Acta Orthop. Belg., 2022, **88**, 255-262

ORIGINAL STUDY

doi.org/ 10.52628/88.2.9117

Quantitative gait analysis in children with osteogenesis imperfecta: relationship between gait deviations and clinical features

Solange De Wouters, Christine Detrembleur, Anne Durnez, Philippe Mahaudens, Brice Henry, Jean Schrooyen, Pierre-Louis Docquier

From the Cliniques universitaires Saint-Luc, Brussels, Belgium

Osteogenesis imperfecta is a rare congenital disease of connective tissue characterized by recurrent fractures and progressive skeletal deformities which may impact on gait. The aims of this prospective study were to identify gait deviations in children with osteogenesis imperfecta compared to age-matched controls and establish relationships with clinical features.

We evaluated 22 patients with different types of osteogenesis imperfecta using three-dimensional gait analysis. The incidence and location of fractures, fracture at birth, age at first fracture, use of intramedullary rodding and number of surgical interventions in the lower extremities, bone mineral density, hypermobility and number of injections of bisphosphonates were recorded for each patient.

Step length was lower in the osteogenesis imperfecta group compared with the control group. Kinematics showed that sagittal pelvic and transversal hip range of motion were higher in the osteogenesis imperfecta group, whereas sagittal knee range of motion during swing phase was reduced. Regarding kinetics, hip flexion moment and hip negative power peak were significantly decreased in the osteogenesis imperfecta group. Mechanical and energetic parameters were considered as normal. The principal component analysis revealed that the bone mineral density was increased in children who had received more injections of bisphosphonates and these had also less deficit in kinematic parameters.

Main modifications in gait parameters were observed in spatiotemporal, kinematic and kinetic data. More studies are necessary to allow stratification of severity of the osteogenesis imperfecta disease, help improve its challenging multidisciplinary treatment and objectively assess treatment outcomes.

Keywords: Osteogenesis imperfecta; instrumented gait analysis; bisphosphonates; gait biomechanical deviations.

■ Solange De Wouters[1], MD,
■ Christine Detrembleur[2], PhD,
■ Anne Durnez[3], MD, PhD,
■ Philippe Mahaudens[2], PhD,
■ Brice Henry[4], MD,
■ Jean Schrooyen[1], MD,
■ Pierre-Louis Docquier[1,2], MD, PhD.

[1,1]*Cliniques universitaires Saint-Luc, Service d'orthopédie et de traumatologie de l'appareil locomoteur, Avenue Hippocrate 10, 1200 Brussels, Belgium.*

[2]*Université catholique de Louvain, Secteur des Sciences de la Santé, Institut de Recherche Expérimentale et Clinique, Neuro Musculo Skeletal Lab (NMSK), Avenue Mounier 53, 1200 Brussels, Belgium.*

[3]*Cliniques universitaires Saint-Luc, Service de rhumatologie, Avenue Hippocrate 10, 1200 Brussels, Belgium.*

[4]*Hôpital Femme Mère Enfant, Service d'orthopédie et traumatologie pédiatrique, Boulevard Pinel 59, 69500 Bron, France.*

Correspondence : Solange De Wouters, MD, Department of Orthopaedic Surgery, Cliniques universitaires Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium.

Email : solange.dewouters@uclouvain.be

No benefits or funds were received in support of this study.
None of the authors have a conflict of interest.

INTRODUCTION

Osteogenesis imperfecta (OI) is a congenital disease of connective tissue most often due to a dominant mutation of the type I collagen gene *(1)*. The estimated prevalence of OI is approximately 1 in 5,000 to 10,000 live births *(2)*. Autosomal dominant is the most common pattern of inheritance *(2)*.

This disorder, characterized by a highly variable clinical expression, results in hypermobility, decreased bone mineral density (BMD), recurrent fractures throughout life and progressive skeletal deformities, which may lead to functional limitations and impact on gait *(3-5)*.

