Calcified Tissue International

Muscle Function in Osteogenesis Imperfecta Type IV

--Manuscript Draft--

Manuscript Number:	CTIN-D-16-00409	
Full Title:	Muscle Function in Osteogenesis Imperfecta Type IV	
Article Type:	Original Article	
Funding Information:	Fonds de Recherche du Québec - Santé	Dr. Louis-Nicolas Veilleux Dr. Frank Rauch
	Canadian Institutes of Health Research	Dr. Louis-Nicolas Veilleux
Abstract:	Results of previous studies suggest that children and adolescents with osteogenesis imperfecta (OI) type IV have muscle force deficits. However, muscle function remains to be objectively quantified in this population. This study aimed to assess upper and lower extremity muscle function in patients with OI type IV. It was carried out in the outpatient department of a pediatric orthopedic hospital. 27 individuals with OI type IV (7 to 21 years; 13 males), 27 age and sex- matched individuals with OI type I and 27 age- and sex-matched controls. Upper extremity muscle force was assessed with hydraulic hand dynamometry and lower extremity muscle function (peak force per body weight and peak power per body mass) was measured by mechanography through five tests: multiple two-legged hopping, multiple one-legged hopping, single two-legged jump, chair-rise test and heel-rise test. Upper-limb grip force was normal for patients with OI type IV when compared to height and sex reference data. Compared to age- and sex-matched controls, patients with OI type IV had lower lower-limb average peak force and power. At the lower-limb level, they also had lower average peak power than age and sex-matched patients with OI type I. Patients with OI type IV have normal upper-limb muscle force but a muscle function deficit at the lower-limb level. These results suggest that lower-limb muscle weakness may contribute to functional deficits in these individuals.	
Corresponding Author:	Louis-Nicolas Veilleux, Ph.D. Universite de Montreal CANADA	
Corresponding Author Secondary Information:		
Corresponding Author's Institution:	Universite de Montreal	
Corresponding Author's Secondary Institution:		
First Author:	Louis-Nicolas Veilleux, Ph.D.	
First Author Secondary Information:		
Order of Authors:	Louis-Nicolas Veilleux, Ph.D.	
	Vasiliki B. Darsaklis, MSc	
	Francis H Glorieux, M.D., Ph.D.	
	Frank Rauch, M.D.	
Order of Authors Secondary Information:		
Author Comments:	Dear editor-in-chief, We hereby submit for publication as original article in the Calcified Tissue International the manuscript entitled "Muscle Function in Osteogenesis Imperfecta Type IV". Studies have examined the muscle function only in patients with mild OI (i.e., OI type 1), reporting a muscle force deficit, which could contribute to bone fragility. Moreover, muscle weakness may have even more important functional consequences in more severe OI types (i.e., OI type III and IV) as children and adolescents with these OI	

	types often have restricted mobility. Although these patients show a decreased forearm muscle size, lower extremity muscle function has not been investigated systematically. The goal of this study is to assess lower extremity dynamic muscle function in OI type IV. The material is original research, has not been previously published and will not be submitted for publication elsewhere while under consideration. We think that this manuscript provides innovative information that will interest the readers of the Calcified Tissue International. Best regards, Louis-Nicolas Veilleux, PhD Assistant Professor Researcher Department of Kinesiology, University of Montreal Researcher Manager, Motion Analysis Laboratory Shriners Hospital for Children®-Canada 1003 Decarie Bld. Montreal, Qc H4A 0A9 Canada Tel: +1-514-282-7175 Fax: +1-514-842-5581
Suggested Reviewers:	Oliver Semler, M.D. Universitat zu Koln joerg.semler@uk-koeln.de He is knowledgeable about this research area.
	Bonny L. Specker, Ph.D. South Dakota State University bonny.specker@sdstate.edu She is knowledgeable about this research area.
Opposed Reviewers:	

