenesis Imperfecta; ys: years; ms: months; BP: bisphosphonate; Ctr: age-matched healthy subjects.

2.3. Statistical Analysis

The GraphPad P10.1.0 software was used for data analysis. Data have been expressed as mean + standard deviation (SD). Even though the study has been conceived as case series (i.e., descriptive study), the inclusion of consecutive adolescents with OI-type I treated with BPs and age-matched HSs in the case series made reasonable and feasible statistical inter- and intra- (pre- and post-analysis) group comparison [35]. To this goal, for the limited size of the samples, the non-parametric Mann–Whitney and Wilcoxon matched-pair signed rank tests were used for independent and paired data, respectively. Post hoc power analysis using G*Power (version 3.19.2; Franz Faul, Christian-Albrechts-Universitat, Kiel, Germany) was performed to evaluate whether our data had sufficient verification power, and ≥0.8 of power was considered to criteria for validation. The statistically significant level was set at $p < 0.05$.

3. Results

3.1. OI-I Patients and Age-Matched Healthy Subjects

A clinical synopsis of the OI-I patients and age-matched HSs included in this study is shown in Table 1. All subjects included in the study were Italian except one OI-I adolescent that was Chilean and all presented a mesio-angular impaction of the mandibular third molar according to Winter's classification [36]. Pre- and post-extraction CBCTs were performed on both sides of the mandible in four out of five adolescents with genetically proven OI-I treated with BPs (three males and two females, mean age: 15.2 ± 1.78 years). In one patient (OI-I-2 in Table 1), pre- and post-extraction CBCTs were performed only on the right side. Bilateral pre- and post-extraction CBCTs were also examined from four age-matched HSs (two males and two females, mean age: 15.5 ± 1.29 years). Personal and family clinical history were negative for all age-matched HSs. All OI-I patients had known the mutation of the COL1A1 gene [36]. CBCTs were performed 12.8 ± 4.60 days in OI-I patients and 11.5 ± 2.51 days in HSs before the extraction and 8.0 ± 1.41 months in OI-I patients and 7.7 ± 0.50 months in HSs after the extraction. Four OI-I patients were treated for 48.0 ± 36.57 months with neridronate according to the scheme licensed in Italy for this condition [37]. One patient was treated with alendronate (70 mg per os once a week) for 24 months and then with neridronate as above for 15 months. In OI-I patients, treatment with BPs was discontinued 62.0 + 36.57 months before the third molar extraction. None of the OI-I patients resumed BPs after the extraction and presented delayed healing of the surgical wound and clinical and imaging features consistent with BRONJ. Normal surgical wound healing occurred in all HSs as well.

3.2. CBCT Analysis

Mean + SD and minimal and maximal values for each ROI in OI-I patients and age matched HSs before and after extraction are shown in Table 2. As no significant statistically differences were observed for the different ROIs between the left (ROI-1, -3, -5 and -7) and right (ROI -2, -4, -6 and -8) side in the CBCT performed either before or after third molar extraction, the comparative analysis was performed combining data obtained at the same ROIs independent of laterality (i.e., ROI-1/-2, ROI-3/-4, ROI-5/-6 and ROI-7/-8).

Before third molar extraction, no significant differences were observed between OI-I patients and age-matched HSs (Figure 2). In contrast, after the extraction, a significant statistical difference was observed for ROI-1/-2 (Figure 2A), ROI-3/-4 (Figure 2B) and for ROI-7/-8 (Figure 2D) with greater mean values for OI-I patients compared to age-matched HSs (OI-I vs. age-matched HSs; ROI-1/-2: 453.30 ± 149.30 vs. 323.35 ± 106.52, $p = 0.0464$; ROI-3/-4: 640.69 ± 151.57 vs. 387.14 ± 122.44, $p = 0.0037$; ROI-7/-8: 1689.96 ± 157.56 vs. 1397.48 ± 152.96, $p = 0.0079$). A statistically significant increase in the ROI values was observed after third molar extraction in OI-I patients (pre- vs. post-extraction: 284.73 ± 148.67 vs. 453.30 ± 149.30, $p = 0.0039$) for ROI-1/-2 (Figure 2A) and in both OI-I patients (pre- vs. post-extraction: 336.76 ± 207.24 vs. 640.69 ± 151.57, $p = 0.0039$) and age-matched HSs (pre- vs. post-extraction: 308.96 ± 83.32 vs. 387.14 ± 122.44, $p = 0.0234$) for ROI-3/-4

