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ORIGINAL ARTICLE

Vertebral fractures in children with Type I Osteogenesis imperfecta

Fracturas vertebrales en niños con osteogénesis imperfecta tipo I

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Abstract

Background: Osteogenesis imperfecta (OI) is an hereditary disease affecting conective tissue, mainly associated to growth retardation and pathological fractures. OI type I (OI type I), is the mildest, most often, and homogeneous in its fenotype. Vertebral fractures are the most significant complications, associated to skeletical and cardiopulmonary morbidity. **Objectives:** To characterize clinically a cohort of children with OI type I. **Patients and Methods:** A cohort of OI type I children younger than 20 year old was evaluated. Demographic, clinical, biochemical and radiological data were registered. Results: Sixty seven patients were included, 55% male, 69% resident in the Metropolitan Region. The mean age of diagnose was 2.9 years, 70% presented vertebral fractures on follow-up, mostly thoracic, and 50% before the age of 5 years. Fifty percentage presented vertebral fractures at diagnose, which was about the age of 5 years. Bone metabolic parameters were in the normal range, without significant change at the moment of vertebral fractures. Calcium intake was found to be below American Academy of Pediatrics recommendations at the time of the first fracture. **Conclusions:** In this study OI type I has an early diagnose, and vertebral fractures show a high incidence, mostly in toddlers. Calcium intake was found to be below reccomended values, and should be closely supervised in these patients.

Keywords:
Osteogenesis imperfecta;
Type I;
vertebral fractures.

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Introduction

Osteogenesis imperfecta (OI) is a hereditary disease of connective tissue, clinically and genetically heterogeneous, characterized by bone fragility, deformity and altered growth[1]. It has a prevalence of 1 per 10,000 to 15,000 live births[2]. Currently, many subtypes of this disease are described. Classics are from I to IV, described by Sillence[1,3]. The most frequent OI is type I (OI type I), which its clinical and genetic phenotype is more homogeneous compared to the others[4]. It is usually not deforming, and it is not necessarily associated with fractures, because the appearance of them begins several months after birth, with ambulation and physical activity. It decreases after puberty and a large number of patients presented normal final height[3,5,6].

In patients with OI type I, vertebral fractures (VF) are generally mild and compromise some vertebrae, however they are the greatest complication presented in this disease, since they are associated with scoliosis, low height, and even in some cases, they are associated with severe orthopedic and surgical complications, producing problems at cardiovascular and pulmonary level. If there is a VF case, the international recommendation is to use bisphosphonates, meeting an agreement with parents[7], considering if there is a positive response.

Bisphosphonates are synthetic analogs of pyrophosphate, whose effect is 'anti-resortive' by suppression of osteoclast activity and apoptosis[8]. They have been shown to be effective in increasing the density and size of vertebral bodies, thickening the cortical bone, increasing the trabecular and improving patient's height[9-11]. However, those mild forms of OI are debatable, since they remain for a long time at the bone level (about 10 years) and its long-term effects are still unknown[6,8,10,12,13].

Currently, there is not much literature regarding the natural history of OI type I, especially with regard to VF, making it difficult to describe the risk factors associated with VF, although, those which are reflected in other forms of osteoporosis, are accepted. In Chile, the demographic and evolutionary characteristics of OI type I are unknown, which may be relevant for pediatrician suspicion and specialist management.

The aim of this study is to determine these characteristics in a cohort of patients with OI type I attended at 'Red de Salud UC Christus', as well as to describe vertebral fractures exposure and the evolution of this population affected over time.

Methodology

Population

Patients younger than 20 years old with a diagnosis of OI type I who were attended by pediatric endocrinology team at 'Red de Salud UC Christus'. They were selected through a database with medical records and through reports of bone densitometry performed in the same institution, to ensure the complete incorporation of patients with this diagnosis into the cohort.