Muscle Function in Osteogenesis Imperfecta Type IV

Louis-Nicolas Veilleux (1), Vasiliki B. Darsaklis (2), Francis H. Glorieux (3), Frank Rauch (3)

(1) Movement Analysis Laboratory, Shriners Hospital for Children-Canada; Department of Kinesiology, Université de Montréal

(2) Clinical Research Department, Shriners Hospital for Children-Canada

(3) Genetic and Metabolic Unit, Shriners Hospital for Children-Canada; Faculty of Medicine, McGill University

Abbreviated Title

Muscle Function in Osteogenesis Imperfecta

Corresponding Author

Louis-Nicolas Veilleux, Shriners Hospital for Children, 1003 Decarie Boulevard, Montréal, Québec, Canada H4A 0A9. Tel.: +1-514-282-7175; Fax: +1-514-842-5581; E-mail: lnveilleux@shriners.mcgill.ca

All reprint requests should be addressed to the corresponding author.

Acknowledgements

This study was supported by the Shriners International. F.R. received salary support from the Chercheur-Boursier Clinicien program of the Fonds de Recherche du Québec – Santé. L.N.V. received postdoctoral fellowships from the Fonds de la Recherche du Québec – Santé and the MENTOR-RSBO (Network for Oral and Bone Health Research), supported by the Canadian Institutes of Health Research (MENTOR) and the Fonds de la Recherche du Québec – Santé (RSBO). The funding agencies were not involved in the design of the study, collection, analysis, and interpretation of data and in writing the manuscript.

We are indebted to Mark Lepik (Shriners Hospital for Children-Canada) for the preparation of the figures.

Abstract

Results of previous studies suggest that children and adolescents with osteogenesis imperfecta (OI) type IV have muscle force deficits. However, muscle function remains to be objectively quantified in this population. This study aimed to assess upper and lower extremity muscle function in patients with OI type IV. It was carried out in the outpatient department of a pediatric orthopedic hospital. 27 individuals with OI type IV (7 to 21 years; 13 males), 27 age and sex- matched individuals with OI type I and 27 age- and sex-matched controls. Upper extremity muscle force was assessed with hydraulic hand dynamometry and lower extremity muscle function (peak force per body weight and peak power per body mass) was measured by mechanography through five tests: multiple two-legged hopping, multiple one-legged hopping, single two-legged jump, chair-rise test and heel-rise test. Upper-limb grip force was normal for patients with OI type IV when compared to height and sex reference data. Compared to age- and sex-matched controls, patients with OI type IV had lower lower-limb average peak force and power. At the lower-limb level, they also had lower average peak power than age and sex-matched patients with OI type I. Patients with OI type IV have normal upper-limb muscle force but a muscle function deficit at the lower-limb level. These results suggest that lower-limb muscle weakness may contribute to functional deficits in these individuals.

Keywords

Osteogenesis imperfect ▪ Mechanography ▪ Maximum isometric grip force ▪ Upper-limb muscle force ▪ Lower-limb muscle function ▪ Muscle power

Background

Osteogenesis imperfecta (OI) is a heritable disorder characterized by increased bone fragility [1]. Most patients with a clinical diagnosis of OI have a mutation in one of the two genes that encode the alpha chains of collagen type I, *COL1A1* and *COL1A2*. The most widely used phenotypic classification distinguishes four major types of OI [2]. OI type I is the mildest form of bone fragility with minimal deformity and normal or near-normal final height. Type II is lethal in the perinatal period. Type III is the most severe non-lethal form of OI, with very short stature as well as limb and spine deformities. Patients with short stature and moderate-to-severe phenotype who do not fit into one of the previously described types are classified as OI type IV.

In a series of recent studies we have shown that, aside from bone fragility, muscle weakness was a clinical manifestation of OI type I. We noted that close to 80% of patients with confirmed *COL1A1*/*COL1A2* mutations and an OI type I phenotype had a muscle force deficit [3]. We have also shown that this muscle weakness may contribute to bone fragility in this population [4]. However, at present, muscle weakness has only been reported in patient with mild OI (i.e., OI type I) [3, 5-7].