(Figure 2B). As a result of post hoc power analysis, adequate power was limited to ROI-3/-4 and ROI-7/-8 after extraction in the inter-group analysis (0.930 and 0.941, respectively) and to ROI-1/-2 and ROI-3/-4 in both OI-I (0.877 and 0.999, respectively) and HSs (0.864 and 0.953, respectively).

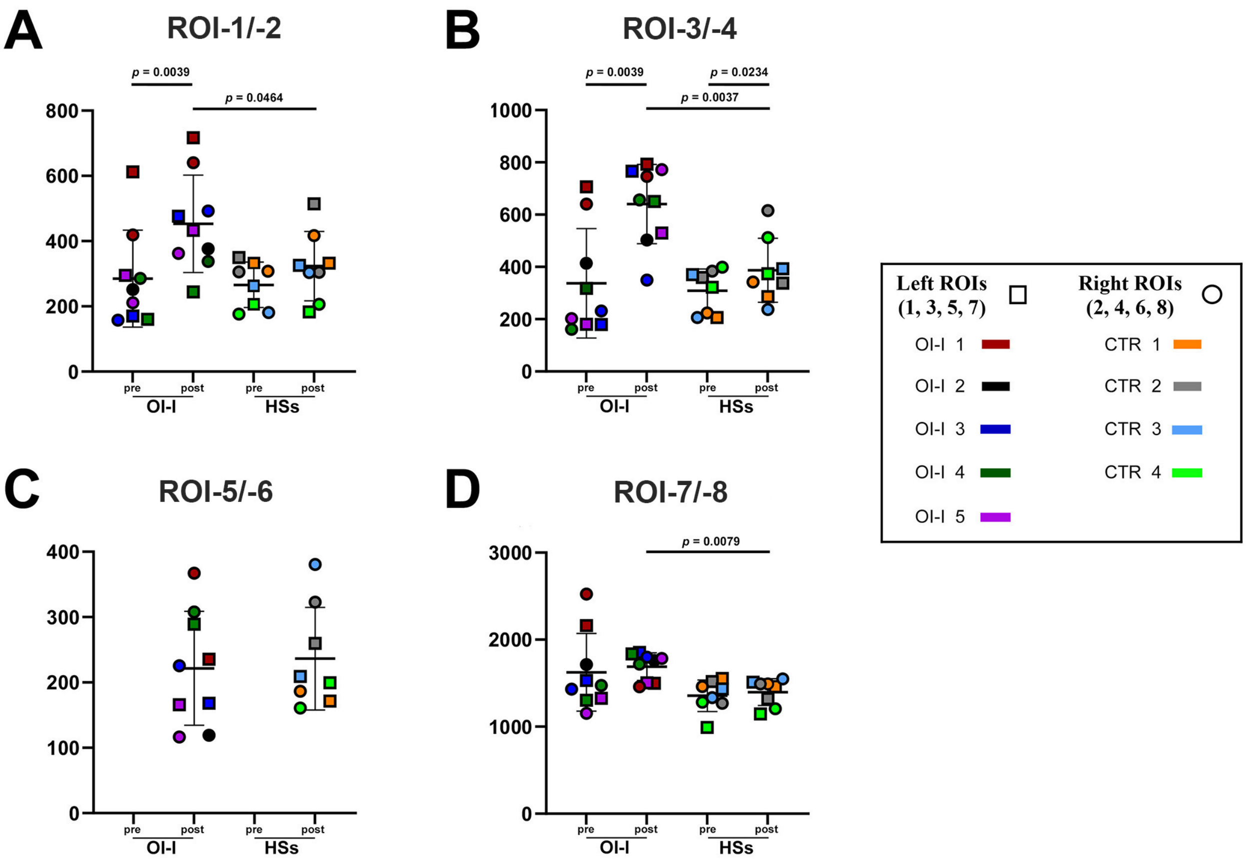

Figure 2. Graphical representation of ROI values from the same regions of the left and right side [ROI-1/-2 (**A**), ROI-3/-4 (**B**), ROI-5/-6 (**C**) and ROI-7/-8 (**D**)] from OI-I patients and age-matched HSs. Mean ± SD and statistically significant differences between different groups are shown. Data are expressed as HU for each ROI.