The main treatment strategies of OI consist in rehabilitation programs, physiotherapy, bracing and orthopaedic surgery. Medical treatment with intravenous cyclical bisphosphonates has been an additional treatment opportunity *(6-8)*.

There is limited knowledge about the ambulatory characteristics of OI patients. Functional limitations were described in several studies *(3,4,9-11)* using mobility metrics such as Gillette Functional Assessment Questionnaire (FAQ) *(9,10)*, Functional Mobility Scale (FMS) *(9)*, distance walked in the 6-minute walk test (6MWT) *(9)*, Pediatric Outcomes Data Collection Instrument (PODCI) *(10)*, muscle strength *(3,4,11)* or level of ambulation according to Land *(11)*.

Three-dimensional gait analysis (3DGA) is a powerful tool for providing objective quantitative information on gait pathology permitting the better understanding of abnormal gait patterns. To date, 3DGA has been widely used to give a comprehensive description of gait deviations among several orthopaedic conditions *(12-18)*. In their multicenter study, Kruger et al. *(9)* said, as a conclusion, that results from 3DGA were vital to understanding the mobility limitations of OI and that such data could inform clinicians about specific gait deviations in this population, allowing clinicians to recommend more focused interventions.

To our knowledge, only two studies *(19,20)* in the literature analyzed gait quantitatively, respectively in 10 and 44 OI patients, only in type I cases.

The aims of this prospective study were to identify gait biomechanical deviations in children with OI compared to age-matched controls in order to improve the current knowledge of gait deviations in different types of OI patients, and establish relationships with clinical features.

MATERIALS AND METHODS

Of the 71 patients with OI treated in our hospital, 40 were followed in our pediatric orthopaedic department. Of those, 35 were ambulatory and were asked to join the study between August 2015 and September 2018. Twenty-two OI patients agreed to participate (mean age 11 years, range 3-21 years). The second group consisted of 25 healthy participants (mean age 11 years, range 2.8-21.8 years) with comparable demographic data (Table 1).

The OI patient group was phenotypically divided into five types (I-V) according to the classification proposed by Sillence et al. *(1)*. Thirteen children had type I disease, three type III, five type IV and one type V.

All subjects were able to walk independently. Children with restricted ambulation were excluded, as well as children who experienced a fracture or underwent a surgical intervention in the three months before the study, considered as the delay needed to recover and be pain free.

The Institutional Review Board (Cliniques Universitaires Saint-Luc, Brussels, Belgium) approved the study and parents of each child provided their informed written consent prior to participation. Our study was registered at ClinicalTrials.gov, Number NCT00825097.

Table 1. — Demographic data of the participants

Variable	**Control group** mean (SD) (n = 25)	**OI group** mean (SD) (n = 22)
Age, years	11 (6.1)	11 (4.8)
Weight, kg	36.25 (16.26)	34.5 (19.9)
Height, m	1.39 (0.26)	1.32 (0.26)
BMI, kg m^{-2}	17.2 (2.6)	18.2 (4.2)

OI indicates osteogenesis imperfecta; SD, standard deviation; BMI, body mass index.

Each patient was measured, weighed and the body mass index (BMI) was calculated. Hypermobility was assessed using the Beighton scale *(21)*. A score of 5/9 or greater defines hypermobility *(21)*. The incidence and location of fractures, fracture at birth, age at first fracture, the use of intramedullary rodding in the lower extremities and number of surgical interventions in the lower extremities were recorded.

Dual energy x-ray absorptiometry (DXA) was performed as a non-invasive method of bone quantity assessment in the anterior-posterior direction at the lumbar spine (L1-L4), femoral neck, total hip and whole body, using a Hologic Horizon A (S/N 200180) device. BMD results were expressed in Z-scores and compared with age-matched values from reference data provide by the National Health and Nutrition Examination Survey (NHANES) reference population data for White men and White women. Treatment with bisphosphonates was started according to following indications: presence of two or more prevalent vertebral fractures; presence of one prevalent vertebral fracture plus at least one peripheral fracture in the last two years; or at least three fractures in the last two years. All children had vitamin D and calcium supplementation if needed according to the recommended daily intake.

