Original Article

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Osteogenesis imperfecta in Peruvian children: Phenotypic and therapeutic insights from a pediatric hospital

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SUMMARY Osteogenesis imperfecta (OI) is a genetic disorder of the connective tissue that is characterized by high bone fragility. It has a worldwide incidence of 1 in 10,000. The diagnosis is mainly clinical-radiological. Treatment is based on the use of bisphosphonates and orthopedic surgeries. The objective of this study was to establish the clinical, radiological, and therapeutic characteristics of OI in pediatric patients of a national reference pediatrics institute. This was conducted through a descriptive and retrospective analysis. All patients under 18 years of age with a diagnosis of OI treated at the Instituto Nacional de Salud del Niño de Breña (INSN-Breña) between 2010 and 2021 were included. In total, 91 patients with OI were studied, more than half of whom were male. A total of 93.4% had a history of fractures, 72.5% had blue sclera, 39.6% had bowed legs and 20.9% had dentinogenesis imperfecta. The minimum-maximum value of fractures was 0-18. A total of 75.8% of patients started treatment with bisphosphonates and 41.8% used adjuvant medications. Less than 50% of patients required surgical treatment. Osteogenesis imperfecta is a genetic and chronic pathology. The use of the Van Dijk severity grade and the Aglan severity scale is simple to apply and therefore should be used to improve the classification of groups with the highest risk of fractures and response to treatment. Due to the low incidence of this disease, it is important to raise awareness and increase the research volume on this subject.

Keywords rare disease, bone fractures, collagen type I-II, antiresorptive therapy

1. Introduction

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a genetic disorder of connective tissue characterized by increased bone fragility and reduced bone mass (*1*). It is a rare and underdiagnosed disease with a global incidence estimated to be 1 in 10,000 in the general population (*1*). In 90% of cases there is a variant in one of the genes that encode the alpha chains of type I collagen (*COL1A1* or *COL1A2*) (*1,2*). Currently, thanks to technological advances, more is known about the biological and genetic factors of OI, which has made it possible to establish a classification with up to 21 different genes (*3*). This condition predisposes patients to multiple fractures due to minimal trauma, bone deformities, as well as growth deficiencies. The classic extra-skeletal clinical manifestations are joint hypermobility, dentinogenesis imperfecta, hearing loss and blue sclerae, which can vary depending on the type of OI (*4,5*).

In Peru, OI is considered a rare disease due to its low prevalence (*6*). There are few epidemiological studies, and knowledge is based mainly on case reports, such as the one published on 11 cases at the Hospital Nacional Daniel Alcides Carrion (*6*). Another study whose objective was to identify genetic diseases in Peru, showed that between 2014 and 2018 at the Instituto Nacional de Salud del Niño-Breña (INSN-Breña), 82 patients with OI were observed (*7*). The diagnosis and treatment of this disease in Peru is made difficult by its complexity and the limited availability of specialized centers, which can lead to underdiagnosed and inadequate management of cases (*7*). Diagnosis is mainly based on clinical evaluation, physical examination and radiology, while molecular diagnosis is useful to determine the specific genetic cause and determine the risk of recurrence (*8*).

Treatment is based on three pillars: antiresorptive drugs (bisphosphonates) that increase bone mass and reduce the risk of fractures; orthopedic - surgical procedures to correct deformities and physical therapy.

Other drugs such as denosumab, which inhibits osteoclastic activity, are being studied to determine their benefit (*4,9*). The purpose of this study is to determine the clinical, radiological and therapeutic characteristics, such as the response to treatment with bisphosphonates, of patients with OI at the INSN-Breña between the years 2010-2021.

2. Patients and Methods

2.1. Study design

A descriptive and retrospective study was carried out. The study was conducted at INSN-Breña, a national reference center for pediatric diseases. It has a Genetics and Inborn Errors of Metabolism Service that has a database of patients with OI for more than 12 years. The present study collected information from patients with OI from 2010 to 2021.

Ethics approval and research approval were obtained from the Ethics Committees of the Universidad Científica del Sur (1048-2021-PRE15) and the INSN-Breña (PI-24/22) before observing the clinical history of the patients, and the study was conducted in accordance with the Declaration of Helsinki.

2.2. Inclusion and exclusion criteria

All patients under 18 years of age with a diagnosis of OI who met the following inclusion criteria were included: diagnosis of OI confirmed by clinical, imaging or molecular examination, bone densitometry with osteoporosis, family history of OI, history of pathological fractures and clinical symptoms compatible with OI. Medical records that were illegible, in poor condition, or lacked information on the variables of interest were excluded.

