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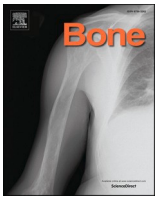

Full Length Article

Cross-sectional and longitudinal analysis of bone age maturation during peri-pubertal growth in children with type I, III and IV osteogenesis imperfecta☆

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ABSTRACT

Osteogenesis imperfecta (OI)is a rare genetically heterogeneous disorder caused by changes in the expression or processing of type I collagen. Clinical manifestations include bone fragility, decreased linear growth, and skeletal deformities that vary in severity. In typically growing children, skeletal maturation proceeds in a predictable pattern of changes in the size, shape, and mineralization on the hand and wrist bones that can be followed radiographically known at the bone age. Assessment of bone age can be clinically used to assess time remaining for linear growth, and the onset and duration of puberty, both of which can be useful in determining the timing of some surgeries or the interpretation of other imaging modalities such as bone densitometry. Additionally, deviations in the expected maturation process of the bone age may prompt or assist in the work up of a significant delay or advancement in a child's growth pattern. The primary aim of our study was to determine whether the bone age in children with a skeletal disorder such as OI follow the same pattern and rate of bone maturation compared to a control population. Using participants from the Natural History Study of the Brittle Bone Disorders Consortium, we analyzed 159 left hand and wrist radiographs (bone age) for a cross-sectional analysis and 55 bone ages repeated at approximately 24 months for a longitudinal analysis of skeletal maturation. Bone ages were read by a pediatric endocrinologist and by an automated analysis using a program called BoneXpert. Our results demonstrated that in children with mild-to-moderate OI (types I and IV), the skeletal maturation is comparable to chronological age-mated controls. For those with more severe forms of OI (type III), there is a delayed pattern of skeletal maturation of less than a year (10.5 months CI 5.1–16) $P = 0.0012$) at baseline and a delayed rate of maturation over the two-year follow up compared to type I ($P = 0.06$) and type III ($P = 0.02$). However, despite these parameters being statistically different, they may not be clinically significant. We conclude the bone age, with careful interpretation, can be used in the OI population in a way that is similar to the general pediatric population.

1. Introduction

Osteogenesis imperfecta (OI) is a genetically heterogeneous skeletal disorder with a broad phenotype caused by pathogenic variants in many genes [1]. The most common are autosomal dominant mutations in genes encoding type I collagen (*COL1A1* or *COL1A2*) which result in alterations in the quantity, or structure and function of the protein [1]. OI can also result from less common recessive mutations in genes involved in type I collagen processing, bone mineralization and osteoblast function [2].

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While OI affects many aspects of connective tissue, the clinical phenotype is commonly classified by the severity of the skeletal disease (i.e., number and type of fragility fractures and bone deformities). Osteogenesis imperfecta can be classified into clinical phenotypes as follows: type I is the least severe with low trauma fractures and minimal to no bone deformities; type II is commonly lethal within the first year of life; type III presents with progressing bone deformities and frequent atraumatic fractures; and type IV has a phenotype that is intermediate in severity [3]. Although there is great variability in the relationship between genotype and phenotype, patients with mutations resulting in loss of the expression of the mutated type I collagen allele (haploinsufficiency) allow the incorporation of quantitatively less, but structurally normal type I collagen into the bone matrix and most often present with milder disease (type I OI). Those with mutations altering the structure and function of type I collagen (e.g., glycine substitution mutations in the triple helical domain) that is still incorporated into the bone matrix usually have more skeletal abnormalities (types II, III, IV OI).

In typically growing children, skeletal maturation progresses at a predictable and reproducible rate throughout skeletal development. As part of the ordered development of the skeleton during growth, the degree of growth plate fusion and mineralization can be quantitated using hand radiographs compared to published standardized images assigned to each year of growth, an assessment clinically referred to as the bone age. Serial bone ages can delineate the rate of change and maturation of the pediatric skeleton.