Design

The design of this study is historic. Electronic medical records (by computer database) were reviewed and, in case of older patients, paper records were reviewed. A new database was created for recording demographic, clinical, biochemical and radiological variables, from the first to the last medical control. Anthropometric variables (weight, height and weight/height ratio and body mass index (BMI)) were added also as standard deviations for age and gender, according to WHO curves[14]. Calcium intake was recorded as the percentage of daily consumption, recommended by the American Association of Pediatrics (AAP). The physical activity percentage was arbitrarily divided as follows:

- 0: The patient has no physical activity except walking,
- 1: The patient practices regulatory physical activity (twice a week) at school,
- 2: The patient performs some extra programmatic sport.

It was also described if they performed some type of risk sport (rugby, karate, etc.). The protocol of this study was approved by the scientific ethics committee of the 'Pontificia Universidad Católica' of Chile, with exemption of informed consent for clinical records review.

Statistics

Values were expressed as means, medians and standard deviations according to the type of variable. The data were analyzed by Kaplan-Meier curve to determine the time in which fractures were performed. Patients who presented vertebral fractures at the time of diagnosis were compared to those who presented them later, during their evolution. Regarding those patients who presented fractures during their monitoring, the different clinical and laboratory variables were compared using Chi-squared test, Fisher's test, linear by linear association, and Mann-Whitney-Wilcoxon nonparametric tests. AP value lower than 0.05 was used as significance level.

Table 1. Patients with Osteogenesis imperfecta type I

	Total n = 67
Male	55% (37)
Metropolitan Region	69% (46)
Family history	35% (24)
No comorbidities	80% (54)
Vertebral fractures	70% (47)

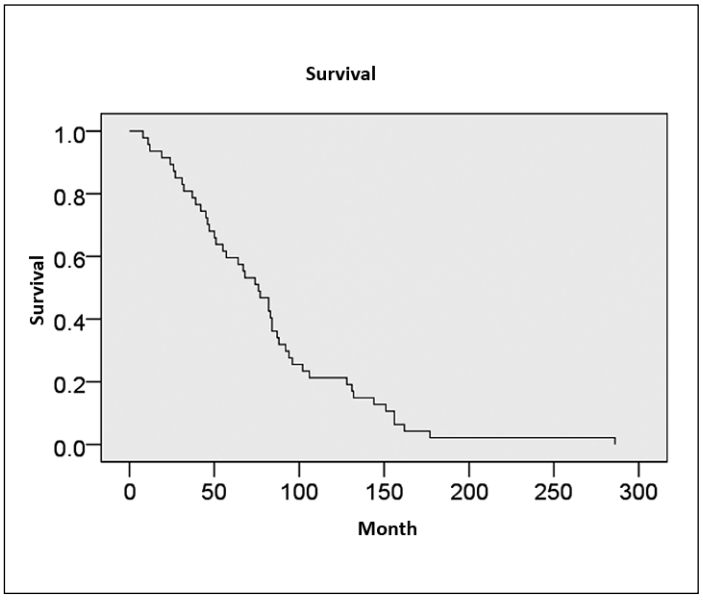

Figure 1. Kaplan Meier curve shows the time (in months) free of vertebral fracture in the evolution of the disease, in those patients who during their evolution had vertebral fractures.

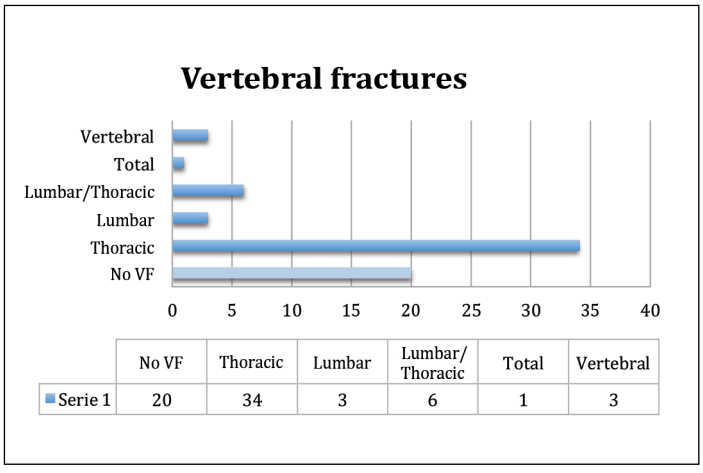

Figure 2. Type of vertebral fracture (First vertebral fracture).