2.3. Data collection

Variables collected included demographic data, familial history, clinical characteristics, bone densitometry, anthropometric values, serological markers, and details of medical and surgical treatment. Patients were categorized according to Van Dijk's severity classification and according to Aglan's severity scale (*10,11*). We assessed severity of each patient with the help of a medical geneticist since the severity wasn't described in the medical record. Data were obtained from the patients' medical records, compiled in a collection form.

Two possible biases were identified: measurement bias due to errors in obtaining data from medical records, and selection bias by including only patients from the INSN-Breña, although this is a national pediatric reference center. The sample size was all patients with OI in the INSN-Breña during 2010-2021, given the low frequency of OI.

2.4. Statistical analysis

Categorical variables were presented with frequencies, and numerical variables with measures of central tendency and dispersion according to normality. It is necessary to mention that all clinical variables are described in their entirety due to the descriptive nature of the study.

An exploratory analysis was carried out, using chi-square tests with goodness of fit for the variables "sex" and "origin", taking into account that presentation of OI is the same in men and women (*2*), the proportion of inhabitants of Lima and other departments is 32.2% and 67.8%, respectively according to the last national census carried out by the National Institute of Statistics in 2017. In addition, to determine if there are differences between the "severity" categories and the values of bone densitometry, serological markers, and fractures, the Kruskal-Wallis's test was used. To identify variables that could be used as predictors of a higher number of fractures, the relationship with bone densitometry and body mass index was analyzed using multiple linear regression. For the multivariate analysis, Poisson regression with robust variance was used to investigate the existence of new human phenotypes associated with severity and response to treatment; likewise, the OpenEpi program was used to calculate the power of said regression.

For statistical analysis, the STATA v.15 program was used with a 95% confidence interval and a p value of less than 0.05.

3. Results

3.1. Sociodemographic characteristics

There were potentially 194 medical records of patients with OI, however, when reviewing them, only 91 medical records met the inclusion criteria. The main reason for exclusion was not having defined diagnoses. Of all patients, 60.4% were male. 52.8% came from Lima and 14.3% of all patients had asthma/bronchial obstruction syndrome as comorbidity. 24.2% had a family history of OI (Table 1). The median age of diagnosis was 20.5 months (male = 21 and female = 19.5); with a mean age of the father and mother at the birth of the patient of 31.9 and 27.8, respectively. The mean birth weight was 2,822 ± 288.3 g and the mean birth height was 45 ± 3.3 cm.

Regarding the variability of birth weight and the Aglan severity scale, a difference was observed (p = 0.0068), with a *post hoc* analysis of difference between the mild and severe group (p = 0.010) (Supplemental Table S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=219*). On the contrary, we did not observe differences in birth weight on the Van Dijk severity groups (p = 0.0988); and in the same sense when evaluating both scales, height (p = 0.5523

Table 1. General characteristics of pediatric patients with OI

Variables	*n*	%	95% CI	*p*
Gender				0.046*
Male	55	60.4	49.9-70.1	
Female	36	39.6	29.9-50.1	
Origin				< 0.001*
Lima (capital)	48	52.8	42.3-62.9	
Other city's	43	47.3	37.0-57.6	
Use of complementary exams				
N-telopeptide	47	51.6	41.4-61.9	
C-telopeptide	24	26.4	17.3-35.4	
Calcium	40	44.0	33.8-54.2	
Phosphorus	51	56.0	45.8-66.2	
Magnesium	14	15.4	8.0-22.8	
Vitamin D (25-OH)	14	15.4	8.0-22.8	
Alkaline phosphatase	24	26.4	17.3-35.4	
Bone densitometry	48	52.7	42.5-63.0	
Comorbidities				
Asma/BOS	13	14.3	4.5-142	
Hypotonia	7	7.7	0.3-7.7	
Malnutrition	7	7.7	0.3-7.7	
Anemia	5	5.5	-0.8-5.5	
Heart disease	5	5.5	-0.8-5.5	
Neurodevelopmental disorder	5	5.5	-0.8-5.5	
Nephrolithiasis	2	2.2	-1.9-2.2	
Prostration	5	5.5	-0.8-5.5	
Family history				
No	69	75.8	65.8-83.6	
Yes	22	24.2	16.4-34.2	
Van Dijk severity grade (*n* = 82)				
Mild	6	7.3	3.2-15.6	
Moderate	47	57.3	46.2-67.7	
Severe	25	30.5	21.3-41.5	
Extremely severe	4	4.8	1.8-12.5	
Aglan severity scale (*n* = 41)				
Mild	17	41.5	27.0-57.5	
Moderate	4	9.8	3.6-24.1	
Severe	20	48.7	33.4-64.3	
Fractures				
Total number	426			
Lower limbs	264	61.9	55.3-66.6	
Upper limbs	110	25.8	21.7-30.0	
Clavicle	32	7.5	5.0-10.0	
Head	13	3.0	1.4-4.7	
Thorax	8	1.9	0.6-3.2	
Anthopometry at birth	Mean/Median	SD/IQR		
Weight (g)	2,903§	582.6	1,500-4,300	
Height (cm)	46.6§	4.3	35-52	
Cephalic circumference (cm)	35.0	2.5	30-37	
Diagnostic age (months)	20.5	58.0	0-180	
Father's age	31.9§	8.1	29.9-34	
Mother's age	27.8§	7.7	25.9-28.7	

