Exercise in osteogenesis imperfecta

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ABSTRACT

Osteogenesis imperfecta (OI) is a genetic disorder of the connective tissue, characterized by bone fragility and low bone density, with a broad spectrum of clinical expression. Oriented physical exercise is recognized as a relevant conservative treatment option. **Objective:** To gather and systematize knowledge related to physical fitness testing, choosing exercises, load progression, and training systematization for persons with OI. **Method:** Databases from SciELO, LILACS, MedLine, Scopus, PubMed, Web of Science, PEDro and the Cochrane BVS were searched. Two independent reviewers selected the eligible studies. All randomized controlled clinical trials, transversal exploratory studies, case reports, and experience reports that described physical exercise intervention and physical fitness testing; general rules for physical activity and reported physical activity effects were included. **Results:** The electronic search yielded a total of 961 references published in English, Portuguese, French, and German. After analyzing previously established inclusion criteria, 9 studies were included, only two of which were controlled clinical trials. All the recommendations and conclusions found were oriented toward children, since all the studies had this population as a target. Only two studies included samples of adolescents up to the age of 12 years. OI types I and IV were investigated and some of the recommendations were extended to the other types of OI. Swimming is the exercise recommended most often. Strengthening exercises, with a slow addition of weight were also recommended, as well as aerobic exercises on bicycles, stationary or not. There are some special considerations in handling and treatment for this public that should be taken to avoid trauma. **Conclusion:** It was possible to obtain some systematization and orientation to conduct conservative treatment interventions with a physical exercise program; however, evidence to support any prescribed exercise and training development for persons with OI is still scarce. **Keywords:** Osteogenesis Imperfecta, Exercise, Review Literature as Topic

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INTRODUCTION

Osteogenesis Imperfecta (OI), also known as Lobstein’s disease, is one of the most common genetic disorders,1 with an incidence estimated in 1:20,000 to 1:25,000 births around the world.2 In Brazil, there are no epidemiological studies about OI, but it is estimated that approximately 12,000 Brazilians live with Osteogenesis Imperfecta.3

Osteogenesis Imperfecta is a genetic disorder characterized by a qualitative and/or quantitative deficiency in the synthesis of collagen type I. About 90% of the patients carry an autosomal dominant inheritance caused by mutations in the genes that codify the COL1A1 and COL1A2 chains.4 Recently, seven other variations of OI have been described, from V to XI, in which the mutations were not found on those genes.5,6

The phenotypical manifestation of OI is quite varied.7 Skeletal clinical characteristics of OI include bone fragility, low bone density, and the presence of Wormian bones in the cranium.8 The blue or grayish sclera, the dentinogenesis imperfecta, hyperlax ligaments and hypermobility of joints, cutis laxa, low height, and auditory deficiency are clinical exoskeletal characteristics commonly observed.9 Less common, but also important, is the occurrence of mitral valve prolapse, aortic stenosis, and aortic dilatation.10

The Sillence classification has been used to categorize OI, considering clinical, genetic, and radiological criteria in up to 4 types: I, II, III, and IV. Types I and IV are those with the best prognoses, with type I affecting approximately 50% of the population with osteogenesis imperfecta. Types II and III are the most severe forms of osteogenesis imperfecta, characterized by severe bone deformities and very short life expectancy, when there is no death in the neonatal period. Recently, seven other types of osteogenesis imperfecta have been identified, with the types V and VI clinically similar to type IV—however, type V has unknown causes and type VI is caused by an alteration in the SERPINF1 gene. Types VII, VII, IX, X, and XI are severe types of osteogenesis imperfecta caused by recessive autonomic mutations in the CRTAP, LEPRE1, PPIB, SERPINH1, and FKBPIC genes, respectively5,6 (Table 1).

The current options for the treatment of OI are not efficacious in curing this disease.12 The treatment of OI then seeks to reach maximum levels of mobility, independence for daily life activities, and social integration, in addition to minimizing the occurrence of fractures and the occurrence of deformities in the upper and lower limbs.1,2,3

In this context, the practice of supervised physical exercise is an important therapeutic resource, even if its effect has not been confirmed in the course of the OI per se. It is noteworthy that the OI is not a disease that precludes the practice of physical exercise, for there are reports in the literature of athletes with OI, such as a weight lifter,14 an American football player,15 and an Olympic rowing champion.16 In the conservative treatment of OI for adults and children, physical exercise can aid in the increase of muscular strength and improvement of cardiovascular conditioning,8 which can help maintain mobility and prevent comorbidities, especially those of the cardiorespiratory system.17

Despite the recognition of these potential benefits and that OI is not an absolute obstacle for the practice of physical exercise, very little has been written on this subject.