Each patient underwent 3DGA at our instrumented gait lab following the protocol described in detail by Stoquart et al. *(12)*, including spatiotemporal, kinematic, kinetic, energetic and mechanical assessments.

Each patient was equipped with 20 passive reflective spherical markers positioned on specific anatomical landmarks, following the International Society of Biomechanics protocol. Data from landmarks were collected with eight infra-red cameras motion capture (Elite, BTSbioengineering, Milan, Italy) at a sampling rate of 200 Hz, while participants walked at a self-selected speed on a force-measuring motor-driven treadmill (Mercury LTmed, HP-Cosmos, Nussdorf-Traunstein, Germany) during 40 s for 10 successive strides. Ground reaction forces were recorded by four strain gauges located under each corner of the treadmill. The metabolic energy cost of walking was determined by the patient's oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Patients were fitted with a nasal mask connected to a portable ergospirometer (Ergocard®, Medisoft, Sorinnes, Belgium).

For each subject, range of motion (RoM) defined as peak-to-peak amplitude were calculated for the pelvis, hip, knee and ankle in the three planes (sagittal, frontal, transverse). We used RoM (rather than maximum and minimum values) because of its high reproducibility *(14)*. Moments and power parameters were calculated as described in Stoquart et al. *(22)*. The total mechanical work (Wtot) performed by the muscles during walking was calculated by the sum of the external work (Wext) (performed to move the center of body mass (CoMb) relative to the surroundings) and the internal work (Wint) (performed to move the body segments relative to the CoMb) as described in Marconi et al *(23)*. Recovery, quantifying the percent of mechanical energy saved by a pendulum-like exchange between potential and kinetic energy of the CoMb was also calculated as described in Marconi et al. *(23)*. The energy expended during walking above the standing value was divided by the walking speed to obtain the net energy cost of walking.

In order to limit the influence of age and walking speed, gait parameters were normalized in Z-scores as described in Detrembleur et al. *(15)*. Patients' gait parameters were compared to the reference value of 0 Z-score using a simple *t*-student test. Only gait parameters superior to 1.5 Z-score were arbitrary selected to the next step for statistical analysis as described in Henry et al. *(16)*.

The statistical structure highlighting the relationships between gait deviations and clinical features was described by a principal component analysis (PCA) *(24)*. The principal components (PCs) were computed by pooling together all the parameters in order to reduce the dimensionality of the dataset and identify the highest relationships between variables. Only factor loadings with a threshold value of 0.6 (considered as significantly associated with PC axis) were used. The five first PCs were retained, explaining more than 77.09% of variance.

All statistical analyses were performed using SigmaPlot software 13.0 from SPSS.

RESULTS

Anthropometric data of the OI patients are represented in Table 2. Review of medical records indicated that five patients presented a fracture at birth. Only two patients didn't sustain any fracture in the lower extremities. Seven patients had their first fracture during the first six months of life. Eleven patients had no prior surgeries in the lower extremities and nine underwent intramedullary

Table 2. — Clinical features of participants with osteogenesis imperfecta according to type

