

Original article

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Atypical femoral fractures in a Mexican cohort of children and adolescents with osteogenesis imperfecta. Analysis of trajectories

*Fracturas femorales atípicas en una cohorte mexicana de niños y adolescentes con osteogénesis imperfecta. Análisis de trayectorias*Bremer A,* Clark P,† Méndez-Sánchez L,‡ García-de la Torre G[§]

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ABSTRACT. Introduction: osteogenesis imperfecta (OI) is a rare inherited bone disorder resulting from defects in type I collagen synthesis or structure. It is characterized by increased bone fragility, recurrent fractures, and early-onset hearing loss. Management requires a multidisciplinary approach aimed at reducing fracture incidence, enhancing mobility, and promoting functional independence. Since 1998, bisphosphonates (BPs) have been used as compassionate therapy in OI. **Objective:** to characterize children with osteogenesis imperfecta (OI) and report the incidence of atypical femoral fractures (AFFs) in relation to the duration of zoledronic acid treatment. **Material and methods:** a single group ambispective cohort study of pediatric patients diagnosed with osteogenesis imperfecta according to the Sillence criteria and treated with zoledronic acid (0.1 mg/kg/year); the retrospective period spanned from January 2008 to July 2017, while the prospective period extended from October 2017 to March 2024. **Results:** a total of 68 patients were included, with 24 fractures identified in 21 patients (31%). Fractures were more frequent in males (67%), adolescents (76%) and those receiving continuous treatment (76%). The duration of treatment before developing an AFF was also shorter in males (69 months) compared to females (77 months). Cox regression analysis showed that male patients with OI had a hazard ratio (HR) 3.13 (95% CI 1.18-8.26, $p = 0.021$)

RESUMEN. Introducción: la osteogénesis imperfecta (OI) es un trastorno óseo hereditario poco frecuente causado por defectos en la síntesis o estructura del colágeno tipo I. Se caracteriza por una mayor fragilidad ósea, fracturas recurrentes y pérdida auditiva de inicio temprano. Su tratamiento requiere un enfoque multidisciplinario dirigido a reducir la incidencia de fracturas, mejorar la movilidad y promover la independencia funcional. Desde 1998, los bifosfonatos (BF) se utilizan como tratamiento compasivo en la OI. **Objetivo:** caracterizar a niños y adolescentes con osteogénesis imperfecta (OI) y reportar la incidencia de fracturas femorales atípicas (FFA) en relación con la duración del tratamiento con ácido zoledrónico. **Material y métodos:** estudio de cohorte ambispectivo de un solo grupo, conformado por pacientes pediátricos diagnosticados con OI según los criterios de Sillence y tratados con ácido zoledrónico (0.1 mg/kg/año). El período retrospectivo abarcó de enero de 2008 a julio de 2017, y el periodo prospectivo de octubre de 2017 a marzo de 2024. **Resultados:** se incluyeron 68 pacientes, con un total de 24 fracturas identificadas en 21 pacientes (31%). Las fracturas fueron más frecuentes en niños (67%), adolescentes (76%) y en aquellos que recibieron tratamiento continuo (76%). La duración del tratamiento antes de presentar una FFA fue menor en hombres (69 meses) en comparación con mujeres (77 meses). El análisis de regresión de Cox mostró que los pacientes con OI

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indicating a significantly higher risk of developing an AFF compared to female patients. **Conclusion:** there may be an association between prolonged use of zoledronic acid and the occurrence of AFFs. Male and adolescents exhibited a higher risk of AFFs (HR 3.13, 95% CI 1.18-8.26). These fractures may not be limited to the femur, as other long bones could also be affected. Larger cohorts and longer follow-up periods, including control groups not exposed to zoledronic acid, are needed to establish causation.

Keywords: osteogenesis imperfecta, atypical femoral fractures, bisphosphonates, pediatric.

presentaron una razón de riesgo (HR) de 3.13 (intervalo de confianza [IC] del 95%: 1.18-8.26; $p = 0.021$), indicando un riesgo significativamente mayor de desarrollar una FFA en comparación con las pacientes femeninas. **Conclusión:** podría existir una asociación entre el uso prolongado de ácido zoledrónico y la aparición de FFA. Los varones y los adolescentes presentaron un mayor riesgo de fractura (HR 3.13; IC95%: 1.18-8.26). Estas fracturas podrían no limitarse únicamente al fémur, ya que otros huesos largos también podrían verse afectados. Se requieren cohortes de mayor tamaño y periodos de seguimiento más prolongados, incluyendo grupos control no expuestos a ácido zoledrónico, para establecer una relación causal.