BOS, bronchial obstruction syndrome; CI, confidence interval; IQR, interquartile range; OI, osteogenesis imperfecta; SD, standard deviation. *Chi2 with adjusted residuals. §Mean and SD.

and 0.7170) and head circumference at birth ($p = 0.3290$ and 0.3614). These results are not presented in any table or supplementary material. It is important to note that the small sample size in the mild group of the Van Dijk severity scale and the moderate group of the Aglan scale may limit the power of these comparisons. This limitation should be considered when interpreting the results.

The mean of the standard deviations for height and body mass index at the time of diagnosis was -2.78 (95% CI = -3.47 to -2.08) and 0.66 (95% CI = 0.33-0.99), respectively.

3.2. Clinical characteristics & severity degree

The mean number of fractures was 4.68, and one patient reported up to 18 fractures. The most frequently fractured location was the lower limbs (61.9%), followed by the upper limbs (25.8%). A total of 147 emergency admissions due to fractures were observed, with a

mean of 1.6 admissions per patient. The main cause was fractures (57.9%), and one patient reported 19 admissions. About the severity, 57.3% of patients had a moderate Van Dijk severity grade and 48.7% had a severe Aglan severity scale. On the other hand, N-telopeptide and bone densitometry were performed in around 50% of patients and alkaline phosphatase and C-telopeptide were only reported in 25% of patients (Table 1).

In respect of the physical characteristics, the most frequent associated phenotypes were blue sclera's (72.5%), bowed legs (39.6%), joint hypermobility (24.2%), and triangular faces (23.1%) (Table 2). In the same matter, a frequency analysis was carried out based on the Aglan severity scale from moderate to severe, where a greater occurrence of umbilical hernia, scoliosis and clinodactyly was observed. On the contrary, in this same group of patients, hearing loss, microcephaly and hypermobility was less dominant.

The analysis of the frequency according to the Aglan severity scale from moderate to severe in the adjusted model, observed a higher frequency of umbilical hernia, single palmar crease, scoliosis, clinodactyly, and asymmetric lower limbs. In the opposite direction, in this group of patients, keratoconus, hypermobility, hearing loss, triangular faces, jaw asymmetry, microcephaly and genu varum were less frequent in the adjusted model (Table 3). Based on the Van Dijk severity scale, the frequencies of phenotypes did not show any significant differences (Supplemental Table S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=219*).

Table 2. Associated phenotypes in pediatric patients with OI

Associated phenotypes	*n*	%	95% CI
Blue sclera	66	72.5	60.15-72.53
Bowed legs	36	39.6	26.01-39.56
Joint hipermobility	22	24.2	12.31-24.18
Triangular face	21	23.1	11.4-23.08
Dentinogenesis imperfecta	19	20.9	9.61-20.88
Short height	12	13.2	3.81-13.19
Scoliosis	9	9.9	1.62-9.89
Bowed arms	9	9.9	1.62-9.89
Asymmetric upper limbs	9	9.9	1.62-9.89
Shortening of lower limbs	5	5.5	-0.82-5.49
Pectus carinatum	5	5.5	-0.82-5.49
Microcephaly	4	4.4	-1.29-4.4
Inguinal hernia	4	4.4	-1.29-4.4
Umbilical hernia	3	3.3	-1.65-3.3
Asymmetric thorax	3	3.3	-1.65-3.3
Coxa vara	3	3.3	-1.65-3.3
Clinodactyly	3	3.3	-1.65-3.3
Macrocephaly	3	3.3	-1.65-3.3
Single palmar crease	2	2.2	-1.87-2.2
Hearing loss	2	2.2	-1.87-2.2
Wide anterior fontanelle	2	2.2	-1.87-2.2
Bot foot	2	2.2	-1.87-2.2
Short thorax	2	2.2	-1.87-2.2
Keratoconus	1	1.1	-1.79-1.1
Sunken nose bridge	1	1.1	-1.79-1.1
Jaw disproportion	1	1.1	-1.79-1.1
Hip Dysplasia	1	1.1	-1.79-1.1
Flat foot	1	1.1	-1.79-1.1
Varying leg	1	1.1	-1.79-1.1
Valgus foot	1	1.1	-1.79-1.1
Cleft lip & palate	1	1.1	-1.79-1.1