Variable	Total	Type I	Type III	Type IV	Type V
n (%)	22 (100)	13 (59)	3 (14)	5 (23)	1 (4)
Gender, male/female	11/11	4/9	2/1	5/0	0/1
Median age, years	11 (3-21)	10 (3-21)	8 (5-10)	13 (7-18)	16 (16)
Median weight, kg	34.9 (11.5-85.5)	33.3 (11.5-85.5)	19.5 (17-23.5)	45.8 (31.3-53)	58.4 (58.4)
Median height, m	1.32 (0.91-1.74)	1.27 (0.91-1.73)	1.11 (0.98-1.22)	1.62 (1.36-1.74)	1.57 (1.57)
Median BMI, kg m^{-2}	18.18 (12.59-28.7)	18.5 (12.59-28.7)	15.87 (14.02-17.9)	17.47 (17.1-18)	23.84 (23.84)
Fracture at birth, n (%)	5 (23)	1 (8)	3 (100)	0	1 (100)
Age at first fracture, n (%), months					
0-6	7 (32)	3 (23)	3 (100)	0	1 (100)
7-12	4 (18)	4 (31)	0	0	0
13-36	5 (23)	3 (23)	0	2 (40)	0
> 37	6 (27)	3 (23)	0	3 (60)	0
Number of fractures in lower limb, n (%)					
0	2 (9)	2 (16)	0	0	0
1	3 (15)	1 (8)	0	2 (40)	0
2	4 (18)	4 (30)	0	0	0
3	2 (9)	1 (8)	0	1 (20)	0
4-9	10 (45)	4 (30)	3 (100)	2 (40)	1 (100)
> 10	1 (4)	1 (8)	0	0	0
Number of surgeries in lower limb, n (%)					
0	11 (50)	8 (62)	0	3 (60)	0
1	3 (14)	2 (15)	1 (33)	0	0
2	1 (4)	1 (8)	0	0	0
3	3 (14)	2 (15)	0	1 (20)	0
> 4	4 (18)	0	2 (67)	1 (20)	1 (100)
Intramedullary rod in lower limb, n (%)	9 (41)	4 (30)	3 (100)	1 (20)	1 (100)
Bisphosphonates injections, n (%)					
0	5 (23)	5 (38)	0	0	0
1-5	5 (23)	2 (16)	0	3 (60)	0
6-10	8 (36)	4 (30)	2 (67)	2 (40)	0
11-15	2 (9)	0	1 (33)	0	1 (100)
> 16	2 (9)	2 (16)	0	0	0
Hypermobility, n (%)	11 (50)	4 (30)	2 (67)	5 (100)	0

BMI indicates body mass index. Number of fractures in lower limb indicates the number of femoral or tibial fractures since birth. Number of surgeries in lower limb indicates the number of femoral or tibial surgeries since birth (intramedullary rod, redo and/or removal). Intramedullary rod in lower limb indicates the presence of a femoral and/or tibial nail (bilateral or not). Hypermobility was assessed using the Beighton scale[9]: a score of 5/9 or greater defines hypermobility.

Table 3. — Spatiotemporal, kinematic, kinetic, mechanic and energetic parameters of patients with osteogenesis imperfecta expressed in absolute and Z-scores