Palabras clave: osteogénesis imperfecta, fracturas femorales atípicas, biofosfatos, pediatría.

Abbreviations:

AFFs = atypical femoral fractures

ASBMR = American Society for Bone and Mineral Research

BMD = bone mineral density

BPs = bisphosphonates

OI = osteogenesis imperfecta

ZA = zoledronic acid

Introduction

Osteogenesis imperfecta (OI) is a rare inherited metabolic bone disorder caused by a defect in type I collagen synthesis and function. This condition is characterized by bone fragility, early-onset hearing loss, and multiple fractures.¹ Clinically, OI can be classified into four subtypes, as classified by Van Dijk and Sillence.² The most common OI phenotypes are types I, III and IV.³ The treatment of OI requires a multidisciplinary approach aimed at reducing fracture incidence, promoting mobility, and fostering patient independence. Bisphosphonates (BPs) are the preferred pharmacological agents, as they inhibit bone resorption, increase bone mineral density, and decrease calcium release from bones into the bloodstream. These drugs have been used in OI management since 1998.⁴

The rationale for using BPs, particularly zoledronic acid (ZA), in OI is based on their ability to enhance bone mineral density and reduce fracture rates by up to 60%.⁵ Additionally, BPs help with pain control.⁶ However, concerns have been raised regarding long-term BP use, particularly the development of atypical fractures. atypical femoral fractures (AFFs) are rare complications associated with prolonged BP use in both adults and pediatric patients with OI.^{7,8} AFFs are defined as subtrochanteric femoral fracture characterized by: (1) occurrence in the femoral shaft, (2) a predominantly transverse and minimally comminuted pattern, (3) lateral cortical thickening at the fracture site, and (4) minimal or no trauma preceding the fracture.⁸ The American Society for Bone and Mineral Research (ASBMR) has established a major and minor

criteria to facilitate AFF identification and classification. For a fracture to be considered atypical, it must be associated with prolonged bisphosphonate use and meet at least four of the five major criteria.

Although these criteria were initially developed for adults, they are also applied to pediatric patients.

Several cohort studies have described AFF in pediatric OI patients following prolonged BP therapy.^{3,9,10} Nicolaou et al.,¹¹ reported 16 AFFs in 11 patients treated with pamidronate for a median duration of six years. Vuorimies et al.⁹ categorized patients into three groups based on treatment duration: a) continuous BP treatment b) intermittent BP treatment with a one-year pause after 2-3 years, and c) untreated patients. They found a higher incidence of fractures in the continuous treatment group compared to the intermittent group after 4.1 years of BP therapy (pamidronate, zoledronic acid or risedronate). Trejo et al.³ reported a shorter time to AFF onset, averaging 2.7 years of BP exposure.

Given these findings, this study aims to characterize children with OI and assess the incidence of AFFs in relation to zoledronic acid treatment duration.

Material and methods

We designed a single-group ambispective cohort study^{12,13} of pediatric patients diagnosed with osteogenesis imperfecta according with the Sillence criteria.

The retrospective period spanned January 2008 to July 2017, while the prospective period extended from October 2017 to March 2024. The inclusion criteria were: (1) Children diagnosed with osteogenesis imperfecta based on the Sillence criteria (both sexes, aged 2 to 18 years) who had been treated with zoledronic acid (0.1 mg/kg/year). Patients with complete clinical record and X-ray documentation were included.

For the prospective study, all patients met the same criteria as the retrospective cases, with the addition of laboratory tests including 25 OHD, creatinine, albumin,

calcium, phosphorus, magnesium, acid phosphatase and bone densitometry. Prospective cases underwent follow-ups every six months. All radiographs were collected and re-evaluated by two of the authors (A.B and P.C). The ASBMR criteria for adult atypical femoral fracture were applied. Traumatic fractures were excluded. Descriptive statistics were used to characterize the sample, with means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Age subgroups were classified as children (2-9 years 11 months) and adolescents (≥ 10 years). A stratified analysis by sex was conducted. A visual trajectories analysis was performed to describe cohort patterns, and Kaplan-Meier curves were generated to define the cumulative incidence of fractures and treatment duration. Cox regression analyses were conducted using age, sex and treatment type as covariates. Statistical analyses were performed using SPSS Version 24.