Puberty is a time of particularly rapid bone mass accrual and accelerated linear growth and characteristic changes in the bone age closely correlate with the timing of pubertal growth acceleration and other markers of puberty (i.e., menarche in females) [4,5]. Although, the rate of bone age maturation is influenced by a variety of other factors, including nutritional status, thyroid hormone, and growth factors, it is the exposure to sex steroids, particularly estrogen in both males and females that starts the process of skeletal maturation and growth plate fusion. Sex steroids elongate and mineralize bone at the growth plate by upregulating the cellular pathways directing chondrocyte maturation, local growth factor production, and vascularization. The end result is the production of mature, mineralized bone and ultimately the fusion of the growth plate marking the cessation of linear growth [6]. Near final adult height (i.e 99 %) is achieved in males by a bone age of 17 years and in females by a bone age of 15 years, and radiographic fusion of the growth plates occurs by age 17–19 years in both sexes. Thus, examining the radiographic pattern of bone maturation during puberty can provide insight on the impact of sex steroids on skeletal development and provide a useful guide for clinicians regarding a patient's skeletal maturation.

Differences in the timing of sexual maturation is not a known feature clinical feature in children with OI and it presumed they progress through puberty at a normal time and develop the expected secondary sex characteristics indicating typical exposure to sex steroids. This presumption is supported by the published OI growth charts demonstrating the normal timing of the pubertal growth spurt in types I and IV OI (Children with type III OI had a significantly blunted growth pattern overall due to bone deformities.) [7]. To the best of our knowledge, there are no studies comparing the rate of bone maturation in children with OI directly to a control group. If the bone age assessment in children with OI can be validated, its use would have important clinical implications such as the interpretation of bone densitometry scans, the timing of certain orthopedic procedures, and decisions about the duration of bisphosphonate therapy. Additionally, the bone age in children with OI could be applied to the work up of delayed or accelerated maturation much in the same way it is used in children without a skeletal dysplasia. For this study, our aim was to determine whether the rate of bone age maturation during adolescent growth is altered in OI compared to standardized bone age template readings from the average pediatric population.

2. Methods

2.1. Study population

Plain radiographs of the left hand and wrist (bone age) were acquired as part of the Rare Diseases Clinical Research Network's Brittle Bone Disorders Consortium's (BBDC) Longitudinal Study of Osteogenesis Imperfecta (NCT02432625). To capture the pre-pubertal through post-pubertal growth phase in both males and females, we examined a cohort of 159 children with OI aged 8 to 17 years. Participating centers within the BBDC with expertise in the diagnosis and treatment of OI typed the participants based on the nosological Sillence classification [3]. Eighty participants had type I, 31 had type III, and 48 had type IV OI. Bone ages were acquired at the baseline evaluation (i.e., on enrollment into the study). In a subset of children, a second bone age, approximately 24 months later was available. Images were de-identified and stored as dicom files. Information on Tanner staging and menses were not available for this study. Each bone age was read by a pediatric endocrinologist (LN) using Greulich and Pyle methodology ("Radiographic Atlas of Skeletal Development of the Hand and Wrist") [8] while blinded to the chronological age of the participant to eliminate reader bias. Bone age was also estimated using BoneXpert, an automated software program validated in reading hand and wrist films and assigning a bone age in several reference populations [9–13]. The mean BoneXpert readings were about 4 months less than the endocrinologist readings with slightly greater discrepancies at the older age range, but the two methods were highly correlated (Supplement Fig. 1A and 1B). The endocrinologist and automated readings were averaged for a final score. Bone age readings that differed by >1.5 years between the two assessments ($n = 6$ (five females; three with type I and two with type III OI and one male with type IV OI) were re-read in a blinded fashion by a second pediatric endocrinologist and the final score was calculated as the average of all three readings. Of the 159 participants who had baseline bone ages, follow-up films were available in 55 participants approximately 24 months later (Table 1). No bone age film within this cohort needed to be excluded for unreadability due to bone deformities or fractures.

2.2. Statistical analysis

Baseline and follow-up bone age readings by endocrinologist and automated program were compared via a one-sample *t*-test on their differences to examine agreement and any potential systematic bias between methods. A Bland-Altman plot of the two methods was constructed along with the limits of agreement to estimate the range of the discrepancy.