Table 2. Descriptive statistics for all ROIs from OI-I adolescents and age-matched HSs before and after third molar extraction.

	OI-I Mean ± SD (Minimum–Maximum)				**HSs Mean ± SD (Minimum–Maximum)**			
	N	**Pre**	**N**	**Post**	**N**	**Pre**	**N**	**Post**
ROI-1	4	309.36 ± 211.21 (160.05–612.56)	4	467.73 ± 194.53 (244.12–717.25)	4	288.43 ± 65.90 (207.24–349.47)	4	338.86 ± 135.68 (183.15–514.28)
ROI-2	5	265.03 ± 98.28 (157.67–418.77)	5	441.77 ± 125.81 (337.57–640.03)	4	243.32 ± 74.76 (176.18–310.62)	4	307.85 ± 86.16 (206.24–417.03)
ROI-3	4	346.04 ± 248.57 (180.52–705.95)	4	684.75 ± 120.65 (529.37–793.10)	4	314.76 ± 75.25 (206.29–370.83)	4	347,70 ± 46.64 (337.73–392.61)
ROI-4	5	337.49 ± 214.65 (161.22–680.85)	5	605.44 ± 177.59 (349.71–772.23)	4	303.15 ± 102,20 (206.62–398.88)	4	426.58 ± 169.28 (237.00–615.32)

Table 2. *Cont.*

	OI-I Mean ± SD (Minimum–Maximum)				HSs Mean ± SD (Minimum–Maximum)			
	N	**Pre**	**N**	**Post**	**N**	**Pre**	**N**	**Post**
ROI-5	-	NA	4	214.60 ± 59.28 (165.73–289.16)	-	NA	4	209.99 ± 36.88 (171.53–259.89)
ROI-6	-	NA	5	227.20 ± 111.81 (116.41–367.03)	-	NA	4	262.74 ± 105.87 (160.98–380.42)
ROI-7	4	1580.87 ± 400.69 (1304.33–2162.02)	4	1672.69 ± 197.85 (1498.86–1852.58)	4	1373.90 ± 260.35 (990.65–1552.27)	4	1360.09 ± 164.62 (1145.43–1512.30)
ROI-8	5	1659.02 ± 523.16 (1430.10–2.524.80)	5	1703.78 ± 140.55 (1458.11–1797.58)	4	1336.22 ± 88.68 (1267.89–1462.00)	4	1434.86 ± 154.16 (1207.30–1549.45)

N: number of patients in which CBCT was performed. Data are expressed as HU. Pre: before third molar extraction; Post: after third molar extraction; NA: unavailable.

4. Discussion

Our study confirms that in OI-I adolescents treated with BPs, the extraction of the third molar is safe, and socket healing after surgery occurs properly. Indeed, all OI-I patients included in this study failed to show a delayed healing of the surgical wound and clinical and imaging features consistent with BRONJ. At the time of extraction, they were all into a "drug holiday" of BPs consistent with that (i.e., 4 months) suggested in different guidelines [4,38]. The absence of features of BRONJ was observed before and also after the third molar extraction indicating that BP treatment and teeth extraction are not associated with its development. These findings are overall consistent with previous studies. For example, in the study of Chahine and colleagues [8], no case of BRONJ was observed among 278 pediatric patients treated with cyclical intravenous pamidronate over a median period of 4.6 years during childhood or adolescence. Notably, 221 of the patients included in this study were affected by OI, and 113 underwent dental extraction either during or after treatment. In addition, in two systematic reviews estimating the risk of MRONJ among children with OI treated for 4.5 to 6.8 years [9] and subjects under the age of 24 treated with BPs for different conditions [10], no cases of MRONJ were identified.