This study was conducted in accordance with the Helsinki Declaration of Clinical Research on Humans.¹⁴ All procedures followed ethical standards established by institutional and/or national research committee, in compliance with the 1964 Declaration and its subsequent amendments. This protocol was approved by the Research, Ethics and Biosafety Committees with the reference number HIM2018/010. Informed consent was obtained from parents or guardians, and informed assent was obtained from participants aged seven years and older.

Results

The total sample consisted of 68 patients, 38 were analyzed retrospectively using clinical and radiographic records, while 30 were diagnosed and followed prospectively. The mean age of the patients was 10.5 years, and half of the population was female (*Table 1*). As the demographic and clinical characteristics were similar in both the retrospective and prospective phase; the data were analyzed as a single cohort.

A visual trajectory analysis was performed for each patient in the cohort. The observation period ranged from 6 to 85 months. Three patients developed two AFFs at different anatomical sites and times during follow-up. All AFFs met the ASBMR criteria. Although no specific pattern was identified, patients receiving intermittent treatment exhibited a lower frequency of AFFs.

Of the 68 patients, 21 (31%) experienced one or more AFFs, 67% of whom were male, and 16 (76%) were adolescents (≥ 10 years). Among the 21 patients with AFFs, 16 (76%) were on continuous treatment, and 5 (24%) were on intermittent treatment. Seventeen of the 21 affected patients had received three or more doses of zoledronic acid (*Table 2*). The OI subtype for each case is also reported in this table.

Kaplan-Meier cumulative incidence curves were used to estimate the time to first AFF in patients undergoing prolonged treatment with bisphosphonates. Half of the cohort experienced an AFF by 69 months of treatment

(95% CI 61-76 months). When stratified by sex, males developed AFFs by 60 months (95% IC50.2-70.3), while females developed them by 77 months (95%IC 67.5-86.9) ($p = 0.12$). When stratified by age, a significant difference was observed: adolescents developed AFFs by month 48 (95% CI 45.6-55.5) compared to 84 months (95% CI 81.6-88.8) for younger children ($p = 0.001$). A Cox regression analysis including sex, age, and treatment type (continuous or intermittent) showed that male patients with OI had a 3.13-fold higher risk (95% CI 1.18-8.26 $p = 0.021$) of developing an AFF compared to females (*Figures 1 to 3*).

Discussion

This study describes the clinical characteristics and fracture incidence in a cohort of 68 children and adolescents with osteogenesis imperfecta (OI) treated with zoledronic acid (ZA), with a focus on the time to development of AFFs (*Figure 4 and 5*). The average duration of ZA exposure before an AFF occurred was 69 months. When analyzed

Table 1. Baseline characteristics of the population with Osteogenesis Imperfecta. This was a homogeneous sample with a mean age of 10.5 years. During the prospective follow-up of the patients, a bone chemistry panel was performed.

	Retrospective N = 38 n (%)	Prospective N = 30 n (%)
Demographic		
Age*	10.8 $\pm$ 4.26	10.2 $\pm$ 4.30
Gender		
Female	21 (55)	13 (43)
Male	17 (45)	17 (57)
Size (cm)*	NA	109.34 $\pm$ 25.34
Weight (kg)*	NA	31.92 $\pm$ 26.70
Clinical Data		
Type of OI [silence classification]		
I	18 (47)	18 (60)
III	15 (40)	9 (30)
IV	5 (13)	3 (10)
Wandering	26 (68)	22 (73)
Blue sclera	38 (100)	18 (60)
Dentinogenesis	21 (55)	20 (67)
Total fractures before BP treatment (types) [‡]		
I	7 [4-9]	6 [2-7]
III	23 [8-31]	7 [3-25]
IV	30 [15-26]	10 [3-22]
Laboratory and cabinet		
Patients with DXA initial	22 (55)	30 (100)
Laboratories*		
Creatinine	NA	0.42 $\pm$ 0.15
Albumin	NA	4.35 $\pm$ 0.22
Calcium	NA	9.56 $\pm$ 0.49
Phosphorus	NA	5.15 $\pm$ 0.77
Magnesium	NA	2.11 $\pm$ 0.23
Alkaline Phosphatase	NA	258 $\pm$ 90.9
25-OHD	NA	28.2 $\pm$ 14.06

* Data indicate mean $\pm$ standard deviation. [‡] Data expressed by range.
BP = bisphosphonate. NA = not available. OI = osteogenesis imperfecta.