	Absolute data Mean [range]	Normalized data in Z-score Mean [range] / ± SD
Spatiotemporal parameters		
Stance phase (%)	65.29 [64.04; 66.97]	-0.85 [-1.45; -0.43]
Cadence (step min^{-1})	120.28 [113.34; 136.93]	1.24 [0.28; 2.53]
Step length (m)	**0.48 [0.39; 0.56]**	**-2.04 ± 0.92**
Segmental kinematic variables		
Frontal pelvic motion (°)	5.16 [3.58; 8.43]	0.95 [-1.85; 7.46]
Sagittal pelvic motion (°)	**3.59 [2.94; 4.96]**	**1.88 [0.2; 4.39]**
Transversal pelvic motion (°)	6.97 [4.78; 10.96]	0.32 [-0.81; 5.21]
Frontal hip motion (°)	7.47 [4.98; 9.71]	-0.89 [-3.56; 1.42]
Sagittal hip motion (°)	36.99 [31.51; 42.11]	-0.62 [-4.58; 4.57]
Transversal hip motion (°)	**13.79 [8.76; 19.27]**	**11.65 [1.41; 27.45]**
Sagittal knee motion (°) « Swing »	**48.94 [42.16; 55.16]**	**-1.75 [-4.63; 4.56]**
Sagittal knee motion in stance phase (°)	9.04 [5.45; 12.71]	-0.69 [-4.4; 2.44]
Sagittal ankle motion (°)	20.89 [17.14; 24.12]	0.05 [-1.4; 1.83]
Transversal ankle motion (°)	10.51 [8.04; 13.87]	0.54 [-1.47; 7.91]
Kinetics		
Hip extension moment (N m kg^{-1})	0.46 [0.3; 0.71]	1.18 ± 1.9
Hip flexion moment (N m kg^{-1})	**-0.47 [-0.65; -0.23]**	**-3.24 [-5.18; -1.08]**
Hip positive power peak (W kg^{-1})	0.58 [0.29; 0.98]	1.2 [0.31; 3.74]
Hip negative power peak (W kg^{-1})	**-0.34 [-0.56; -0.18]**	**-1.86 [-5.1; -0.81]**
Knee extension moment (N m kg^{-1})	0.55 [0.34; 0.67]	-0.62 ± 2.46
Knee negative power peak (W kg^{-1})	-1.22 [-1.88; -0.66]	-0.74 ± 3.13
Ankle plantar flexion moment (N m kg^{-1})	0.65 [0.5; 0.87]	-0.35 [-1.13; 0.45]
Ankle positive power peak (W kg^{-1})	1.02 [0.56; 1.89]	-0.95 [-1.65; -0.27]
Ankle negative power peak (W kg^{-1})	-0.19 [-0.41; -0.12]	-0.43 [-1.09; 0.18]
Mechanics		
W_{ext} (J $kg\ m^{-1}$)	0.28 [0.25; 0.35]	0.4 [-0.3; 1.44]
W_{int} (J $kg\ m^{-1}$)	0.26 [0.23; 0.31]	0.87 ± 2.27
W_{tot} (J $kg\ m^{-1}$)	0.58 [0.51; 0.61]	0.73 [-0.89; 1.98]
Rendement (%)	20.35 [15.15; 25.45]	-0.4 ± 1.01
Recovery (%)	51.1 [32.4; 61.77]	-0.29 [-3.9; 0.08]
Energetics		
Energy cost (J $kg\ m^{-1}$)	2.77 [2.1; 3.96]	0.24 [-0.88; 0.98]

Bold: values superior to 1.5 Z-score. W, indicates work; ext, external; int, internal; OI, osteogenesis imperfecta.

rodding in the lower extremities before the study. Seventeen patients were receiving intravenous cyclical bisphosphonates during the time of testing; five patients had between one and five injections; eight patients had between six and 10 injections; two patients had between 11 and 15 injections; and two patients had more than 16 injections. Hypermobility was present in 11 subjects.

Gait parameters and gait parameters expressed in Z-scores are summarized in Table 3. Step length was lower in the OI group compared with the control group (-2.04 Z-score). Stance phase and cadence were inferior to 1.5 Z-score. Kinematic parameters showed that sagittal pelvic RoM and transversal hip RoM were higher in the OI group when compared with reference values, whereas sagittal knee RoM during swing phase was reduced in patients with OI compared with the control group. Regarding the kinetic parameters, hip flexion moment and hip negative power peak were significantly decreased in

Table 4. — Results of principal component analysis (PCA) highlighting the relationships between gait deviations and clinical features with 77.09% of variance

	PC 1	PC 2	PC 3	PC 4	PC 5
OI type	-0.126	-0.334	**0.77**	0.152	0.449
Age at first fracture	**-0.643**	-0.0945	0.252	-0.0225	0.25
Number of fractures (femur)	**0.809**	-0.248	0.112	0.144	0.00996
BMD (total hip)	-0.407	**0.675**	0.304	-0.184	-0.194
Intramedullary nailing	**0.849**	0.0986	0.136	-0.308	0.0122
Hypermobility	-0.25	-0.382	**0.77**	0.0693	-0.212
Number of surgeries	**0.888**	0.0138	0.0893	-0.2	-0.0205
Bisphosphonates therapy	0.19	**0.603**	0.575	-0.128	-0.209
Step length	0.284	**0.707**	0.283	-0.321	0.168
Sagittal pelvic motion	0.439	-0.438	0.15	0.423	-0.0784
Transversal hip motion	0.0742	**0.603**	0.126	0.615	-0.262
Sagittal knee motion «Swing»	-0.141	**0.7**	-0.226	0.171	0.118
Hip flexion moment	0.212	0.31	0.00183	**0.767**	0.041
Hip negative power peak	0.158	0.297	-0.0494	0.0967	**0.876**