CI, confidence interval; OI, osteogenesis imperfecta.

The prevalence of phenotypes associated with the Van Dijk severity degree and the Aglan severity scale was analyzed; however, no significance was observed in the frequency when determining the means of the total phenotypes according to the scale and degree of severity ($p = 0.608$ and 0.940, respectively).

3.3. Treatment

Of all patients 75.8% started a treatment with bisphosphonates, with alendronate (1 mg/kg weekly, oral) being the most frequently used (27.5%) followed by zoledronate (0.5 mg/kg every six months, intravenous). Only 42.9% completed at least one year of treatment and 12.1% completed three or more years. Surgical treatment was required in 34.1% of patients due to fractures. Regarding the use of adjuvant medications, such as calcium (30-75 mg/kg/day) and vitamin D (doses diverse, *e.g.* 600,000 UI stat), 41.8% of patients used them (Table 4).

When analyzing the treatment response in relation to the increase in the standard deviation scores of bone densitometry, no differences were found when comparing it with the Aglan severity scale and the Van Dijk severity grade ($p = 0.7639$ and 0.2470, respectively). In that same sense, no changes were observed in densitometry in relation to any associated phenotype ($p > 0.05$).

3.4. Bone densitometry analysis

Regarding bone density, a trend towards improvement over time was observed, however, some patients only had a single measurement (Figure 1A). We observed that those who presented a favorable evolution according to bone densitometry had a mean number of fractures of 3.6 (SD = 1.73) versus those who presented an unfavorable response, the average was 11.1 (SD = 4.87) ($p < 0.001$). In the same sense, the number of fractures increases if bone densitometry remains the same or decreases over time ($R^2 = 0.138$; coefficient = 0.213; 95% IC = -0.422 to -0.003; constant = 2.5; $p = 0.047$) (Figure 1B). Additionally, it was observed that as the body mass index increases, the response to treatment calculated, according to bone density, is lower ($R^2 = -0.043$; coefficient = 0.0; 95% CI = -0.029 to -0.059; constant = 0.24; $p = 0.078$) (Figure 1C).

3.5. Comparative analysis

A comparison was made of the median of the difference between the last and first value of the serological

Table 3. Prevalence of associated phenotypes in patients with osteogenesis imperfecta according to the Aglan severity scale