Table 2: Atypical fractures observed during the follow-up period of the cohort from 2008 to 2024.
Most fractures occurred in patients under continuous treatment.

Type of OI	Age	Gender	Number of doses	Location	Type of treatment
I	15	Female	10	Femur	Continuous
I	11	Male	6	Femur	Continuous
I	12	Female	10	Bilateral femur	Continuous
IV	6	Female	3	Femur	Continuous
III	15	Male	15	Femur	Continuous
III	3	Female	3	Femur	Intermittent
III	15	Male	4	Femur	Continuous
IV	8	Male	14	Humerus	Continuous
IV	18	Female	9/13	Femur/ulna	Continuous
III	10	Male	10	Femur	Continuous
I	12	Male	14	Femur	Continuous
III	9	Male	4	Femur	Continuous
I	15	Male	12	Radius	Intermittent
I	15	Male	9	Femur	Continuous
III	8	Male	6	Femur	Intermittent
III	14	Male	3	Femur	Intermittent
III	12	Male	6/12	Right femur /left femur	Continuous
IV	14	Female	7	Femur	Intermittent
I	14	Male	6	Femur	Continuous
IV	10	Male	3	Femur	Continuous
I	11	Female	10	Femur	Continuous

OI = osteogenesis imperfecta. F = female. M = male. C = continuous treatment. I = intermittent treatment.

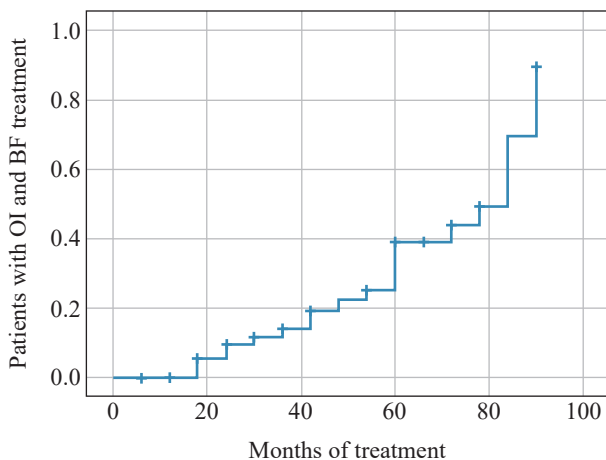


Figure 1: Kaplan-Meier cumulative incidence curves of patients with osteogenesis imperfecta and bisphosphonate treatment by month of follow. BP = bisphosphonate. OI = osteogenesis imperfecta.

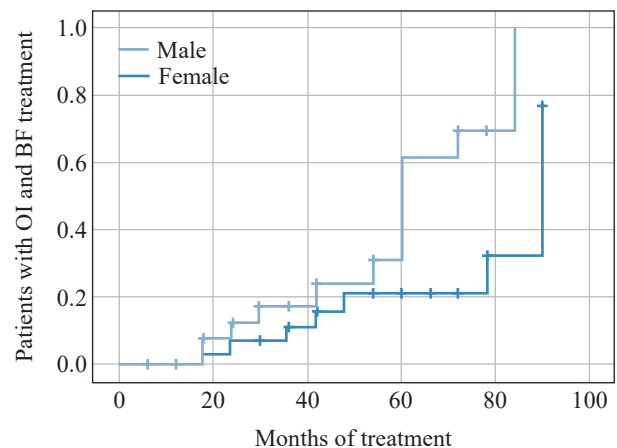


Figure 2: Kaplan-Meier cumulative incidence curves of male and female patients with osteogenesis imperfecta and bisphosphonate treatment by month of follow ($p = 0.021$). BP = bisphosphonate. OI = osteogenesis imperfecta.

by sex, males developed AFFs earlier than females (60 vs 77 months). Similarly, adolescents (≥ 10 years) developed AFFs sooner than younger children (48 vs 84 months). Cox regression revealed that male sex was associated with a significantly higher risk of AFF (HR 3.13, 95% CI 1.18–8.26, $p = 0.021$).