Demographic variables for baseline and follow-up visits were compared between OI types using Kruskal-Wallis rank sum test or Fisher's exact test, as appropriate. A paired *t*-test was performed within each OI group to determine whether bone age readings significantly differed from chronological age on average. Pearson's correlations were also used to assess the strength of the linear relationships between baseline bone age and chronological age. A multivariable linear regression model was constructed to estimate the conditional expected difference between bone age and chronological age, with OI type, sex, race, ethnicity, linear and quadratic BMI (body mass index) terms, and a OI type-by-BMI interaction term as regressors. Marginal means were calculated and pairwise contrasts between OI types at various levels of BMI were performed using Tukey's method to control for the family-wise error rate.

To ascertain differences in bone age maturation between OI types, we calculated the change in bone (annualized) and regressed it against OI type, baseline age, baseline bone age - chronological age difference, BMI, sex, race, and ethnicity. We again constructed the marginal means and performed a Tukey-adjusted pairwise contrasts between OI types. A two-sided α-level of 0.05 was used to establish significance. Data were

Table 1
Demographics of the cross-sectional (A) and longitudinal (B) cohorts.

A

	OI type			p-Value[b]
	I, $N = 80$[a]	III, $N = 31$[a]	IV, $N = 48$[a]	
Sex				0.3
Female	42 (53 %)	21 (68 %)	30 (63 %)	
Male	38 (48 %)	10 (32 %)	18 (38 %)	
Treated with Bisphosphonates				**<0.001**
Untreated	36 (45 %)	0 (0 %)	1 (2.1 %)	
Treated	44 (55 %)	31 (100 %)	47 (98 %)	
Race				0.11
Asian	2 (2.5 %)	1 (3.2 %)	3 (6.3 %)	
Biracial	2 (2.5 %)	3 (9.7 %)	1 (2.1 %)	
Black	1 (1.3 %)	2 (6.5 %)	3 (6.3 %)	
Native American	1 (1.3 %)	0 (0 %)	0 (0 %)	
Unknown or Other	0 (0 %)	1 (3.2 %)	2 (4.2 %)	
White	74 (93 %)	24 (77 %)	39 (81 %)	
Ethnicity				0.3
Hispanic, Latino, or Spanish origin	11 (14 %)	2 (6.5 %)	9 (19 %)	
Not Hispanic, Latino, or Spanish origin	69 (86 %)	29 (94 %)	39 (81 %)	
Baseline age (years)	12.51 (2.83)	13.42 (2.96)	13.48 (2.79)	0.12
Baseline BMI	19.5 (4.3)	24.0 (6.9)	22.6 (5.1)	**<0.001**
Baseline BA-CA difference (years)	0.26 (1.29)	−0.88 (1.23)	0.19 (1.08)	**<0.001**

B

	OI type			p-Value[b]
	I, $N = 26$[a]	III, $N = 13$[a]	IV, $N = 16$[a]	
Sex				**0.004**
Female	9 (35 %)	10 (77 %)	13 (81 %)	
Male	17 (65 %)	3 (23 %)	3 (19 %)	
Treated				**<0.001**
Untreated	11 (42 %)	0 (0 %)	0 (0 %)	
Treated	15 (58 %)	13 (100 %)	16 (100 %)	
Race				0.090
Asian	0 (0 %)	0 (0 %)	1 (6.3 %)	
Biracial	1 (3.8 %)	2 (15 %)	0 (0 %)	
Black	0 (0 %)	0 (0 %)	2 (13 %)	
Native American	1 (3.8 %)	0 (0 %)	0 (0 %)	
Unknown or Other	0 (0 %)	0 (0 %)	1 (6.3 %)	
White	24 (92 %)	11 (85 %)	12 (75 %)	
Ethnicity				>0.9
Hispanic, Latino, or Spanish origin	3 (12 %)	1 (7.7 %)	2 (13 %)	
Not Hispanic, Latino, or Spanish origin	23 (88 %)	12 (92 %)	14 (88 %)	
Baseline age	11.75 (2.69)	12.08 (2.60)	11.80 (1.89)	>0.9
Baseline BMI	19.5 (4.5)	24.0 (8.3)	20.0 (3.9)	0.051
Follow-up time (years)	2.03 (0.13)	1.89 (0.24)	1.94 (0.25)	0.089
Baseline BA-CA difference (years)	0.53 (1.33)	−1.19 (1.22)	−0.18 (1.12)	**<0.001**
BA maturation rate	1.00 (0.49)	0.83 (0.42)	1.31 (0.38)	**0.015**