Muscle weakness may have even more important functional consequences in OI type III and IV. Children and adolescents with these OI types often have restricted mobility despite multidisciplinary treatment with bisphosphonates, intramedullary rodding surgery and rehabilitation [8]. We have recently reported that forearm muscle size is frequently decreased in OI types III and IV [9] suggesting lower muscle force, but lower extremity muscle function has not been investigated systematically.

In the present study we therefore aimed to characterize muscle function in youth with moderate to severe OI, using isometric grip force test for upper limb and mechanography for lower limb muscle function assessment. As children and adolescents with OI type III are usually not able to perform such tests, the present study focused on OI type IV.

Methods

Study Population

The study population comprised patients between 7 and 21 years of age with a clinical diagnosis of OI type IV who were followed at the Shriners Hospital for Children-Canada. The classification of OI types followed the criteria established by Sillence [2]. However, the OI-IV category did not include patients who fulfilled the Sillence criteria for this diagnosis, but who could be classified as having OI type V, VI, or VII on the basis of our expanded classification [10-12]. Exclusion criteria were fractures of the lower limbs in the past 6 months or lower limb surgery in the past 12 months.

27 individuals with OI type IV (male, n = 13; female, n =14; age range: 7.7 to 20.6 years; mean age [SD]: 13.2 [4.1] years) met the inclusion/exclusion criteria and were included in this study. Data set from 27 age- and sex-matched individuals with OI type I (age range: 7.4 to 21.0 years; mean age [SD]: 13.3 [4.0] years) were selected from a previous study [3] who had performed the same muscle function tests as in the present study. 25 out of 27 individuals with OI type I had a confirmed mutation in *COL1A1* or *COL1A2*. The remaining two individuals had a negative molecular diagnosis test result but fulfilled the clinical criteria for this diagnosis [2]. 27 age- and sex-matched control individuals (age range: 7.2 to 21.4 years; mean age [SD]: 13.3 [4.2] years) were selected from our database which is composed of unaffected siblings of patients, and children of hospital employees who agreed to perform the same mechanographic tests.

Anthropometric Measurements

Height was measured using a Harpenden stadiometer (Holtain, Crymych, UK). Weight was determined using the Leonardo Mechanograph® Ground Reaction Force Plate. Height and weight measurements were converted to age- and sex-specific z-scores on the basis of reference data published by the Centers for Disease Control and Prevention [13].

Upper Limb Muscle Function Assessment: Maximal Isometric Grip Force

Grip force was measured, unless pain or recent fracture made the measurement impossible. 7 patients with OI type IV did not perform grip force test for these reasons. Maximal isometric grip force of the non-dominant hand was determined with a standard adjustable-handle Jamar hydraulic hand dynamometer (Preston, Jackson, Michigan). The maximal value of 3 trials was noted. Grip force results (in N) were transformed to age- and height-specific z-scores by using reference data from Rauch et al. [14]

Lower Limbs Muscle Function Assessment: Mechanography

A force plate (Leonardo Mechanograph® Ground Reaction Force Plate; Novotec Medical Inc, Pforzheim, Germany) was used to measure vertical ground reaction forces. Force measurements were sampled at a frequency of 800 Hz. As described in detail elsewhere, all muscle function parameters reported here were derived from these force-time data using proprietary software (Leonardo Mechanography GRFP Research Edition® software, version 4.2-b05.53-RES; Novotec Medical Inc) [15].