OBJECTIVE

The objective of this review was to collect and systematize the knowledge referring to physical evaluation, indication of exercises, load progression, and systematics of training for people with osteogenesis imperfecta.

METHOD

Data search

The databases of SciELO, LILACS, MedLine, Scopus, PubMed, Web of Science, PEDro, and Cochrane BVS were used to search for articles, with no limit on dates. The keywords “osteogenesis imperfecta” and “Lobstein’s disease” were combined with the Boolean operator AND with the following keywords: “exercise,” “exercise program,” “physical activity,” “sport,” “physical training”, “exercise therapy,” “physical rehabilitation,” and “physical education.” In the search, articles in Portuguese, English, French, and Spanish were considered.

Inclusion criteria

Randomized clinical studies, transversal exploratory studies, clinical case reports, and experience reports in which there was a description of physical exercises used and/or tests used in physical evaluations were included.

Studies made with both genders of children, adolescents, adults, and the elderly diagnosed with any type of OI were eligible.

Studies that investigated or compared the interventions made in a hospital environment, in adapted physical activity programs, or in multidisciplinary rehabilitation programs that involved physical exercises were selected. Transversal studies that investigated appropriate tests for the physical evaluation of patients with OI, performed in a hospital environment, in adapted physical activity programs, or in multidisciplinary rehabilitation programs were also selected.

Studies that described the physical exercises and the physical evaluation tests used, that described load progression, that identified types of appropriate exercise for the population or that described general care in the handling of the patient with OI during the practice of physical exercise were listed.

Table 1. Classifications of the OI types5,6

| Type of OI | Inheritance | Sev. | Gene where the mutation is located |
|-----------|-------------|------|-----------------------------------|
| I         | Autosomal dominant | Slight | COL1A1 |
| II        | Autosomal dominant | Severe, potentially lethal | COL1A1 or COL1A2 |
| III       | Autosomal dominant | Becomes severe by progressive deformation | COL1A1 or COL1A2 |
| IV        | Autosomal dominant | Moderate | COL1A1 or COL1A2 |
| V         | Autosomal dominant | Moderate | Unknown |
| VI        | Autosomal recessive | Moderate | SERPINF1 |
| VII       | Autosomal recessive | Severe to lethal | CRTAP |
| VIII      | Autosomal recessive | Severe to lethal | LEPRE1 |
| IX        | Autosomal recessive | Moderate to lethal | PPIB |
| X         | Autosomal recessive | Severe to lethal | SERPINH1 |
| XI        | (Bruck syndrome I) | Autosomal recessive | Becomes severe by progressive deformation | FKBP10 |
Selection system for the articles

Two independent researchers selected the eligible studies, identifying them by title and eliminating those that clearly were not related to the central theme of the review. After that, all the abstracts of the articles selected were analyzed in accordance with the inclusion criteria previously established for this study. In the third stage of identification of the relevant works, complete texts of the articles selected were read and analyzed, also in accordance with the inclusion criteria. In this stage, the references of the articles selected for a complete reading were also analyzed so as to identify any relevant work that might not have been identified in the electronic search. At the end of the independent selection, the researchers compared their lists and found only one divergence, which was solved by consensus. Finally, the list of works for the review was established.

All the articles selected were analyzed and organized by category, according to the type of information they contained: (1) physical evaluation, (2) types of physical exercises recommended, (3) training protocols, (4) general recommendations in the handling during the physical exercise, and (5) effects of physical exercise done regularly. These categories are shown in the results section.

RESULTS

The bibliographic research was done including the titles published until July of 2013. The electronic search resulted in a total of 961 references. The final selection was defined through consensus between both researchers and resulted in nine studies (Figure 1): a randomized clinical study, a non-randomized clinical study, a transversal study, a case report, and the remaining were experience reports.

It is noteworthy that, in accordance with the PEDro criteria, the randomized clinical study can be considered as of good quality, reaching grade 8. Among all the studies identified, only two had conclusions and recommendations specific to adolescents and children, while all the other studies were directed exclusively to children. Table 2 summarizes the main information referring to the studies included in this review.