BA = bone age, CA = chronologic age.
[a] n (%); Mean (SD).
[b] Fisher's exact test; One-way ANOVA.

analyzed in R (Version 4.1.2, Vienna, Austria) using the 'emmeans' package (Version 1.8.6).

3. Results

The characteristics of the study cohort are shown in Table 1A and B. Participants were predominately non-Hispanic white in both the cross-sectional and longitudinal cohorts. The mean BMI was statistically higher in those with type III OI, and types III and IV OI had greater bisphosphonate exposure.

The cross-sectional analysis of baseline radiographs in the 159 children showed a strong correlation between bone age and chronological age in all study subjects ($r = 0.912$–0.938) (Fig. 1). The bone age and chronologic ages were very similar in children with type I and type IV OI; in type I OI mean bone age was ~3 months higher than mean chronological age (adj $P = 0.15$), in type IV OI mean bone age was ~2 months higher than mean chronological age (adj $P = 0.24$). Participants with type III OI had a significant delay in their bone age compared to their chronologic age (mean delay of 10.5 months CI 5.1–16) $P = 0.0012$). An un-blinded review of the bone ages from the type III cohort did not reveal any unique radiographic features, deformities or fractures that could have contributed to the result of a delayed bone age.

Longitudinal analyses of 55 children (Table 1B) revealed the same trends that were observed with the cross-sectional analyses. In type I and IV OI, bone age tended to advance similarly compared to the chronologic age over the two-year follow up, but there was a statistically significant delay of BA advancement in the OI type III cohort (Fig. 3).

In the cross-sectional analyses, there was no effect of sex, age or ethnicity on the relationship between bone age and chronologic in all OI types. Within each OI type, higher BMI was associated with a more advanced bone age. The relationship between BMI and bone age was not linear in types I or IV (Fig. 2) and suggested that the effect of BMI on bone age was maximal at a BMI of 25 kg/m^2.

The effect of previous bisphosphonate treatment on bone age maturation could not be determined in the type III or IV OI groups because nearly all these children had a history of treatment exposure (Table 1). In the type I OI group, a history of bisphosphonate treatment was not a significant coefficient in the cross-sectional (55 % treated) or longitudinal analyses (58 % treated) and was not associated with either a more advanced or delayed bone age in the type I OI group (Fig. 4).

4. Conclusions

Our study is the first to evaluate bone age and bone maturation in a large cohort of children clinically categorized with types I, III, and IV OI during the pubertal growth phase. We chose to study children during puberty because it is a critical stage of bone development and growth. Our cross-sectional data showed that there were no significant differences between the bone age and the chronologic age in children with type I and IV OI. These findings suggest that despite mutations causing alterations in type I collagen expression or processing, radiographic bone maturation appears to advance at a normal rate in children with type I and IV OI. The bone age in children with type III OI was delayed by about 10 months compared to chronologic age and showed a slower bone maturation rate in longitudinal analyses. These differences however, are small and may not be clinically impactful.