Five different tests were performed: (1) Multiple one-legged hopping (M1LH) and (2) multiple two-legged hopping (M2LH), representing vertical hopping on one or both forefeet (similar to rope-skipping), respectively. The aim of these hopping tests is to achieve maximal ground reaction forces during eccentric muscle contraction. These tests (#1-2) provide an indication of the maximal load that muscles exert on the skeletal system [16]. (3) Single two-legged jump (S2LJ), a vertical countermovement jump to achieve maximum jump height during a stretch-shortening cycle movement. (4) Heel-rise test (HRT), consisting of five bilateral heel rises with the aim to achieve maximal speed during the upward movement. (5) Chair-rise test (CRT), a sit-to-stand test repeated five times, with the aim to achieve maximal speed during the upward movement. The chair-rise test made use of a bench anchored to the force plate. These tests (#3-5) assess power, which is determined as the ground reaction force multiplied by the speed of the body's movement in a vertical direction. Power thus depends on the speed of muscle contraction in addition to force. Low muscle power can lead to functional deficits such as increased fall risks and limited mobility [17].

Each test was repeated three times and the ‘best’ result was retained. The 'best' result was: the highest peak force for a given hop in the multiple one- and two-legged hopping; the highest peak power during the take-off phase for the single two-legged jump, during the first rise of the heel-rise test and for the second rise of the chair-rise test [15]. For the multiple one- and two-legged hopping, the main outcome parameter was peak force relative to body weight (‘force tests’), whereas for the single two-legged jump, the heel-rise test and the chair-rise test, the main outcome parameter was peak power relative to body mass (‘power tests’).

Statistical Analyses

Descriptive statistics are presented as means and standard deviations. To determine whether patients with OI type IV had upper-limb muscle force deficits, grip force z-scores were computed for all three groups on the basis of age/sex and height/sex specific reference data [18]. A one-sample t-test was then performed to determine whether the average z-score differed from zero. To determine whether patients with OI type IV had lower-limb muscle function deficits, random block design ANOVAs were used to assess lower limb muscle function differences between groups of OI type IV, OI type I and controls (the random-block factors). Age and sex were already accounted for by our matched-control design.

To investigate the effects of different clinical parameters on mechanographic outcome variables, the difference of the results (in percent) between each patient with OI type IV **a**nd their respective matched control/matched OI type I participant was computed for each of the five tests. Independent stepwise multiple regression analyses were then performed with the percent difference parameter set as the dependent variable (i.e. difference between OI type IV and type I; difference between OI type IV and controls). Time under bisphosphonate treatment (years), time since last tibia and/or femur fracture (years), number of lower-limb fractures prior to testing and the gene involved (*COL1A1* = 0; *COL1A2* = 1) were set as independent variables. Anthropometrics such as age (years) and height (expressed as age- and sex-specific z-scores) were also set as independent variables.

For the S2LJ, the M2LH and the M1LH-Left and Right leg, the number of individuals with OI type IV who were able to perform the test was not sufficient to perform regression analyses. Instead, univariate logistic regression analyses were used to evaluate the relationship between individuals with OI type IV who were or were not able to perform the tests (able = 0; unable = 1) and the clinical/anthropometric characteristics described above. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI).

All tests were two tailed, and throughout the study, $P < 0.05$ was considered significant. All statistical analyses were performed using PASW Statistics software version 20.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Children and adolescents with OI type IV were lighter than the Controls and shorter than both OI type I and Controls (Table 1). Only 3 individuals with OI type IV did not have a history of rodding surgery at the lower extremities; 11 patients had rodding of all four segments (bilateral femur and tibia) (Table 2). Finally, 14 individuals had at least one fracture at both the tibia and femur prior to testing, 11 had at least one fracture at the femur and the remaining 2 had sustained no fracture prior to testing.

Isometric grip force results showed that patients with OI type IV had normal grip force (average z-score = 0.17±1.30; $P = 0.88$) when compared to height reference data but showed upper-limb force deficit when compared to age reference data (average z-score = -0.74 ± 0.90; $P < 0.001$). With regard to lower-limb power tests (S2LJ, HRT, CRT), the random-block analyses revealed that relative power was significantly lower in OI type IV than OI type I and Controls for all three tests. OI type I had lower relative power than controls only for the S2LJ. Lower-limb force tests (Figure 1A, B; Table 3) analyses revealed that patients with OI type IV and type I did not differ from one another but both had lower force than control participants on the M2LH and the M1LH-Left leg. For the M1LH-Right leg, only the OI type I group had significantly lower force. It is however important to note that, because of muscle weakness, a larger number of patients with OI type IV were unable to perform the multiple hopping tests and the single two-legged jump compared to OI type I (see Figure 2A and B).