The application of the physical evaluation before any physical activity and in the monitoring of the physical exercises program is a practice inherent to any physical training program, in order to guarantee the safety and effectiveness of the work.20

In a transversal design, Takken et al.19 evaluated the muscular strength and the cardiorespiratory conditioning of 17 patients with OI type I. For the strength evaluation, the isometric strength of the shoulder abductors, hip flexors, dorsal flexor of the ankle was measured, as well as the maximum isometric form of manual gripping with the use of a hand dynamometer. The same choice for the type of test and variables evaluated was used by Van Brussel et al.18 in his randomized clinical study, to evaluate the strength of 34 patients with OI types I and IV.

The equipment used to evaluate the cardiorespiratory capacity in the study of Takken et al.19 was also identical to that chosen by Van Brussel et al.18 - a cycle ergometer with electronic brakes. However, Takken et al.19 adopted a protocol to conduct the test, in which the workload increased by 10, 15 or 20 Watts/minute, depending on the estimated physical capacity of the participant, with the test lasting between 8 and 12 minutes maximum. Van Brussel et al.18 adopted a different protocol in which the participant pedaled for 1 minute without load, as a warm-up, followed by an increased load of 15 to 20 watts/minute. In this study, a cardiac monitor was used to determine the maximum heart rate. In both studies, a gas analyzer was used for the evaluation of the VO₂ peak.

No incident, muscular injury, or fracture resulting from the physical evaluation was reported in the studies.
The practice of aerobic exercise to prevent chronic-degenerative diseases and to preserve the respiratory capacity seems to be a consensus in the studies selected. Among the aerobic exercises, swimming was the most frequently mentioned, including people with more severe types of OI. There is no mention of a suitable temperature for the practice of aquatic exercises for the population with OI.

Localized muscular resistance exercises are also mentioned, including for very small children. For them, the recommendation is that the resistance work not be generalized, but focused on the most weakened muscles: the hip extensors, abductors, and postural musculature, with more emphasis for those children who need tutors. For older children and adolescents, there is no description of this focus, even with the inclusion of general strength training used in the 12-week intervention protocol. However, there is no description of a more appropriate type, whether with free weights or in regular or adapted machines.

For small children, it is recommended that playful breathing exercises, such as making soap bubbles, filling in air balloons, and blowing pinwheels be part of the repertoire of playful activities of the child.

### Table 2. Characteristics of the studies selected

| Study | Type of study | Sample/Target public | Type of OI | Physical evaluation | Supervised exercise | Type of exercise recommended/ performed | Characteristics of the physical training performed |
|-------|---------------|----------------------|------------|---------------------|---------------------|----------------------------------|----------------------------------|
| Brooks29 | Case report | 1 child, female, 10 years old | Not specified | Not specified | Yes | Localized resistance exercises | Not provided |
| Binder et al.22 | Experience report | 3 babies and 1 pre-adolescent | III | Not specified | Not applicable | Swimming and resistance exercises; playfull breathing exercises, restricted to passive stretching | Swimming: 2x/week, the most the child can tolerate. Strength: light weights, set away from extremities, with increases of 28 grams at a time. Breathing exercises: not provided |
| Gerber24 | Experience report | 12 small children | I, III, and IV | Not specified | Not applicable | Resistance exercises for weakened musculature, swimming | Strength: practiced daily, for a few minutes. Swimming: not specified |
| Binder et al.26 | Non-randomized clinical study | 49 children less than 7 years old; 12 children between 8 and 10 years of age | III or IV (majority) | Not specified | Yes | Aerobic aquatic exercises and resistance exercises | Program established in a development sequence (cephalocaudal; centrodistal) |
| Binder et al.24 | Experience report | Not applicable | Not specified | Not specified | Not applicable | Aerobic aquatic exercises and resistance exercises; solo resistance exercises; stretches for upper limbs | Program established in a development sequence (cephalocaudal; centrodistal) |
| Takken et al.28 | Transversal study | 17 patients from both genders, between 8 and 21 years of age, with average age of 13.3 (± 3.9 years) | I | Evaluation of the VO2 peak through the protocol for bicycle with electrical brakes; evaluation of strength with manual dynamometer | Not applicable | Not applicable | Not applicable |
| van Brussel et al.28 | Randomized clinical study | 33 children and adolescents, between 8-18 years old | I and IV | Evaluation of the VO2 peak through the protocol for bicycle with electrical brakes; evaluation of strength with manual dynamometer; evaluation of HRmax with cardiac monitor | Yes, in 2x/week; not in 1x/week | Aerobic exercises and resistance exercises | 12-week program (30 sessions) Typical session: 10 minutes warm-up, 10 minutes of aerobic activity, 15 minutes of resistance exercises and free playful activities. 10 minutes to cool down and return to rest. Aerobic exercises between 60%-80% of the HRmax; resistance exercises with light weights, maximum of 1 kg |
| Monti et al.27 | Experience report | Not applicable | I, III, IV, VI, VII, VIII, and XI | Not specified | Not applicable | For OI type I and IV: aerobic exercises and resistance exercises For OI types III to IX: swimming and localized exercises in water | Not provided |
| van Brussel et al.28 | Experience report | Children | I | Not specified | Not applicable | Aerobic exercises combined with resistance exercises | Aerobic exercises: moderate intensity Resistance exercises: with no additional load or with loads no greater than 1 kg |
Passive exercises for joint mobility are strictly forbidden for small children with any type of OI. For older children with OI type I or IV, contact sports, physical activities or sports that demand sudden rotation movements, and also high intensity interval aerobic training are contraindicated.

