Bone Reports 8 (2018) 168–172

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

# Adults with osteogenesis imperfecta: Clinical characteristics of 151 patients with a focus on bisphosphonate use and bone density measurements

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ARTICLE INFO

*Keywords:*
Osteogenesis imperfecta
Adult
Expert center
Fractures
Bisphosphonates
Bone density

ABSTRACT

An expert center for adults with Osteogenesis Imperfecta (OI) has been founded at the Isala Hospital in Zwolle, the Netherlands to achieve optimal care for adults with OI. Clinical data such as patient history, Dual Energy X-ray Absorptiometry measurements and laboratory findings are collected with patient consent. This study provides an overview of clinical characteristics of the patients who visited the clinic during its first 5 years, a total of 151 patients. In this study, we focus on bisphosphonate use and bone density measurements at time of presentation at the expert center. As such, insight into the natural history of OI in adults will be increased. Analysing the data of a large group of adults with this rare disorder within a national expert center will allow detailed exploration of the course of OI over time.

## 1. Introduction

Osteogenesis Imperfecta (OI) is primarily characterized by liability to fractures, often accompanied by low bone mineral density (BMD) (Van Dijk et al., 2011). Secondary features that may be present are blue sclerae, dentinogenesis imperfecta (DI), hearing loss, ligamentous laxity and short stature. The birth prevalence of OI is estimated at 6–7 per 100,000 (Steiner et al., 2015). Approximately 90% of patients have dominant OI due to heterozygous pathogenic variants in the *COL1A1* or the *COL1A2* genes, that encode the α1-chains and α2-chain of collagen type I respectively (Sykes et al., 1990; Körkkö et al., 1998). Recently, rare recessive and X-linked variants have been reported to cause OI, the majority of which result in disturbed collagen type I biosynthesis (van Dijk and Sillence, 2014; Lindert et al., 2016).

In OI patients there are significant differences in severity (amount of bone fractures, bone deformation) and the presence of secondary clinical features. This clinical variability in OI has led to a classification in five types of OI (van Dijk and Sillence, 2014). Type 1 is the most frequent type of OI. People with OI type 1 rarely have congenital fractures but when they start to walk and consequently fall, fractures occur. They have an increased number of fractures, especially during childhood, usually without bone deformation. Blue sclerae are present and all other secondary features may also occur. OI type 2 is the perinatal lethal form with fractures showing as early as 14–16 weeks of gestation. In people with OI type 3, bone fractures are visible around 18 weeks of pregnancy, and after birth fracture frequency is very high, leading to severe deformationss of the skeleton. DI is observed in many cases. The severity in people with OI type 4 is variable. Type 4 can be progressive and deforming although typically not as deforming as in OI type 3. Type 5 is a rare subtype and characterized clinically by inability of pronation and supination due to uni-or bilateral calcification of the interosseous membrane between bones of the forearm. Furthermore, in type 5 increased callus formation is often observed (van Dijk and Sillence, 2014).

No cure for OI exists. Supportive management consists of orthopedic treatment, physical therapy, dental treatment and/or treatment for hearing loss. Calcium and vitamin-D supplements are considered useful supportive agents as they are vital in bone physiology (Clarke, 2008), and are often prescribed as they are well tolerated and inexpensive. Pharmacological treatment is also available for patients with OI, namely oral or intravenous bisphosphonates (BP). These medications inhibit bone turnover by decreasing osteoclast activity, therefore increasing overall bone mass, and providing greater skeletal strength (Glorieux et al., 1998). This treatment is often started in all types of OI

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https://doi.org/10.1016/j.bonr.2018.04.009
Received 19 September 2017; Received in revised form 16 April 2018; Accepted 23 April 2018
Available online 25 April 2018

patients as they frequently have significantly reduced bone density in at least one area of the skeleton.

A recent Cochrane systemic review concluded that bisphosphonates indeed increase BMD in children and adults with OI. It is still unclear whether they consistently decrease fractures, though multiple studies report this independently. The studies that were analyzed did not show that bisphosphonate treatment conclusively improves clinical status (reduce pain, improve growth and functional mobility) (Dwan et al., 2016). BP are the mainstay of care in children with moderately deforming to severe OI but may be less effective in adult patients with OI. Discussion exists as well on the long term side effects of BP's such as atypical femur fractures, osteonecrosis of the jaw (ONJ) and continuous suppression of bone turnover affecting linear growth in children (Marom et al., 2016).

The main limitation of bisphosphonate therapy is that BP are not aimed at the primary defect in OI: abnormal and/or decreased collagen type I production by osteoblasts. Other pharmacological therapies that are currently being investigated as treatment for OI include Denosumab (a RANKL inhibitor) and anabolic agents such as Teriparatide (recombinant form of parathyroid hormone), Cathepsin K inhibition, Growth hormone, Sclerostin-inhibitory antibodies and TGFβ inhibition (Marom et al., 2016).

To achieve optimal care for adult people with OI and increase insight into all aspects of this disorder, an expert center for adults with OI was founded in the Netherlands with strong support of the Dutch OI patient organization. Clinical data obtained as part of routine care, such as patient history, BMD measurements and laboratory findings have been stored, with patient consent, into an anonymized database. This study reports the clinical characteristics of 151 adult patients with OI with a focus on both current as previous bisphosphonate use and bone density measurements at time of visit.