Bisphosphonates have been used in pediatric patients with OI for more than a decade as a compassionate treatment to improve bone mineral density (BMD) and reduce fracture incidence. All patients in this cohort received bisphosphonates as part of standard care at our institution.

A review of the literature identified four pediatric OI cohorts with similar objectives, all of which focused on the association between prolonged bisphosphonate therapy and AFF risk.^{15,16} These cohorts included patients with moderate to severe OI. In contrast, our study also included patients with mild OI, based on BMD z-scores of -2 SD or lower, as per our inclusion criteria.

Our cohort combined retrospective ($n = 38$) and prospective ($n = 30$) data. While most AFFs in previous studies were in the femur, three atypical fractures observed in our prospective group occurred in locations not previously reported (arm and

forearm). These fractures met all ASBMR criteria for AFFs except for anatomical location. To our knowledge, only one other report by Carpintero in 2014¹⁷ has described a non-femoral atypical fracture (tibia) in a pediatric patient with OI type IV treated with pamidronate nine cycles.¹⁸

Unlike other studies, we analyzed our cohort by sex and age, revealed key insights. Specifically, 31% of patients developed at least one AFF, slightly higher than the 8-26% reported in other studies. The average time to AFF in our cohort (69 months) was also comparable to previous studies (4.1-6 years).

Our trajectory analysis showed that patients receiving intermittent treatment had fewer AFFs than those on continuous therapy (24 vs 76%). In adults, continuous ZA use may cause over-suppression of bone turnover, leading to the concept of a «drug holiday» to reduce AFF risk.^{19,20} A similar approach could be advisable in children, with treatment cessation considered after three years of continuous ZA therapy. In this study, most AFFs were treated surgically with a telescopic femoral nail; treatments also included high-dose vitamin D (4,000 IU/day) and cessation of ZA therapy.

Age and sex were notable risk factors. Adolescents (≥ 10 years) had a higher incidence of AFFs than younger children (16 fractures vs 5). This may reflect physiological bone growth and hormonal changes during adolescence, especially the pronounced bone mass accrual seen in males. Since peak bone mass accrual in males is more prolonged than in females,²¹ this may contribute to the threefold higher risk of AFFs in males observed in this study.

Conclusion

This study suggests a possible association between continuous bisphosphonate use and the development of AFFs in children with OI. While most AFFs occur in the femur, other long bones may also be affected. Male sex and adolescence are associated with higher risk, with male patients showing

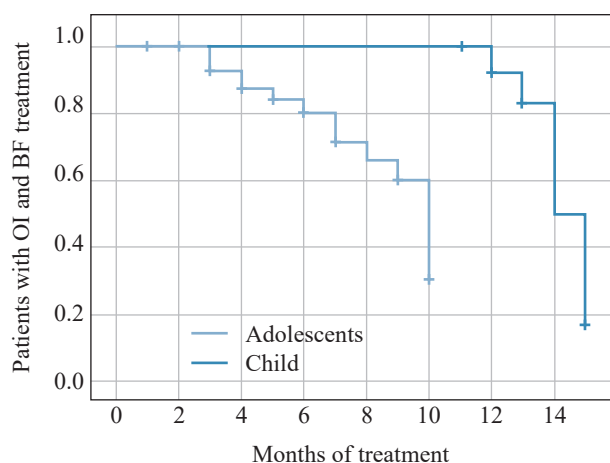


Figure 3: Kaplan-Meier cumulative incidence curves of adolescents and child patients with osteogenesis imperfecta and bisphosphonate treatment by month of follow ($p = 0.001$). BP = bisphosphonate. OI = osteogenesis imperfecta.



Figure 4:

Anteroposterior (AP) radiograph of the thigh, a previously performed osteotomy can be observed. The absence of cortical bulging at this site distinguishes it from an atypical femoral fracture.



Figure 5:

Anteroposterior (AP) radiograph of the hip, showing bulging of the lateral cortex followed by an incomplete fracture line extending toward the medial cortex.

a threefold increase in AFF incidence; further research involving larger cohorts, longer follow-up, and ideally control groups not exposed to bisphosphonates is warranted.

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