For very small children the logic in the organization of the sequence of exercises and the type of exercise to be practiced varies a sequence of development, cephalocaudal and centrodistal, beginning with controlling the upper part of the trunk and head, going to the acquisition of a prone position, to the seated position and to the standing position, if that is possible. As for the load increments in aquatic activities, the idea of wearing clothes with long sleeves was observed in the pool, for it would absorb water and create more resistance, distributing it more equally on the upper and lower limbs.

The recommendation to practice swimming at least twice a week was also observed, for as long as the child could tolerate. For the resistance exercises, as soon as the child begins to move its limbs against gravity, the use is recommended of progressively heavier toys, with increments of weight limited to 1 ounce (approximately 28 grams). Resistance exercises must be practiced for a few minutes every day. All the general recommendations described above were developed through the work of teams with small children and older children - babies up to about seven years old - with various types of OI, especially the types I, III, and IV.

Still, in general, for older children with OI type I or IV, a program is recommended of moderate aerobic exercises combined with resistance exercises with light weights (such as weights equal to or lighter than 1 kg).

The only study that describes a training protocol that can be reproduced, at least for the most part, is the one from Van Brussel et al. intended for children and adolescents with OI type I or IV. A typical session of this program lasted 45 minutes, with 10 minutes of warm-up, 10 minutes of aerobic activity, 15 minutes of resistance exercises and free playful activities, and 10 minutes to cool down and return to rest. In the 12-week program, the aerobic activities (not specified in the study) had an intensity that varied between 60% and 80% of the maximum work capacity. The resistance exercises were done with light weights not over 1 kg. The frequency of the exercises varied from 2 to 3 times a week, with 2 times a week at the hospital under the rehabilitation team’s supervision and once a week at home (but only after the sixth week of intervention).

The studies that mentioned the importance of physical exercise for patients with OI emphasized the need for the training program to be individualized and supervised.

It is recommended that the professional guiding the exercise for the patient with OI of any type, not apply pressure or weight to the extremity of the limbs, to prevent creating a long lever arm, which could cause a fracture. Thus, the professional must avoid holding the patient by the arm or by the hands while helping the patient to position or balance himself when changing exercises, equipment, or postures. The patient should preferably be supported by the trunk, so that the pressure of the hands and the strength of the therapist can be better distributed. Diagonal movements or those with rotation of the limbs must be avoided with the special purpose of preventing fractures.

Evidence of the effects of physical exercise done regularly is scarce. Only one randomized clinical study was made with a sample of patients with OI and with a physical exercise program as an independent variable. After an intervention and 12 weeks of moderate aerobic exercises and resistance exercises, Van Brussel et al. reported a statistically significant improvement for his experimental group in the VO2 peak (17% improvement), in the maximum aerobic work capacity (10%), and in the contraction force (12%), when comparing them with the control group. However, after two months of interruption in the exercises, significant reductions of these gains could be noticed and that was intensified after 5 months of interruption in the exercise program. In relation to the psychological aspects, Van Brussel et al. reported that the exercise program promoted significant alterations in the perception of fatigue, but not in the quality of life and in the perceived competence. No fracture was reported during the practice of the exercises.

It is relevant to bear in mind that the reports and experiences of the specialized treatment centers show that children with higher levels of physical activity are more prone to have and/or have had more fractures than sedentary children. Nonetheless, they emphasized that the fractures were due to falls and traumas, rather than from the practice of physical exercises per se.