## 2. Materials and methods

The results of this study are derived from the data of a large group of adults with OI that have been seen in clinic by the multidisciplinary team from the Isala Teaching Hospital, Zwolle, the largest non-university hospital in the Netherlands. In one day, patients are seen separately by members of the multidisciplinary team: the coordinator (an advanced nurse practitioner), orthopedic surgeon, internist-endocrinologist, rehabilitation physician, occupational therapist and clinical geneticist. Informed consent was obtained from the patients to retrieve and store clinical, radiological and laboratory data in a database. Data from the first visits of 151 patients ≥18 years with a clinically confirmed diagnosis of OI were included in this study. Data presented in this study are obtained from medical history as reported by the patient and regarding bisphosphonate use (which of the BP were used, time course of treatment, which dose of BP was used, and mode of administration) medical correspondence was also analyzed to confirm whenever possible. Furthermore, data were obtained based on physical (orthopedic) examination (height and weight are measured with standardized equipment), laboratory tests, radiographs, and DXA-scans.

### 2.1. Bone mineral density

Bone mineral density (BMD) was assessed by means of a DXA-scan (Discovery-A, Hologic). All analyses were performed at our clinic and the same scanner was used. BMD was measured at the lumbar spine (LS) L1 to L4 and at the proximal femur (PF) of the left leg. In an age-matched normal population sample, the coefficients of variation (CV) were 0.669% at the LS and 1.0% at the femoral neck. Data from severely deformed bones or implants in the measured region were excluded. When assessment of the left PF was not possible, the BMD at the right PF was measured, if possible. BMD is expressed in T (age specific)- and Z (age and sex-specific)-scores. To gain insight in the clinical status of the patient, BMD was categorized according to the International Society for Clinical Densitometry (Schousboe et al., 2013) and subsequently the WHO-osteoporosis classification (Organization WH, 1994).

### 2.2. Laboratory tests

The laboratory tests that were performed were part of routine care and were done by using standard laboratory techniques and included determination of: erythrocyte sedimentation rate, hemoglobin, leukocytes, creatinine, calcium, phosphate, alkaline phosphatase, y-glutamyl transferase, albumin, c-reactive protein, free T4, thyroid stimulating hormone, parathyroid hormone, telepeptide-C and 25-OH vitamin D levels.

### 2.3. Statistical analysis

Clinical characteristics and biochemical measurements are presented as the mean ± the standard deviation (SD) or as proportions (%). To investigate the difference in measured BMD (for T-scores and *Z*-scores separately) per OI type at the lumbar spine and proximal femur in individual patients, a paired *t*-test was used. The mean differences are presented as the mean with 95% confidence intervals (95%CI). To explore a difference in BMD among males and females, per OI type, an independent *t*-test was conducted, and mean differences are presented with 95%CI.

## 3. Results

### 3.1. Overview of clinical characteristics

Clinical characteristics of the study cohort are shown in Table 1. Most patients ($n = 107$) have been diagnosed with OI type 1, and most patients were female ($n = 100$). In type 1, 30/107 (28%) were male, in type 3 9/21 (43%) were male and 12/23 (52%) type 4 patients were male. The median age was 41 years for type 1 patients, 26 years for type 3 and 31 years for type 4. The oldest patients were 76 for type 1, 62 for type 3 and 63 years for type 4. Type 1 patients had a median height of 164 cm, this was 105 and 155 cm for type 3 and 4 respectively. Independent of age, most type 1 patients had sustained 0–15 fractures at time of presentation, the majority of type 3 patients had > 45 fractures when visiting our clinic. The amount of fractures sustained was more variable in type 4 patients: 39.2% had 0–15 fracture, whereas 26.1% had 36 or more fractures. Of the patients for whom data were available, all with type 1 had blue sclera. Dentinogenesis imperfecta was the most common among type 3 (67%) patients, followed by type 4 (31%), and was observed in 21% of those type 1 patients where this information was available.

### 3.2. BMD measurements

Table 2 shows the *Z*-scores of patients < 50 years and the T-scores for patients ≥50 years, per region of measurement according to the International Society for Clinical Densitometry. Independent of BP use, for type 1 patients the average *Z*-score ( ± SD) for the LS was −1.77 ± 1.08 for females aged < 50 compared with −2.86 ± 1.37 for males aged < 50 (mean difference 1.08, 95% CI 0.38 to 1.78). For the Z-score of the PF this was −0.93 ± 0.91 for the females aged < 50 and −1.55 ± 1.53 for the males < 50 (mean difference 0.61, 95%CI −0.17 to 1.21). For type 1 females aged ≥50 the average Z-score at the LS was −1.63 ± 1.2, and for the PF -0.84 ± 1.01. This was −2.12 ± 1.47 at the LS (mean difference 0.49, 95%CI −0.54 to 1.52) and − 0.55 ± 1.25 at the PF (mean difference − 0.29, 95%CI −1.2 to 0.62) for males with type 1 aged ≥50.

For type 1 patients, the mean T-score of the LS was 1.15 lower (95%CI −1.38 to −0.91, $p \leq 0.001$) compared to the T-score at the PF, in the same patient at the same time. This was −1.35 lower at the LS compared to the PF for type 4 patients (95%CI −2.35 to −0.35,