In addition to these analyses, data from the S2LJ and M1LH were compared to age and weight reference data [19]. Analyses (Table 4) showed that data from the force test (M1LH) were significantly different from 0 for both age and weight reference data and for both OI type IV (all Ps < 0.01) and OI type I (all Ps < 0.001) groups. Data from the Control group did not differ significantly from 0 (all Ps > 0.19). For the power test (S2LJ), only the data from OI type IV compared to age reference data were significantly lower than 0 (P = 0.006). The analyses also revealed that data from the Control group were significantly higher than 0 for both age and weight reference data (All Ps > 0.02).

Regression analyses showed that an increased number of fractures prior to testing (independent from age) was related to a larger difference between OI type IV and Controls as well as between OI type IV and OI type I for both the CRT and the HRT (Figure 3A and B). Stated otherwise, this indicates that the number of fractures prior to testing is proportional to the power deficit that is observed between OI type IV and the other two experimental groups (OI type I and controls) as measured during the CRT and the HRT. None of the parameters, including height z-score, a marker of disease severity, were found to be significant predictors of force tests, including grip force.

Univariate logistic regression analyses (Table 5) also showed that the number of fractures prior to testing was associated with an increased risk of being unable to perform the mechanographic S2LJ, M2LH and M1LH-Left. Put in other words, these data indicate that if the number of fractures increases by one then the risk of not performing the test is multiplied by the odds ratio.

Discussion

In this study we found that patients with a clinical diagnosis of OI type IV and known mutations in the *COL1A1*/*COL1A2* genes produced less force and power than healthy age and sex matched controls. This remained true when compared to age- or weight-related reference data. An upper-limb force deficit was also observed when compared to age-specific reference data but grip force was normal when compared to height-related reference data.

Patients with OI type IV also had reduced muscle power as compared to patients with OI type I whereas muscle force did not differ between both OI groups. However, given that a larger number of patients with OI type IV were unable to perform the hopping tests compared to OI type I (n = 8 vs. 18 for the M1LH and n =11 vs. n = 27 for M2LH; for OI type IV and OI type I respectively), it is assumed that muscle force was also lower in patients with OI type IV than in patients with OI type I. Thus, both muscle functions were in deficits in OI type IV as compared to OI type I.

Among the potential determinants of lower limb muscle function in OI type IV, only fracture history emerged as a significant negative predictor. The number of fractures is likely to reflect periods of physical inactivity and thereby may have contributed to lower muscle function. Physical activity was not measured in the present study, but a recent study in adults indicates that increased OI severity is related to decreased engagement in physical activities [20].

Muscle function in OI type IV may also be impaired by a direct effect of collagen type I mutations on tendons, ligaments and intramuscular connective tissue, which contain abundant amounts of collagen type I [21]. Even though not measured in the present study, mutations in collagen type I encoding genes may alter the structural and mechanical properties of these tissues. Joint hyperlaxity is a typical feature of OI [2, 22]. In a mouse model of severe OI, tendons contained an abnormally low amount of collagen type I and were biomechanically compromised [23]. Collagen type I is also present in the extra-cellular matrix surrounding muscle fibers [24], which plays an important role in transmitting muscle force to tendons [25]. More detailed studies on the effect of collagen type I mutations on tendons, ligaments and extracellular muscle matrix are required to clarify these issues.