There is some reduction in final height in all types of OI compared to the average population [14,15], which could reflect a deficit of bone elongation at the growth plate. In type III OI, bone deformity, scoliosis and fractures have a major impact on height, but these abnormalities cannot completely explain the deficit in linear growth [7,16]. Similarly, in children with milder disease and fewer deformities, growth deficits are also observed. Although our study does not address the histologic or physiologic factors affecting bone maturation during growth, it does provide information about the radiographic signs of fusion and mineralization in the area of the growth plate during puberty. The use of hand

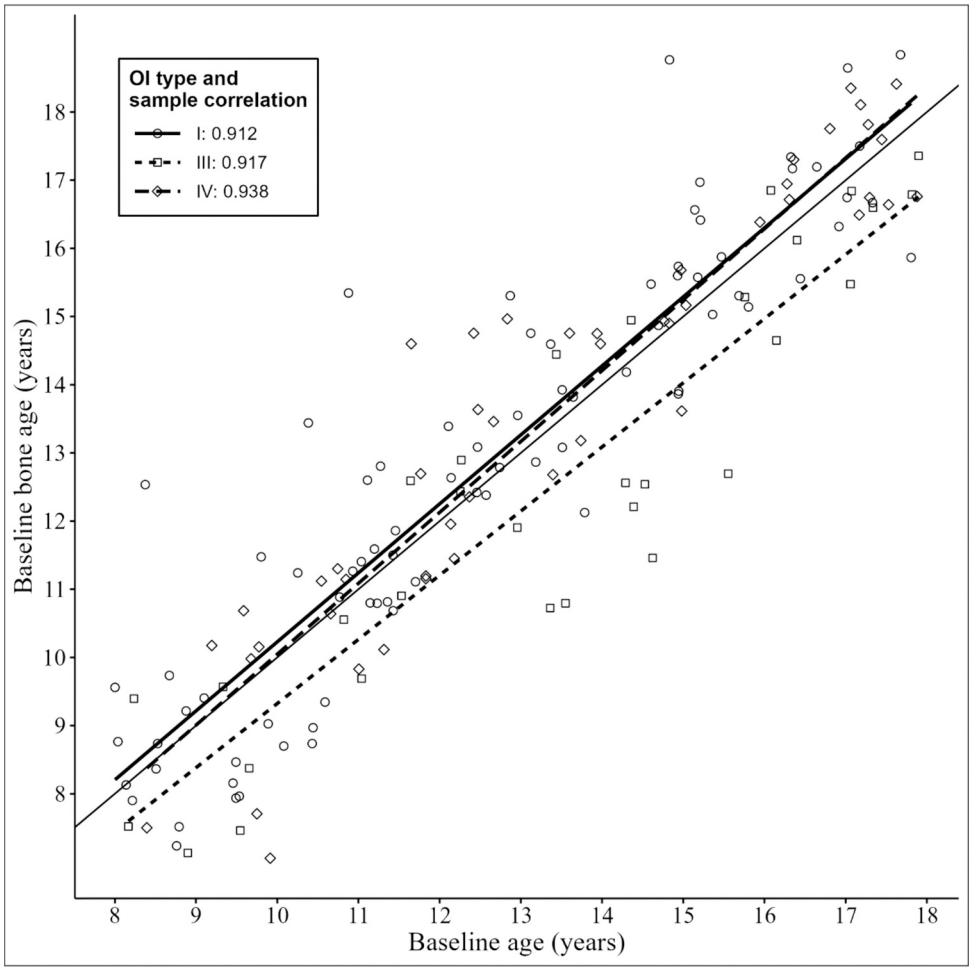

Fig. 1. Average cross-sectional bone age versus chronologic age by OI type.

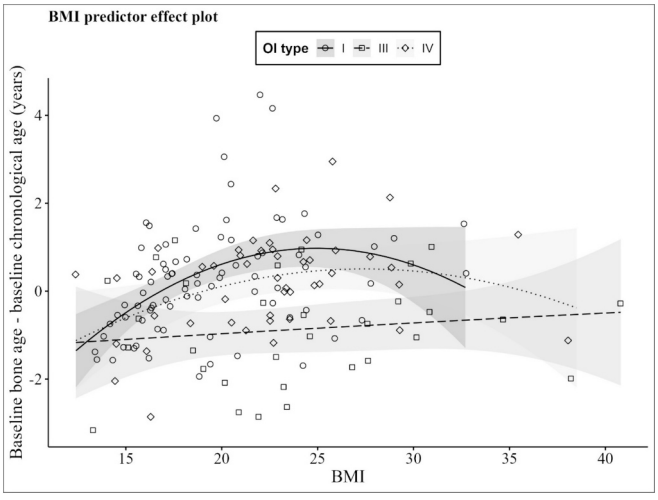

Fig. 2. BMI versus baseline bone age by OI type. There is a positive predictor effect on advancing the bone age versus chronologic age in OI types I and IV up through a BMI of 25 kg/m^2.