Phenotype	PRc	95% CI	*p*	PRa	95% CI	*p*
Umbilical hernia	0.667	0.130-3.407	0.5782	10,059	1.961-51.608	0.006
Inguinal hernia	2,105	1.519-2.916	0.2995	1,984	0.492-8.007	0.335
Blue sclera	1,857	0.773-4.460	0.1159	2,074	0.821-5.241	0.123
Dentinogenesis imperfecta	1,375	0.715-2.645	0.3869	1,178	0.439-3.162	0.745
Poor sphincter control	-	-	-	-	-	-
Keratoconus	-	-	0.3231	9.35 x 10-7	5.7 x10-8-1.51 x10-5	< 0.001
Joint hipermobility	0.682	0.291-1.596	0.3355	0.053	0.008-0.343	0.002
Single palmar crease	2,105	1.519-2.916	0.2995	201,156	12.82-3155.69	< 0.001
Hearing loss	0	-	0.3231	1.20 x 10-8	1.38 x10-9-1.03 x10-7	< 0.001
Triangular face	1,524	0.831-2.794	0.2243	0.232	0.083-0.648	0.005
Short height	1,271	0.574-2.813	0.5922	1,007	0.293-3.470	0.99
Scoliosis	1,458	0.745-2.853	0.3428	5,434	1.702-17.348	0.004
Sunken nose bridge	-	-	-	-	-	-
Jaw disproportion	2,105	1.519-2.916	0.2995	0.027	0.002-0.448	0.012
Wide anterior fontanelle	-	-	-	-	-	-
Macrocephaly	-	-	.	-	-	-
Microcephaly	0	-	0.3231	2.35 x 10-8	2.17 x10-9-2.56 x10-7	< 0.001
Shortening of lower limbs	0	-	0.157	3.13 x 10-9	2.51 x10-10-3.90 x10-8	< 0.001
Flat foot	-	-	-	-	-	-
Coxa vara	1,026	0.247-4.258	0.9718	0.392	0.063-2.417	0.313
Genu varum	0	-	0.3231	9.35 x 10-7	5.7 x10-8-1.51 x10-5	< 0.001
Valgus foot	0	-	0.3231	0.169	0.002-10.199	0.395
Pectus carinatum	2,105	1.519-2.196	0.2995	3,389	0.279-41.049	0.337
Bot foot	-	-	-	-	-	-
Clinodactyly	1,407	0.591-3.351	0.5197	6,624	1.649-26.618	0.008
Bowed arms	1,407	0.591-3.351	0.5197	1,868	0.555-6.290	0.313
Asymmetric lower limbs	1,944	1.151-3.283	0.0669	41,757	4.918-354.508	0.001
Asymmetric thorax	2,167	1.544-3.040	0.1373	0.307	0.0197-4.789	0.4
Short thorax	0	-	0.3231	4.66 x 10-6	2.12 x10-7-1.02 x10-5	< 0.001
Cleft lip/palate	0	-	0.3231	1.07 x 10-8	9.58 x10-10-1.19 x10-7	< 0.001
Bowed legs	0.923	0.461-1.848	0.8187	1,788	0.769-4.158	0.177
Severe short height	1,436	0.783-2.633	0.2655	0.794	0.278-2.268	0.667

PRa, adjusted prevalence reason; PRc, crude prevalence reason; CI, confidence intervals.

markers according to the Van Dijk severity grade and the Aglan severity scale. However, no significant difference was found between these values (Table 5). Another comparison of the median number of fractures was made according to the Van Dijk severity grade and the Aglan severity scale. It was observed that the median number of fractures was more frequent in the group that was of moderate severity, according to the Van Dijk severity grade (p = 0.0003) and the Aglan severity scale (p = 0.0957) (Supplemental Table S3, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=219*).

4. Discussion

This is the second and largest study in the country about the pediatric population with OI and although it is not a national study, it allows us to have a great overview of this disease in Peru (*6*). In our country there is no information about the incidence of OI. However, Guio *et al.* determined that in one of the main Peruvian reference hospitals, 101 cases of skeletal dysplasia were diagnosed during the years 2014-2018, and it is worth mentioning that within this group of diseases is OI (*7*). Another study in a different national reference hospital observed 11 patients with OI over a period of 3 years (2007-2009) (*13*).

A greater frequency was observed in the male sex (60.4%), which is contrary to what is indicated in the international literature, which mentions that there is no sex predominance in OI, this could be because this disease is still underdiagnosed in our country (*14,15*), or it might be related to social or familial factors. However, in a Portuguese study (n = 21) results like ours were shown with a significant male population (61.9%) (*16*).

The average age of diagnosis of our study was 20.5 months of age, which is early compared to a national study of the Vietnamese population with OI (n = 146), where the most frequent age of diagnosis ranged from 6-10 years (27.4%) (*17*). In Spain (Valencia) it was observed (n = 40) that the average age of diagnosis was 8.4 ± 14.6 years, and 0.04 ± 0.3 years in severe cases where presentation at birth have only been seen in extremely severe cases (*18*). In a Turkish study (n = 29), average age of diagnosis was 3.6 years, which reflects a later age compared to our results (*19*). However, in a Portuguese hospital the mean age of diagnosis was 20.6 months, like this study (*16*). This may be explained since more than 60% of patients in this hospital debuted with a fracture before the first three years of life (*16*); or by the differences in population size and the types of OI across