In contrast with the observed force deficit at the lower limbs, upper-limb grip force was normal in OI type IV when compared to height-related reference data. This is in contrast with a previous study in which forearm muscle size, a surrogate of muscle force, was lower in patients with OI type IV as compared to healthy controls [9]. These observations suggest that grip force is adapted to height and consequently to

muscle size. It also suggests that taken alone, muscle size is an imperfect surrogate of muscle force. This difference between upper- and lower-limb could also reflect differences in function. Patients with OI type IV use their arms for everyday life activities quite vigorously, and may sometimes need to use their arms to rise from a chair to compensate for lower-limb muscle weakness. Finally, differences may arise from the fact that grip force was measured through isometric test whereas lower-limb was measured trough eccentric muscle contraction. These two types of tests respectively represent static and dynamic muscle contractions and are known to correlate poorly in that matter [26].

Conclusion

In summary, this study on a group of relatively functional children and adolescents with OI type IV found deficits in lower-limb muscle force and power. These muscle function deficits may contribute to limitations in mobility despite multidisciplinary treatment with bisphosphonates, intramedullary rodding surgery and rehabilitation [8].

Contributors

Veilleux LN conceptualized and designed the study, carried out the analyses, drafted the initial manuscript. He is the guarantor.

Darsaklis VB participated in data collection and interpretation.

Glorieux FH contributed patient information and participated in the interpretation of data.

Rauch F contributed patient information, conceptualized and designed the study and participated in the interpretation of data. All authors revised the paper critically for intellectual content and approved the final version. All authors agree to be accountable for the work and to ensure that any questions relating to the accuracy and integrity of the paper are investigated and properly resolved.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from study participants or the legal guardians.

Conflicts of Interest

The authors declare that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet. 2004;363:1377-85. doi: 10.1016/S0140-6736(04)16051-0
2. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979;16:101-16.
3. Veilleux LN, Lemay M, Pouliot-Laforte A, Cheung MS, Glorieux FH, Rauch F. Muscle anatomy and dynamic muscle function in osteogenesis imperfecta type I. J Clin Endocrinol Metab. 2014;99:E356-62. doi: 10.1210/jc.2013-3209
4. Veilleux LN, Pouliot-Laforte A, Lemay M, Cheung MS, Glorieux FH, Rauch F. The functional muscle-bone unit in patients with osteogenesis imperfecta type I. Bone. 2015;79:52-7. doi: 10.1016/j.bone.2015.05.019
5. 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;27:1182-90. doi: 10.1002/jor.20871
6. Caudill A, Flanagan A, Hassani S, Graf A, Bajorunaite R, Harris G, et al. Ankle strength and functional limitations in children and adolescents with type I osteogenesis imperfecta. Pediatr Phys Ther. 2010;22:288-95. doi: 10.1097/PEP.0b013e3181ea8b8d
7. 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;145:813-8. doi: 10.1016/j.jpeds.2004.08.003
8. Montpetit K, Palomo T, Glorieux FH, Fassier F, Rauch F. Multidisciplinary Treatment of Severe Osteogenesis Imperfecta: Functional Outcomes at Skeletal Maturity. Arch Phys Med Rehabil. 2015;96:1834-9. doi: 10.1016/j.apmr.2015.06.006
9. Palomo T, Glorieux FH, Schoenau E, Rauch F. Body Composition in Children and Adolescents with Osteogenesis Imperfecta. J Pediatr. 2016;169:232-7. doi: 10.1016/j.jpeds.2015.10.058
10. Glorieux FH, Rauch F, Plotkin H, Ward L, Travers R, Roughley P, et al. Type V osteogenesis imperfecta: a new form of brittle bone disease. J Bone Miner Res. 2000;15:1650-8. doi: 10.1359/jbmr.2000.15.9.1650