radiographs for bone age assessments should avoid confounding effects of fractures and bone deformities. Indeed, in our current study, no hand films were deemed unreadable due to underlying deformities. Similarly, a prior study used hand films to demonstrate metacarpal bone length deficits that correlated with height outcomes without the interference of fractures or deformities, concluding that abnormalities in linear bone accrual, presumably at the level of the growth plate, contribute to short stature in OI [17].

The biological events that are represented by the radiographic phenotype of bone age maturation are not well defined, but presumably include growth plate function and matrix mineralization. The delay we noted in type III OI could reflect the effects of abnormal collagen biology on either process. The possibility of disordered growth plate function in OI has been explored in several other studies [18–23]. Early reports described radiographic changes such as rickets-like features and abnormal calcifications in the growth plate in certain forms of severe OI [18,19]. Histologic changes in the growth plate were found in animal models of OI including elongation of the hypertrophic zone and differences in the expression of alkaline phosphatase in patients with OI [20,22,24]. Alterations in growth plate hypertrophic chondrocytes have also been identified in OI, with changes in morphologic structure and alterations in the endoplasmic reticulum in murine models [23,25]. Additionally, we previously reported that in moderate and severe forms of OI (types IV and III respectively), there is a disassociation of growth velocity and levels of the growth plate marker from the non-collagenous domain of type X collagen (CXM) [26]. CXM is strongly correlated to growth velocity in average growing children [27,28]. Whether these factors play a role in the delayed bone age we observed in type III OI need further investigation.

Several endocrine factors are known to influence bone growth and maturation such as thyroid hormone, growth factors, and sex steroids. Levels of thyroid hormones were not measured in this study, but thyroid disease was not reported in the subjects' histories at the baseline visit. In

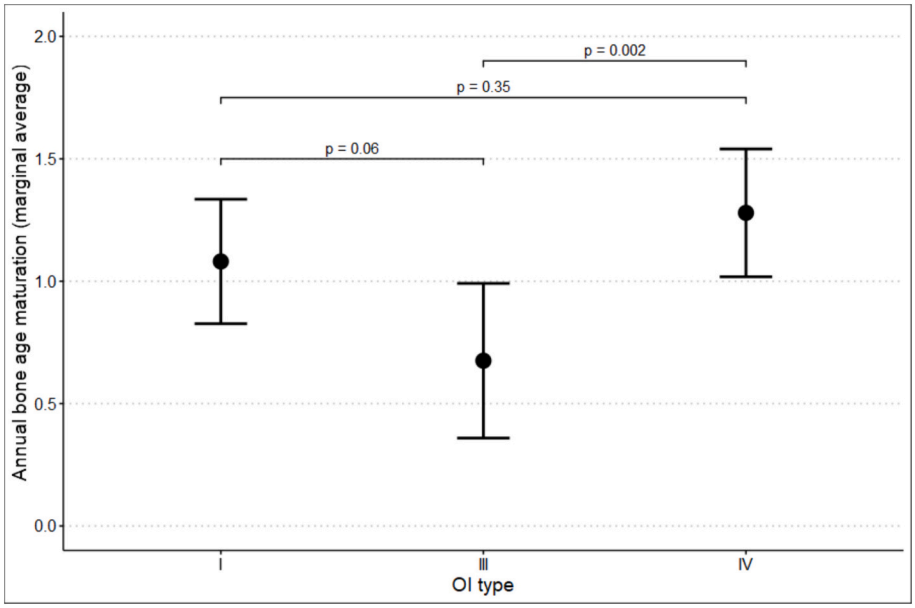

Fig. 3. The rate of the annualized bone age advancement over 24 months by OI type.