Results

Population

A complete registry of a cohort of 67 patients with OI type I (table 1) was performed, from which 55% were males. 69% percent of the patients were from the metropolitan region, Chile, and 31% were from other regions (from the second to the ninth), who were regularly attended at 'Red de Salud UC'. Approximately, a percentage of one of three of the patients had a family history (mother, father, brothers or sisters with the disease). However, only 6% were referred to specialist control; 91% did so because of frequent appendicular fractures and 3% because of antenatal suspicion. From all of patients, 20% had comorbidity during monitoring procedure, including asthma, hypertrophic cardiomyopathy, hypoacusis, hypothyroidism, insulin resistance, anorexia, prematurity, hypercalciuria and coagulation disorder. There were no endocrinological diseases related. None of the patients performed physical activity with risk of trauma; almost all of them performed some type of physical activity related to daily living activities.

First vertebral fracture

The mean age at diagnosis was 2.9 years. 15% of the patients presented VF at the time of diagnosis and in them the age of diagnosis was 5.9 years. 70% of the patients had VF during their follow-up. The average age of the first VF was 6.7 years. Fifty percent of the patients presented the first VF in their first 5 years of life (figure 1). Of these the majority were multiple and of thoracic location (figure 2). At the time of presenting the first VF (table 2), half of the subjects presented normal nutritional status, highlighting a significant difference between those who presented VF at the time of diagnosis and those who presented it later, during in their evolution. The first group had the highest risk of malnutrition. Regarding bone mineral density (BMD), parathormone, 25 OH2 vitamin D and daily calcium intake, there were no significant differences between these two groups, with the mean values in normal ranges.

Monitoring and follow-up

Using the historical record of these patients from diagnosis at the time of first vertebral fracture or until initiation of treatment with bisphosphonates, excluding those who presented vertebral fractures at diagnosis or used bisphosphonates from the beginning of monitoring procedure, the change or the evolution was compared to same variables registered at the moment of diagnosis of the first VF presented (table 3). We found a significant difference only in the recommended intake of calcium, daily. While the disease was

Table 2. First vertebral fracture in OI type I patient

	No VF at diagnosis n = 56	VF at diagnosis** n = 11	Total n = 67	Valor p*
Normal Nutritional state (nº patients)	50% (28)	36% (4)	47% (32)	0.04
BMD >- 2DE (nº patients)	44% (25)	36% (4)	43% (29)	0.20
Vitamin D (mg/dL and SD)	27.2 (8.8)	22.1 (4.8)	26.1 (8.3)	0.09
PTH (mg/dL and SD)	30.6 (15.2)	27.4 (10.7)	30 (14.3)	0.55
Calcium intake (average and SD)***	93.4 (12.4)	97.4 (3.6)	94 (11.5)	0.86

*Significant P Value < 0.05. **Vertebral fracture or biphosfonato at diagnosis. ***% DRI AAP.

evolving, 79% of patients required bisphosphonates. The initial age average was 7.4 years old.

Table 3. Clinical factors assosiated to first vertebral fracture in OI type I patients

	At diagnosis	1ª VF	Delta	P value*
Vitamin D (mg/dL)	25.38 (3.8)	27.25 (8.8)	4.6 (9.6)	0.08
PTH (mg/dL)	31.7 (27.4)	30.6 (15.2)	-3.8 (20.7)	0.83
BMD (SD)**	-0.73 (3.2)	-1.14 (1.1)	-0.3 (3.9)	0.79
IBMI/Weight/Height (SD)*	-0.06 (0.5)	0.37 (0.8)	0.35 (0.8)	0.09
Calcium^	96.9 (9.8)	93.3 (12.3)	-5.28 (9.4)	0.017

*Significant P < 0.05. **Standar desviation. ^ % DRI AAP.

Discussion

Our study shows the first historical cohort of children with OI type I and their evolution over time. It is possible to highlight three different topics with clinical importance: 1) Frequency and radiological characteristics of vertebral fractures; 2) Age and reason of diagnosis; 3) Clinical evolution of children with OI type I.