In our study, we also evaluated BMD focusing on different ROIs. Our analysis failed to detect significant differences for all ROIs between OI-I patients and age-matched healthy subjects before third molar extraction. In contrast, after the extraction, the OI-I patients showed a statistically significant increase for ROI-1/-2 (p = 0.0464), ROI-3/-4 (p = 0.0037) and ROI-7/-8 (p = 0.0079) compared to age-matched HSs. This result is consistent with the positive and persistent effect of BPs on BMD in osteopenic patients including OI-I ones [39–41]. Indeed, as synthetic analogues of pyrophosphate, BPs absorb to mineral surfaces, have antiresorptive and antiangiogenic effects and have a cumulative inhibitory effect on pathological bone loss [42,43]. As in bone remodeling, bone resorption and formation are coupled and BPs suppress bone turnover [39,40], and the increase in BMD could reflect the increased secondary mineralization related to the BP-dependent reduction in bone turnover [44–46].

Relevant limitations are associated with this study. The strongest limitation is the small sample size for both OI-I adolescents (five patients, nine sites) and age-matched HSs (four subjects, eight sites). Even though OI-I is a rare disease and its prevalence, even though not unequivocally proven in any population, has been estimated to be 5.16/100,000 [47], this small sample size limits the ability to make reliable inferences or generalize findings. A second important limitation of this study is the wide range of "drug holidays" of BPs as, at least in one patient (OI-I-1 in Table 1), the use of different BPs that, inevitably, introduce significant heterogeneity among the subjects make it difficult, if not impossible, to draw valid comparisons or conclusions. A third limitation is that our study is a descriptive study, and, in this type of study, statistical tests yielding *p* values (or confidence intervals) are not needed and in most cases are also inappropriate as they typically do not include inferences or comparisons [34]. In addition, as a growing number of patients are particularly sensitive to ionizing radiation [48], CBCT in pediatric dentistry is controversial, and, consequently, it should be performed according to appropriate indications [26–28,48,49]. Thus, even though CBCT is a reliable tool that can be used for diagnosis, treatment planning and follow-up, unnecessary radiation exposure must be avoided. A further limitation of this study is the use of CBCT to assess BMD. Indeed, even though the gray values in the CBCT image are theoretically equivalent to the BMD, multiple factors including device/equipment (e.g., noise, scatter artifacts and beam hardening), software (e.g., reconstruction algorithm and FOV size) and patient (e.g., streak artefact) factors have to be considered to obtain reliable values [22,23,25]. As a consequence, CBCT does not appear a valid tool for the determination of BMD especially when values are used to compare different sites or for comparison with predetermined standard values [21,25]. To overcome these limitations, deep-learning-based methodologies have been developed providing promising results [24]. In our study, CBCTs before and after third molar extraction in the OI-I patients and age-matched HSs were performed using the same equipment, ROIs and imaging conditions. In addition, the image resolution was improved by using a small FOV to increase the variability of gray values. Moreover, we did not make any comparison to predetermined standard values and evaluated symmetric sites in the right and left side of the mandible where the effects on the gray values are expected to be the same [25]. This approach made possible a comparative analysis of different ROIs between OI-I patients and age-matched HSs within the same group.

5. Conclusions

Our study confirms that, in OI-I adolescents treated with BPs, the extraction of the third molar is safe, and the healing process after the extraction occurs properly. In these patients, as in healthy subjects, CBCT can be useful to monitor the alveolar bone status after teeth extraction and to evaluate time-dependent change in BMD if, as in this study, the same device, imaging conditions and small FOV are used, and comparisons to predetermined standard values are avoided.

Author Contributions: Methodology: G.D., F.Z., F.A., D.M. and G.L.S.; software: D.M. and F.A.; investigation: G.D., F.Z., F.A., D.M. and M.C.; data curation: G.D., F.Z., D.M. and G.L.S.; data analysis, G.D., F.Z., F.A. and D.M.; writing—original draft preparation: G.D. and F.Z.; writing—review and editing: I.V., M.R., A.P. and A.C. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from the parents/legal guardians of all of the subjects involved in the study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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