Bold: factor loadings superior to 0.6 and considered significantly associated with principal component axis. OI indicates osteogenesis imperfecta; PC, principal component; BMD, bone mineral density.

the OI group compared with typically developing group. Mechanical and energetic parameters were inferior to 1.5 Z-score, indicating no abnormalities.

The orthogonal solution of PCA allowed the determination of five axes (Table 4). The first axis (PC1) meant that a child who had a first fracture at a very young age had more femur fractures, more intramedullary nail and more fractures in total. The second axis (PC2) revealed that the BMD was increased in children who had received more injections of bisphosphonates. It also showed less deficit in kinematic parameters. The third axis (PC3) demonstrated that the more the OI type was high (not related to severity), the more hypermobility was present. The fourth axis (PC4) explained only the hip moment and the fifth axis (PC5), the muscular power.

DISCUSSION

The aims of this prospective study were to identify gait deviations with 3DGA in 22 ambulatory children with different types of OI and establish relationships with clinical features.

All parameters were compared with reference values from our lab norms which have been established by performing 3DGA in 25 healthy patients at different walking speed (one to six km h^{-1} on treadmill) using the same instrumentation as the current study (Table 1).

Regarding to gait parameters (Table 3), we observed that mechanical and energetic variables were close to normal. Modifications were observed for spatiotemporal parameters with a decreased step length. Kinematics exhibited an increase of sagittal pelvic RoM and transversal hip RoM whereas a decrease of sagittal knee RoM was demonstrated. Kinetic variables showed modifications with decreased hip flexion moment and hip negative power peak. Our results were in line with Graf et al. *(19)* and Garman et al. *(20)*. These authors also described a lower step length, a higher transversal hip RoM and a lower hip flexion moment in the OI group compared with controls. The knee extension moment, the plantar flexion moment and the ankle power peak were decreased in our study too, but less than 1 Z-score. These authors analyzed gait during overground walking while we used

a treadmill walking. Nevertheless, as treadmill gait is qualitatively and quantitatively similar to overground gait liked stated by Riley et al. *(25)* and Watt et al. *(26)*,the comparison is possible.

In our study, mechanical and energetic variables, which are indicators of the efficiency of gait activity, remained normal in the OI group. This could mean that OI patients developed adaptive gait strategies to limit their energetic cost during walking. Wallard et al. *(14)* performed 3DGA in 63 hip osteoarthritis patients and 72 healthy subjects. Their results displayed significant differences in all biomechanical parameters between the groups, except for the energetic cost which remained normal in the hip osteoarthritis group. The authors explained that this could correspond to a law of optimization of the resources of the system which implies an adapted regulation of the muscular forces in order to move.

OI is characterized by a decreased BMD *(1)*. Studies demonstrated that bisphosphonates therapy was effective in OI patient with increased BMD, decreased occurrence of fractures and relief from chronic bone pain *(6-7)*. In the study of Sakkers et al. *(8)*, they performed a randomized, placebo-controlled, clinical trial on the use of bisphosphonates in OI children and found that, although BMD increased, no beneficial effects on functional ability and level of ambulation were found. Our results contrariwise revealed that the number of injections of bisphosphonates was associated not only with higher BMD but also with a decrease of kinematic deviations.

Our results revealed no significant association between kinetic deviations and clinical data or OI type. We didn't find any relationship between hypermobility and gait impairment. Hypermobility is frequent in OI *(4)* and our results showed that hypermobility was more frequent in type IV-OI. Finally, we found a relationship between the age at first fracture and the need for surgery. Scoliosis was not reported because there is no correlation between gait deviations and the severity of scoliosis *(17,18)*.