Regarding with VF, 70% of the children had vertebral fractures at some time during the disease, and half of them presented VF for the first time before the age of 5 years old. There is no available data in literature in which this finding can be compared with. From these fractures, the most frequent ones were the thoracic, and the second one were lumbar fractures, as described in fractures of osteoporotic bone in the adult population[16], which is produced by a the greater mechanical pressure due to the angulation level in that area. There is no similar cohort of patients with OI type I described at internationally, which it makes it difficult to compare these data.

According to the time and the diagnostic suspicion, it should be noted that the diagnostic age of these patients is early, averaging 2.9 years old, and in most cases, the main motivation for specialist to study them was the presence of multiple appendicular fractures, unlike what is described in a retrospective study of 68 patients with OI, in which only 10% of patients had more than 2 fractures at the time of diagnosis[17]. This finding is relevant, considering that fractures (not only the vertebral fractures) have negative effects on the disease, as evidenced by a study carried out in a population of 35 patients with OI, where it is shown that any type of fracture, both in its acute form and in its chronic form, has repercussions on the quality of life of the patient and his family[18]. In addition, while this happens at a younger age, the behavior of patient is worse, as well as patient's cooperation (19). On the other hand, since OI type I has an autosomal dominant inheritance, with a good family medical record, diagnostic suspicion may be reached before recurrent fractures[3,10]. However, in our cohort, this referral cause belongs only to 6% of the cases, although there was one case of a parent affected by this disease among the 35% of patients, unlike the one described in one of the previously mentioned studies, in which the presence of family medical record reached 46% of the cases, which makes the diagnosis easier to perform[17].

Patients who presented VF at the time of diagnosis compared to those who did not, have the same clinical and laboratory characteristics, except for the nutritional status, with no significant difference regarding the age of the first vertebral fracture, which makes us think that the age of the first fracture is independent and not connected with the age of diagnosis. Those patients who were attended at the moment of diagnosis presenting a VF had more frequency of malnutrition than those who presented VF during monitoring and follow-up, which could mean that the latter were under medical control. Thirdly, regarding patient's medical records, comorbidities were described at during the disease's evolution in 20% of patients. Only one

patient presented hipoacusia, which is proved in literature, highlighting that hipoacusia is more common during adulthood.

In our cohort we did not find a link between a decrease in the value of bone densitometry of the spine with the presence of VF, although there are reports where it has been found this fact, being the densitometry a good fractures predictor[8]. We also did not find association between VF and parathormone levels, 25 (OH2) vitamin D and nutritional status. However, these kept in normal ranges throughout the disease evolution observed during study, so it was expected to find no significant differences[20,21]. The daily calcium intake of these patients[22] showed a decrease of 96% to 93% of the daily intake recommended by AAP, which, despite being a very slight difference, it was statistically significant at the time of VF. This emphasizes the need to keep a strict monitoring of nutritional indications in clinical controls.

There were no children who presented a disability to perform the regulatory physical activity, as described in the literature[15]. The quality and quantity of physical activity was evaluated globally and coarsely, so in future studies it would be recommended to use measurement scales to quantify it. The literature shows that there is an association between quality physical activity and better BMD[23]. Rehabilitation is a fundamental, as well as personalized process, depending on the needs of each patient. Follow-up studies of patients with all types of OI, show an increased self-care and better social function when they are part of a training plan[7], so it is recommended that patients with OI I should have a regular physical exercise plan[6].

Our study presents some limitations, which are important to consider, since it is a retrospective analysis, with a non-standardized record of variables. Thus, it is possible that unrecorded data could have been left in the historical record. Although it is a study carried out in a single center of reference, we consider that the sample of patients could represent the entire Chilean population, since the percentage of patients from different regions is concordant with the population in each region. We recommend creating a prospective and multicentral study, with an optimal record of clinical variables and standardized controls to patients' monitoring, including multidisciplinary evaluations according to the current treatment recommendations of these patients[7].