addition, prior studies in children with OI have demonstrated normal growth factors levels (IGF-, IGFBP-3) and stimulated growth hormone values suggesting that classic growth hormone deficiency in not a feature of this disorder [29,30]. However, it should be noted that a portion of the children with OI had a blunted response in somatomedin stimulated IGF1 levels and lower growth hormone levels in response to growth hormone releasing factor [30]. These findings point to the possibility of a hypoactive growth hormone axis in some children with OI but given that it was not specific to the OI type it may not explain the delay in bone age our study identified in the type III cohort. Sex steroids, in particular estrogen, are major contributors to bone maturation and growth in both males and females [31,32]. Sex steroid levels were not obtained in this study and no other study has examined pubertal hormone levels in growing children with OI. Yet, without evidence of significantly delayed puberty as a typically reported feature in children with OI, it is reasonable to expect that sex hormones are generally produced at normal physiologic levels in this population [7,16]. In our study, the evolution of bone age maturation in OI type I and IV appears to reflect a relatively normal skeletal response to pubertal hormones, but the delay in bone maturation in the children with OI type III suggests a less robust response.

Similar to what is seen in average growing children, we observed that higher BMI was associated with more advanced bone age in children with OI [33]. Future studies could delineate whether this effect in OI is also associated with earlier onset of puberty that is observed in obese females in the general population by examining BMI and onset of menses (the latter of which was not available for our study). The effect of increased BMI on bone age advancement was lost in those subjects with type III OI suggesting the effects of aberrant collagen function supersede the effects of body composition. Exposure to bisphosphonates was not associated with a change in bone age maturation in this study, although the analysis was limited to those with OI type I.

Within the type III OI group, there are statistically significant delays in the bone age and radiographic maturation both when comparing it to the chronological age as well as delays in the rate of maturation. These findings may reflect the effects of under-mineralized bone in this cohort. The differences however, are less than a year and thus the implications may not be clinically significant.

Strengths of our study include the availability of a relatively large cohort that included all common types of OI, careful assessments of bone age using 2 methods, useful information on covariates, and the availability of both longitudinal and cross-sectional data. We lacked Tanner staging, information on menarche and measurements of hormone levels, which would have provided an objective assessment of pubertal status and would be interesting to correlate in future studies. We also were not able to include the genotype of each participant and although most forms of type I OI involve null mutations in the COL1A1/A2 gene we were not able to analyze data conclusively based on this criterion. We were also not able to differentiate whether rarer forms of autosomal recessive OI, which would have clinically been categorized into the type III group, had a unique effect on the bone age assessment. Additionally, the small sample size in the male type III and type IV longitudinal cohorts reduces our ability to confidently assess changes within these groups.

Overall, our cross sectional and longitudinal evidence shows that the bone age advances congruently with the chronologic age in children with OI types I and IV, and its use in assessing the rate of skeletal maturation appears valid in this population despite the underlying collagen abnormalities and associated low bone mineral density. Given the delay of bone age compared to chronological age and the delay in the rate of progression of the maturation care must be taken in regarding its clinical use in the children with OI type III. We suggest that this methodology of assessing skeletal maturation is still generally relevant in type III OI given the changes we found were small and may not be clinically important in most situations. If bone age is more delayed than our data suggest is characteristic of type III OI, an evaluation for other causes of the abnormality would be appropriate.

CRediT authorship contribution statement

L.E. Nicol: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **H. Baines:** Writing – review & editing, Methodology, Data curation. **S. Koike:** Writing – review & editing, Methodology, Formal analysis. **W. Liu:** Writing – review & editing, Investigation. **E. Orwoll:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation.