Our main limitation is the small sample size of the OI group due to recruitment difficulties because of the low prevalence of the disease. Second, there is an inherent selection bias towards ambulatory OI patients based on excluding those using assistive devices for walking. Moreover, regarding to gait parameters, we had to combine all types of OI together rather than stratifying them by type due to the small data set divided into four strata types. Future research with a large number of patients stratified by type should provide quantitative comparison of specific type of OI gait with age-matched controls. Finally, the variance of the PCA was 77.09%, which means that 22.91% of variance was not explained by our results.

These findings providing a comprehensive description of gait deviations in different types of ambulatory OI patients may help clinicians to better understand the impact of OI on gait. More studies are necessary to allow stratification of severity of the OI disease, help improve its challenging multidisciplinary treatment by developing more focused individual-based rehabilitation strategies and objectively assess orthopaedic or surgical treatment outcomes.

REFERENCES

1. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. Am J Med Genet. 2014;164A(6):1470-1481.
2. Byers PH, Steiner RD. Osteogenesis imperfecta. Annu Rev Med. 1992;43:269-282.
3. Takken T, Terlingen HC, Helders PJ, Pruijs H, Van der Ent CK, Engelbert RH. Cardiopulmonary fitness and muscle strength in patients with osteogenesis imperfecta type I. J Pediatr. 2004;145(6):813-818.
4. Engelbert RH, Uiterwaal CS, Gerver WJ, van der Net JJ, Pruijs HE, Helders PJ. Osteogenesis imperfecta in childhood: impairment and disability. A prospective study with 4-year follow-up. Arch Phys Med Rehabil. 2004;85(5):772-778.
5. Hill CL, Baird WO, Walters SJ. Quality of life in children and adolescents with osteogenesis imperfecta: a qualitative interview based study. Health Qual Life Outcomes. 2014;12:54.
6. De Graaff F, Verra W, Pruijs JE, Sakkers RJ. Decrease in outpatient department visits and operative interventions due to bisphosphonates in children with osteogenesis imperfecta. J Child Orthop. 2011;5(2):121-125.
7. Land C, Rauch F, Montpetit K, Ruck-Gibis J, Glorieux FH. Effect of intravenous pamidronate therapy on functional abilities and level of ambulation in children with osteogenesis imperfecta. J Pediatr. 2006;148(4):456-460.

8. Sakkers R, Kok D, Engelbert R, van Dongen A et al. Skeletal effects and functional outcome with olpadronate in children with osteogenesis imperfecta: a 2-year randomised placebo-controlled study. Lancet. 2004;363(9419):1427-1431.
9. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet. 1998;77(1): 31-37.
10. Stoquart GG, Detrembleur C, Palumbo S, Deltombe T, Lejeune TM. Effect of botulinum toxin injection in the rectus femoris on stiff-knee gait in people with stroke: a prospective observational study. Arch Phys Med Rehabil. 2008;89(1):56-61.
11. Marconi V, Hachez H, Renders A, Docquier PL, Detrembleur C. Mechanical work and energy consumption in children with cerebral palsy after single-event multilevel surgery. Gait Posture. 2014;40(4):633-639.
12. Graf A, Hassani S, Krzak J, Caudill A, Flanagan A, Bajorunaite R, et al. Gait characteristics and functional assessment of children with type I osteogenesis imperfecta. J Orthop Res. 2009;27(9):1182-1190.
13. Garman CR, Graf A, Krzak J, Caudill A, Smith P, Harris G. Gait deviations in children with osteogenesis imperfecta type I. J Pediatr Orthop. 2019;39(8):e641-e646.
14. Wallard L, Boulet S, Cornu O et al. Intersegmental kinematics coordination in unilateral peripheral and central origin: effect on gait mechanism? Gait Posture. 2018; 62:124-131.