11. Glorieux FH, Ward LM, Rauch F, Lalic L, Roughley PJ, Travers R. Osteogenesis imperfecta type VI: a form of brittle bone disease with a mineralization defect. J Bone Miner Res. 2002;17:30-8. doi: 10.1359/jbmr.2002.17.1.30
12. Ward LM, Rauch F, Travers R, Chabot G, Azouz EM, Lalic L, et al. Osteogenesis imperfecta type VII: an autosomal recessive form of brittle bone disease. Bone. 2002;31:12-8.
13. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics. 2002;109:45-60.
14. Rauch F, Neu CM, Wassmer G, Beck B, Rieger-Wettengl G, Rietschel E, et al. Muscle analysis by measurement of maximal isometric grip force: new reference data and clinical applications in pediatrics. Pediatr Res. 2002;51:505-10. doi: 10.1203/00006450-200204000-00017
15. Veilleux LN, Rauch F. Reproducibility of jumping mechanography in healthy children and adults. J Musculoskelet Neuronal Interact. 2010;10:256-66.
16. Anliker E, Rawer R, Boutellier U, Toigo M. Maximum ground reaction force in relation to tibial bone mass in children and adults. Med Sci Sports Exerc. 2011;43:2102-9. doi: 10.1249/MSS.0b013e31821c4661
17. Foldvari M, Clark M, Laviolette LC, Bernstein MA, Kaliton D, Castaneda C, et al. Association of muscle power with functional status in community-dwelling elderly women. J Gerontol A Biol Sci Med Sci. 2000;55:M192-9.
18. Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. Am J Occup Ther. 1986;40:705-11.
19. Sumnik Z, Matyskova J, Hlavka Z, Durdilova L, Soucek O, Zemkova D. Reference data for jumping mechanography in healthy children and adolescents aged 6-18 years. J Musculoskelet Neuronal Interact. 2013;13:297-311.
20. Tosi LL, Oetgen ME, Floor MK, Huber MB, Kennelly AM, McCarter RJ, et al. Initial report of the osteogenesis imperfecta adult natural history initiative. Orphanet J Rare Dis. 2015;10:146. doi: 10.1186/s13023-015-0362-2

21. Misof K, Landis WJ, Klaushofer K, Fratzl P. Collagen from the osteogenesis imperfecta mouse model (oim) shows reduced resistance against tensile stress. J Clin Invest. 1997;100:40-5. doi: 10.1172/JCI119519
22. Brizola E, Staub AL, Felix TM. Muscle strength, joint range of motion, and gait in children and adolescents with osteogenesis imperfecta. Pediatr Phys Ther. 2014;26:245-52. doi: 10.1097/PEP.0000000000000042
23. Sims TJ, Miles CA, Bailey AJ, Camacho NP. Properties of collagen in OIM mouse tissues. Connect Tissue Res. 2003;44 Suppl 1:202-5.
24. Gillies AR, Lieber RL. Structure and function of the skeletal muscle extracellular matrix. Muscle Nerve. 2011;44:318-31. doi: 10.1002/mus.22094
25. Huijing PA. Muscle as a collagen fiber reinforced composite: a review of force transmission in muscle and whole limb. J Biomech. 1999;32:329-45.
26. Murphy A, Wilson G. Poor correlations between isometric tests and dynamic performance: relationship to muscle activation. Eur J Appl Physiol Occup Physiol. 1996;73:353-7. doi: 10.1007/bf02425498