DISCUSSION

The objective of this review was to collect and systematize the knowledge referring to physical evaluation, indication of exercises, progression of load, and systematics of training for people with osteogenesis imperfecta. This systematization could be an interesting resource for multidisciplinary teams that care for the severely disabled, since the gathering of information presented here offers a direction as to the form of action and expected effects of the practice of physical exercises and sports for people with OI.

The studies found in which the intervention with physical exercises is described, with greater or smaller details and information, concentrate on small children, with OI types I and IV. Adolescents were recruited for only two studies, and even then they were included in mixed samples with children as young as 8 years old. There is a clear gap in the investigation of the effects and parameters for physical exercise training for the OI types other than I and IV, as well as for adults and adolescents with all types of OI. It is a fact that, after adolescence, the number of spontaneous fractures not related to traumas tends to diminish. However, women with OI who reached menopause are more susceptible to fractures, and probably the recommendations and conducts gathered here do not apply directly to this group. These alterations related to age and hormonal changes may have an important impact on the prescription and monitoring of physical exercise training, but so far, this is a theoretical speculation, since no transversal studies have been conducted yet to confirm the pertinence of the impact of these alterations.

In general, for small children and adolescents up to 12 years old with OI type I or IV, aerobic exercises confirm their relevance in preventing cardiorespiratory complications that may occur either due to muscle weakness in the respiratory musculature, to heart valve alterations, or to vascular alterations. Swimming is the aerobic exercise most recommended, but there are no reports of its effect in the aerobic capacity of people with OI. In terms of intensity, for older children and adolescents, the load recommended is from light to moderate (60%-80% maximum capacity), with a frequency of 2 to 3 days a week, with sessions lasting 20 minutes, between warm-up (10 minutes) and the main session.
(10 minutes). Aquatec exercises can also strengthen muscles, in hydrogymnastics or in hydrotherapy, especially for small children, even before they start walking. In this environment, the use of pants or shirts with long sleeves is the recommended way to increase the load in distributed form. As for the remaining strength exercises, there is the recommendation to avoid long arm levers, which can be accomplished by not applying a load on the distal extremity of the limbs. Despite the relevant information in the works identified in this study, which allowed us to systematize recommendations for the work of the physical educator and physiotherapist regarding physical exercises and sports, there is a clear need for more scientific research that will help establish a safer practice of intervention determining parameters for the evaluation and prescription of exercises, as well as for the load progression and for the planning of physical training. Brazil, especially, needs this type of study. The fact is that large samples of this specific public are not easy to gather. Nevertheless, if the rehabilitation teams that care for these patients and the para-sports technicians who work with athletes with OI describe their way of intervention by reporting tests, chosen exercises, intervention protocols, and/or the training cycles adopted, as well as the evolution of the patient or athlete with OI, a more comprehensive understanding and an improvement in the care of this population may be achieved in the future. The same goes for the technicians of Paralympic teams with athletes with OI.