Declaration of competing interest

LN: Consultant for Ultragenxy, Data Safety Monitoring Committee, Consultant Egetis, Data Safety Monitoring Committee, **HB:** No

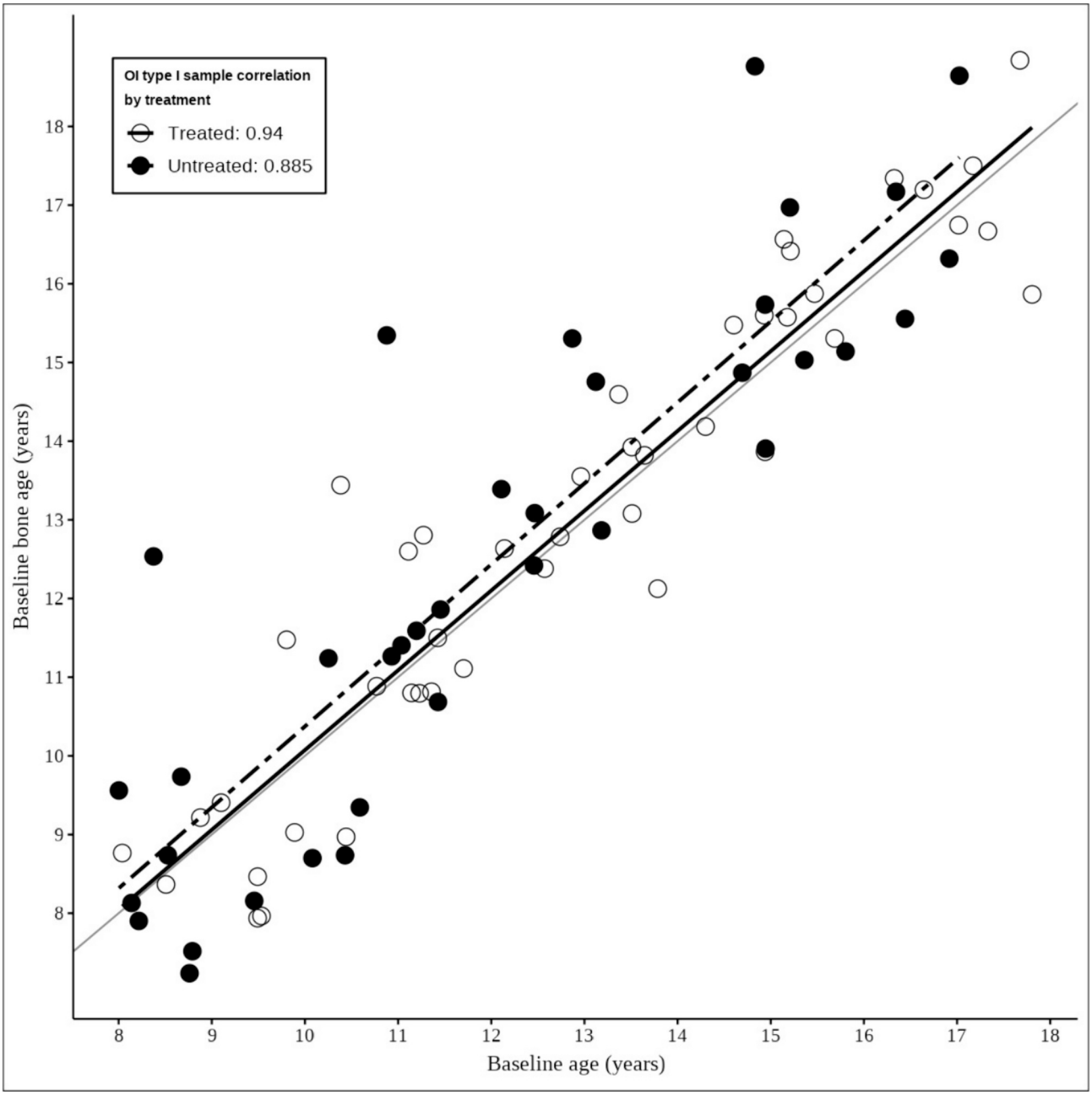

Fig. 4. Th correlation of baseline bone age versus chronologic age based on bisphosphonate expoure in type I OI.

disclosures, **SK:** No disclosures, **WL**: No disclosures, **EO:** No disclosures.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2024.117192.

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