We can conclude that OI type I is an early diagnosis in our country, suspected mainly of multiple appendicular fractures, and it is associated with a high prevalence of vertebral fractures in infants who suffer from this disease, which may be associated with a decrease in the recommended calcium intake.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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References

1. Rauch F, Glorieux F. Osteogenesis imperfecta. Lancet 2004;363:1377-85.
2. Starr S, Roberts T, Fisher P. Osteogenesis imperfecta: Primary care. Pediatrics in Review 2010; 31;e54-64.
3. Forlino A, Cabral WA, Barnes AM, Marini JC. New perspectives on osteogenesis imperfecta. Nat Rev Endocrinol. 2011;7(9):540-57.
4. Van Dijk F, Cobben J, Kariminejad A, et al. Osteogenesis Imperfecta: A review with clinical examples. Mol Syndromol 2011;2:1-20.
5. Roughley P, Rauch F, Glorieux F. Osteogenesis imperfecta-Clinical and molecular 17 diversity. European Cells and Materials 2003;5:41-7.
6. Monti E, Mottes M, Fraschini P, et al. Current and emerging treatments for the management of osteogenesis imperfecta. Therapeutics and Clinical Risk Management 2010:6 367-81.
7. Biggin A. Munnus C. Osteogénesis Imperfecta: Diagnosis and treatment. Curr Osteoporos Rep 2014; 12:279-88.
8. Hernández M, Talesnik E, García C, Reyes M. Enfrentamiento clínico de la osteoporosis en el niño. Rev Chil Pediatr 2003;74(6):568-77.
9. Glorieux F. Experience With Bisphosphonates in Osteogenesis Imperfecta. Pediatrics 2007;119:S163-65.
10. Cundy T. Recent advances in osteogenesis imperfecta. Calcif Tissue Int 2012;90:439-49.
11. Dwan K, Philipi C, Steiner R, Basel D. Biphosphonate theraphy for osteogenesis imperfecta (review). Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD005088. DOI: 10.1002/14651858. CD005088.pub3.
12. Boyce A , Gafni R . Approach to the Child with Fractures. J Clin Endocrinol Metab 2011;96(7):1943-52.
13. Gutiérrez-Díez M, Molina M, Prieto L, Parra J, Bueno A. Osteogénesis Imperfecta: Nuevas perspectivas. Rev Esp Endocrinol Pediatr 2013;4(Suppl): 75-85.
14. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006.
15. Van Dijk F, Sillence D. Osteogenesis imperfecta: Clinical Diagnosis, Nomenclature and Severity Assesment. Am J Med Genet Part A 164A:1470-81.
16. Cons Molina F. La identificación de las fracturas vertebrales. Rev Metab Óseo Min 2004;2(1):127-36.
17. Spencer C, Donaruma-Kwoh M, Vettimattam M, Lobo C, Williard C, Mazur L. Fractures at diagnosis in infants and children with Osteogenesis imperfecta. J Pediatr Orthop. 2013;33(1): 32-6.
18. Zack P, Franck L, Devile C, Clarck C. Fracture and no Fracture pain in children with Osteogénesis Imperfecta. Acta Pædiatrica 2005;94:1238-42.
19. Engelbert R, Van deer Graaf Y, Van Empelen R, Beemer F, Helders P. Osteogenesis Imperfecta in childhood: Impairment and disability. Pediatrics 1997;99;e3.
20. Topor L, Melvin P, Giancaterino C, Gordon C. Factors associated with low bone density in patients refered for assesment of bone health. Int J Pediatr Endocrinol 2013;4.
21. Wisford L, Sullivan E, Mazur L. Risk factors for vitamin D deficiency in children with osteogenesis imperfecta. J Pediatr Orthop. 2013;33(5):575-9.
22. Greer F, Krebs N. Optimizing bone health and Calcium intakes of infants, childrens and adolescents. Pediatrics 2006;117:578-85.
23. Kok D, Sakkers R, Prujis H, Joosse P, Castelein R. Bone mineral density in developing children with Osteogenesis imperfecta. A longitudinal study with 9 years of follow up. Acta Orthopaedica 2013;84(4):431-6.