REFERENCES

1. Byers PH, Steiner RD. Osteogenesis imperfecta. Am J Pediatr. 1992;39:269-82. DOI: http://dx.doi.org/10.1144/annurev.me.34.020192.001413
2. Engelbert RH, Pauwe SE, Jansen JA, van der Windt DA. Osteogenesis imperfecta in childhood: treatment strategies. Arch Dis Child. 1998;79(12):1500-4. DOI: http://dx.doi.org/10.1136/adc.79.12.1500
3. Centro de Referencia de Osteogénesis Imperefecta [Texto na Internet]. Rio de Janeiro: Instituto Fernandes Figueira/Fiocruz; c2010 [citado 2013 Set 09]. Disponível em: http://www.fiofcruz.br/ofc/cgi/ cgi.bin/sgula.exe/start.htm?tp=home
4. Wirth T. Osteogenesis imperfecta. Orthopade. 2002;32(7):773-82. DOI: http://dx.doi.org/10.1007/s00132-002-1959-y
5. Baldridge D, Schwarz U, Morello R, Lennington J, Bertin TK, Pace JM, et al. CRTAP and LEPRE1 mutations in recessive osteogenesis imperfecta. Hum Mutat. 2006;29(12):1345-42. DOI: http://dx.doi.org/10.1002/humu.20799
6. Forlino A, Cabral WA, Barnes AM, Marin J. New perspectives on osteogenesis imperfecta. Nat Rev Endocrinol. 2011;7(9):540-57. DOI: http://dx.doi.org/10.1038/nrendo.2011.81
7. Coppin C, Eckchott Y. L’ostéogénèse imparfaite des mutations aux phenotypes. Med sciences. 1995;67(11):853-9.
8. Byers PH, Wallis GA, Willing MC. Osteogenesis imperfecta: translation of mutation to phenotype. J Med Genet. 1991;28(7):433-42. DOI: http://dx.doi.org/10.1136/jmg.28.7.433
9. Rauch F, Glioure FH. Osteogenesis imperfecta. Lancet. 2004;363(9418):1377-85. DOI: http://dx.doi.org/10.1016/S0140-6736(04)16051-0
10. Pyertz RE, Levin LS. Aortic root dilatation and valvular dysfunction in Osteogenesis imperfecta. Circulation. 1981;64:1193A.
11. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979;16(2):101-16. DOI: http://dx.doi.org/10.1136/jmg.16.2.101
12. Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck-Gibis J, Travers R, et al. Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. J Clin Endocrinol Metab. 2000;85(5):1846-50.
13. Stoltz MR, Dietrich SL, Marshall GJ. Osteogenesis imperfecta: Perspectives. Clin Orthop Relat Res. 1989(242):120-36.
14. Yochum TR, Kulkaba S, Seibert RE. Osteogenesis imperfecta in a weightlifter. J Manipulative Physiol Ther. 2002;26(5):334-9. DOI: http://dx.doi.org/10.1016/j.jmpt.2002.124418
15. Jansen JA, Haddad FS. Distal patellar tendon avulsion fracture in a football player with osteogenesis imperfecta. Knee Surg Sports Traumatol Arthrosc. 2012;20(2):327-30. DOI: http://dx.doi.org/10.1007/s00167-011-1599-6
16. Reith K. Olympic Medal winner Doug Herland: rises to the occasion. Olympian. 1985;11(7): 8-11.
17. Haskell WL, Leem MK, Patra RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007;39(9):1423-34. DOI: http://dx.doi.org/10.1249/01.mss.0b013e3180616d67
18. van Brussel M, Takken T, Ulterwaal CS, Pruiss HJ, Van der Net J, Helders P, et al. Physical training in children with osteogenesis imperfecta. J Pediatr. 2008;152(1):111-6. DOI: http://dx.doi.org/10.1016/j.jpeds.2007.06.029
19. Takken T, Terlingen HC, Helders P, Pruiss H, Van der Ent CK, Engelbert RH. Cardiopulmonary fitness and muscle strength in patients with osteogenesis imperfecta type I. J Pediatr. 2004;145(5):813-8. DOI: http://dx.doi.org/10.1016/j.jpeds.2004.08.003
20. Guedes DP, Guedes JRP. Manual prático para avaliação em educação física. Barueri: Manole; 2006.
21. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasmann K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. J Appl Physiol Respir Environ Exerc Physiol. 1983;55(5):1558-64.
22. Godfrey S. Exercise testing in children. London: W. B. Saunders; 1974.
23. Binder H, Hawks L, Graybill G, Gerber NL, Weintrob JC. Osteogenesis imperfecta: rehabilitation approach with infants and young children. Arch Phys Med Rehabil. 1984;65(9):537-41.
24. Gerber LH, Binder H, Weintrob J, Grange DK, Shapiro J, Fromherz W, et al. Rehabilitation of children and infants with osteogenesis imperfecta. A program for ambulation. Clin Orthop Relat Res. 1990;(251):254-62.
25. Binder H, Conway A, Gerber LH. Rehabilitation approaches to children with osteogenesis imperfecta: a ten-year experience. Arch Phys Med Rehabil. 1993;74(4):386-90.
26. Binder H. Rehabilitation of infants with osteogenesis imperfecta. Connect Tissue Res. 1995;31(4):537-9. DOI: http://dx.doi.org/10.3109/03008209509116831
27. Monti E, Mottes M, Fraschini P, Brunelli P, Forlino A, Venturi G, et al. Current and emerging treatments for the management of osteogenesis imperfecta. Ther Clin Risk Manag. 2010;6:367-81.
28. van Brussel M, van der Net J, Hulzebos E, Holders P, Takken T. The Utrecht approach to exercise in chronic childhood conditions: the decade in review. Pediatr Phys Ther. 2011;23(1):2-14.
29. Brooks BM. Physical therapy in osteogenesis imperfecta. Phys Ther. 1974; 54:1198-9.
30. Antoniazzi F, Mottes M, Fraschini P, Brunelli PC, Tatò L. Osteogenesis imperfecta: practical treatment guidelines. Paediatr Drugs. 2000;2(6):465-88. DOI: http://dx.doi.org/10.2165/00128072-200002060-00005