Table 4. Therapy in pediatric patients with OI

	n	%	95% CI
Bisphosphonates			
No treatment	22	24.2	16.3-34.2
Only alendronate	25	27.5	19.1-37.7
Only zoledronate	19	20.9	13.6-30.6
Alendronate→Zoledronate	15	16.5	10.0-25.7
Only pamidronate	4	4.4	1.6-11.3
Alendronate→Pamidronate →Zoledronate	3	3.3	1.04-9.92
Pamidronate→Zoledronate	2	2.2	0.53-8.57
Alendronate→Pamidronate	1	1.1	0.14-7.6
Years of Bisphosphonates (*n* = 65)			
0	22	24.2	16.35-34.2
1	39	42.9	32.9-53.3
2	19	20.9	13.6-30.6
3	8	8.8	4.39-16.8
4	2	2.2	0.53-8.57
7	1	1.1	0.14-7.64
Treatment continuity for 3 or more years			
Yes	11	12.1	0.6-2.0
No	80	87.9	79.2-93.2
Surgeries for fractures			
No	60	65.9	55.4-75.1
Yes	31	34.1	24.9-44.6
Number of surgeries			
0	49	53.9	43.4-63.9
1	24	26.4	18.2-36.6
2	14	15.4	9.2-24.5
3	3	3.3	1.0-9.9
4	1	1.1	0.1-7.7
Adjuvants (vitamin D/ calcium)			
Yes	38	41.8	31.9-52.3
No	53	58.2	47.7-68.07

CI, confidence intervals. →, "followed by".

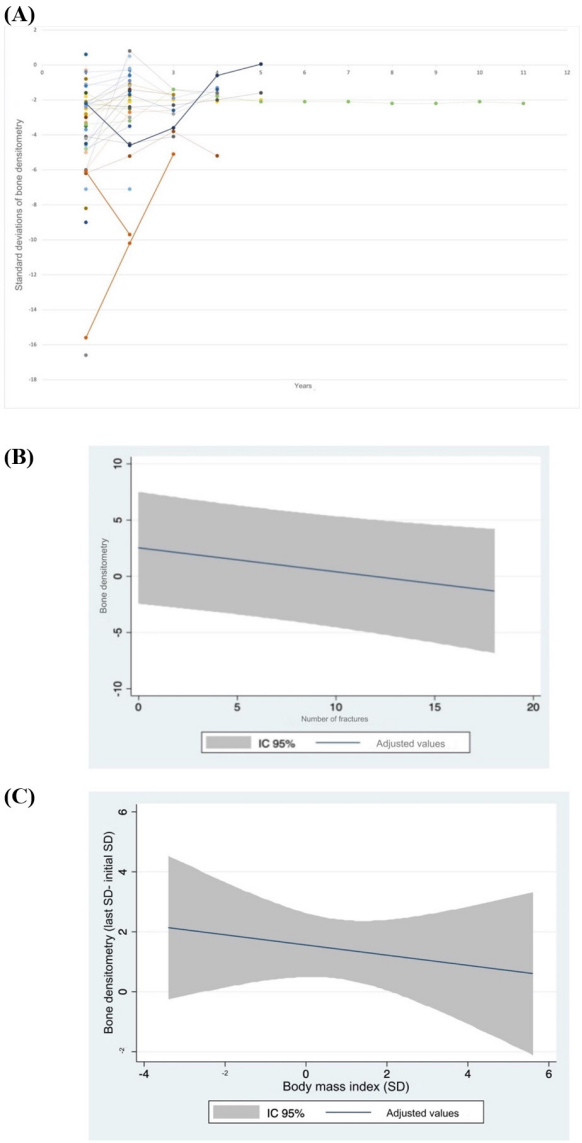

Figure 1. (A) Evolution of lumbar bone densitometry, each color represents a patient. **(B)** Relationship between the number of total fractures and the response of bone densitometry according to its standard deviation in patients with osteogenesis imperfecta. (R^2 = 0.138; coefficient = 0.213; 95% CI = -0.422 to -0.003; constant = 2.5; p = 0.047). **(C)** Relationship between body mass index and response to treatment according to bone densitometry (R^2 = -0,043; coefficient = 0.0; 95% CI = -0,029 to -0,059; constant = 0.24; p = 0.078).

the cohorts being compared.

It was also determined that most patients came from the capital of Peru (52.8%). We propose that this could be due to the shortage of specialists (mainly geneticists), in regional hospitals to diagnose and refer patients to specialized hospitals, and most of them are in our capital (*7*).

Most of our patients (75.8%) did not have any family history. Which would imply that many of the genetic variants in these patients are likely de novo and the frequency of mild type OI is low. A study carried out in Portugal also showed that 66.6% of its patients had no family history (*16*). On the contrary, a study carried out in Spain (Valencia) observed that more than 50% of its patients had a family history (*20*). This difference could be attributed to the fact that, depending on the population groups, there may be greater awareness of the importance of timely diagnosis, making family history more relevant. Alternatively, patients with rare diseases in high-income countries might generally have greater survival rates.

Regarding the extra-skeletal characteristics, we observed that the most prevalent were the presence of blue sclerae, bowed legs, joint hypermobility, triangular faces and dentinogenesis imperfecta (DI) with 72.5%, 39.6%, 24.2%, 23.1%, and 20.9%, respectively. Multiple studies agree with our findings since they observe that the most prevalent extra-skeletal characteristic of OI is blue sclerae (79%-86%), and DI (20.9% *vs.* 22.5%-61%), but this may vary depending on the population and type of OI (*16,18,20*) or the experience of clinical experience for found and registered phenotypes.

To evaluate the severity of OI in our study we used two grading scales. The first, developed by Van Dijk *et al.,* which allows us to establish a pre or post-natal severity based on clinical or ultrasound characteristics

Table 5. Comparison of median difference between the first and last values of serological markers according to grade and severity scale

Markers	*n*	median	*p**
Van Dijk severity grade			
N-telopeptide			
Mild	3	128	
Moderate	8	104.45	
Severe	5	-136	0.0274
Extremely severe	3	-41	
Total	19	67.4	
C-telopeptide			
Mild	0	0	
Moderate	7	-8.7	
Severe	3	24	0.7324
Extremely severe	0	0	
Total	10	7.65	
Alkaline phosphatase			
Mild	1	-417	
Moderate	5	-52	
Severe	3	-109	0.133
Extremely severe	1	-524	
Total	10	-108	
Bone densitometry			
Mild	2	2.2	
Moderate	13	1.4	
Severe	6	1.2	0.8066
Extremely severe	3	4.7	
Total	24	1.35	
Aglan severity scale			
N-telopeptide			
Mild	17	134.75	
Moderate	20	456.02	0.8104
Severe	4	294.7	
Total	41	226.8	
C-telopeptide			
Mild	3	195.7	
Moderate	3	-8.7	0.2752
Severe	0	0	
Total	6	17.65	
Alkaline phosphatase			
Mild	5	-82	
Moderate	2	-219.5	0.7408
Severe	1	-121	
Total	8	-108	
Bone densitometry			
Mild	5	1.6	
Moderate	4	0.8	0.0971
Severe	2	3.85	
Total	11	1.1	

PRa, adjusted prevalence reason; PRc, crude prevalence reason; CI, confidence intervals. *Median differences by Kruskall wallis.

(*10*). In this study, we observed that most cases were moderate (57.3%). In contrast, Caudevilla *et al.* observed that mild cases were the most frequent (68.3%) (*18*). This discordance may be due to the fact that the study mentioned before wasn't done in a completely pediatric population.

The second scale uses a scoring system based on five parameters and was developed by Aglan *et al.* with the severe form being the most frequent (48.7%) (*11*). The same author observed (n = 43) that, as in our study, the severe form was the most frequent (37.2%) (*11*). Otaify *et al.* observed in his study (n = 33) that all his patients presented a moderate or severe degree of severity (*21*).

In our study, 93.4% of patients had at least one fracture in their lives and one case even had 18. Furthermore, we observed that, like other studies, the most affected location were the lower limbs, followed by the upper limbs. In Spain (Valencia) the results were similar, with lower limbs slightly more frequent than upper limbs with 36.5% and 33.6%, respectively (*20*). In Vietnam, it was observed that 142/146 patients presented fractures with a total of 1,932 fractures. Likewise, fractures in this population were most common in the lower limb, especially the femur (*17*). Similarly, in Turkey, it was observed that the most frequent fractures were the lower limbs, especially the tibia, followed by the femur (*19*). In Portugal, results were similar with the lower limb (55.6%) being the most common, followed by the upper limb (37.8%) (*16*).

The treatment is based in the use of bisphosphonates, commonly being alendronate, pamidronate and zoledronate (*4*). In addition, many specialists opt for adjuvant therapy using calcium and vitamin D supplements (*9*). We observed that 75.8% of patients started a treatment with bisphosphonates. However, only 41.8% used adjuvant medications. Regarding bisphosphonates, in this study alendronate (27.5%) was the main one indicated, followed by zoledronate (20.9%). The therapeutic regimen of alendronate followed by zoledronate was used in 15 patients (16.5%). We emphasize that nearly 50% of patients did not complete the year of treatment with bisphosphonates. We propose that this could be due to multiple factors such as the shortage of medications, lack of follow-up, difficulty in scheduling appointments, distance to the hospital, limited knowledge about rare diseases or administrative barriers.

In Turkey, it was observed that 75% of patients started a treatment with bisphosphonates, where pamidronate (77%) and alendronate (23%) were the most indicated (*21*). In Vietnam, a low-resource country, only 25% of patients started treatment with bisphosphonates where zoledronate predominated, since it is the most accessible in the country (*17*). In said country access to bisphosphonates and specialists is difficult, which is why most patients do not complete treatment. It should be noted that these difficulties are like our national reality (*17*). It is important to emphasized that in Vietnam surgical treatments are the most frequently indicated with 163 surgeries performed in all 58 patients (*17*).

In Portugal, 85% of patients started a treatment with bisphosphonates, specifically with pamidronate, and the mean age at which treatment began was 50 months (*16*). In Valencia evidence showed that 52.1% of patients received treatment, where bisphosphonates were the most common (44.8%). In addition, 24.7% of patients received exclusively adjuvant treatment with vitamin D,

calcium or parathyroid hormone (*20*). Finally, in Spain it was observed that 19 patients (47.5%) started treatment with bisphosphonates, six of which added recombinant growth hormone (pamidronate + rhGH). All patients treated with bisphosphonates showed a decreased fracture rate and increased activity (*3*).

As shown in the studies mentioned before, the rate of patients starting treatment with bisphosphonates in our hospital is in line with the international literature. However, we can observe that the main problem is related to its continuity, since around 50% of our patients do not complete the year of treatment for the reasons mentioned above. Furthermore, the follow-up of patients must be improved, given that about 50% of our patients do not have control tests such as bone densitometry or bone resorption markers. In our hospital, compared to others abroad, we used alendronate more frequently due to its availability, although in recent years, zoledronate has been used in most patients.

In the bivariate analyzes it was observed that there is no significant difference with respect to the difference of the first and last value of the serological markers, with respect to the degree and severity scale mentioned above. On the other hand, we have managed to establish in our population that if bone densitometry remains the same or decreases over time, it means a greater risk of presenting new fractures. Likewise, we determine which patients have a favorable and unfavorable evolution based on bone densitometry and the average number of fractures. We also observed a higher median number of fractures in patients with moderate severity according to the Van Dijk severity grade (p = 0.0003). It should be emphasized that such analyzes have not been previously reported in similar OI studies, although these differences are likely due to sample size.

Although the Aglan scale showed differences in birth anthropometry based on the severity of OI, these findings could be influenced by variations in the frequency of occurrence by sex.

About the clinical manifestations (human phenotype), a frequency analysis was carried out based on the Aglan severity scale from moderate to severe, where a greater predominance of umbilical hernia, scoliosis and clinodactyly was observed. Conversely, in this same group of patients, hearing loss, microcephaly and hypermobility are less common. It should be emphasized that these types of analyzes have not been done before in similar OI studies.

Among the limitations we had a small sample, although it is the study with the largest number of participants with OI in Peru. Furthermore, data collection was based exclusively on clinical records (loss of information), and since this is a national reference center, the concentration of cases in a single center could induce a selection bias, therefore the patients treated in this institute may not be representative of all patients with osteogenesis imperfecta in Peru. Although, being one of the few reference centers, the results let us estimate the characteristics of patients with OI in Peru.

Among the limitations, it is important to mention that not all patients had adequate follow-up, some even had only one consult, and this may cause a lack of data on the variables and the analysis of the treatment response may not be precise. On the other hand, this is a small sample, despite being the study with the largest number of participants with OI in Peru. Furthermore, data collection was based exclusively on clinical records (loss of information), and since the institution is a national reference center, the concentration of cases in a single center could introduce a selection bias, since the patients treated in this institute may not be representative of all patients with osteogenesis imperfecta in Peru. Although, being one of the few reference centers, it could show what happens in patients with OI, especially those with severe OI.

In conclusion, the present study represents a significant advance in the understanding of OI in the pediatric population of Peru. When compared with international studies, some similarities were observed in the degrees of severity, clinical and therapeutic characteristics, but also differences in prevalence, proportion in men, and family history. The use of tools such as the Van Dijk severity grade and the Aglan severity scale is recommended since they are easy to apply and will help improve the classification of patients with a higher risk of fractures and response to treatment. It is necessary to ensure the care of these patients, the monitoring and evaluation of the use of bisphosphonates as the first line of treatment in all patients, given that encouraging results in the reduction of fractures and improvement of quality of life have been reported in other countries.

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