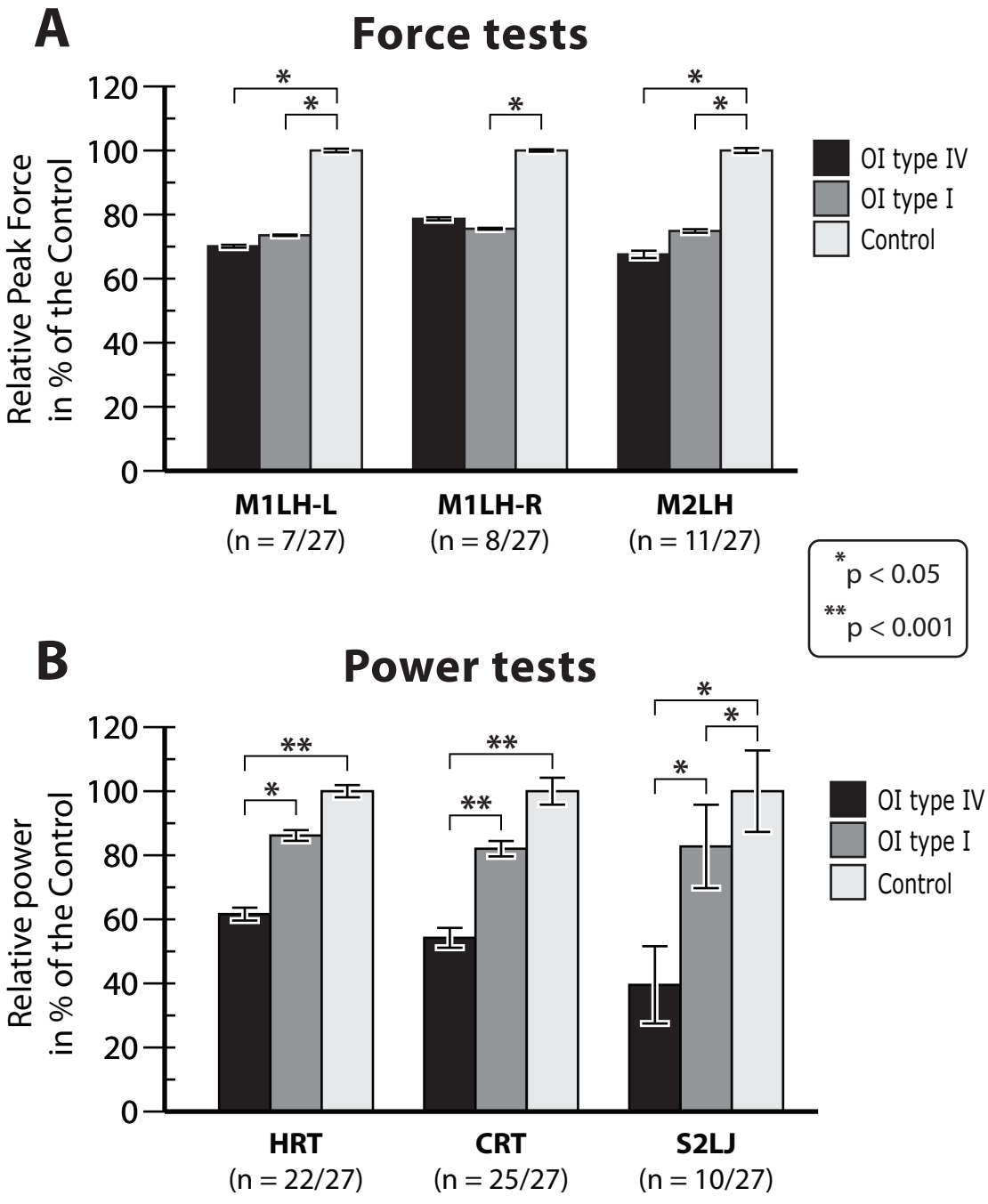
Figure Legends

Figure 1. (A) OI Type IV and OI Type I relative peak force for the multiple two-legged hopping (M2LH) and multiple one-legged hopping (M1LH; Left and Right) tests presented in percent of the Control values; (B) relative peak power for the chair-rising test (CRT), the heel-rising test (HRT) and the single two-legged jump (S2LJ) presented in percent of the Control values. OI type IV: black bars; OI type I: dark grey bars; controls: light grey bars.

Figure 2. Proportion of participants (%) able to perform mechanography tests for (A) force tests and (B) power tests.

Figure 3. Linear regression on the percent difference in relative peak power for (A) the chair-rising test and the number of fractures prior to testing; (B) the heel-rising test and the number of fractures prior to testing. Correlations between OI type IV and OI type I (black filled circles and plain line) and between OI type IV and Controls (white filled circle and dashed line) are presented.

Figure 01



e.LNV.fig01AB_b ß¶[cs5].ai

Figure 02

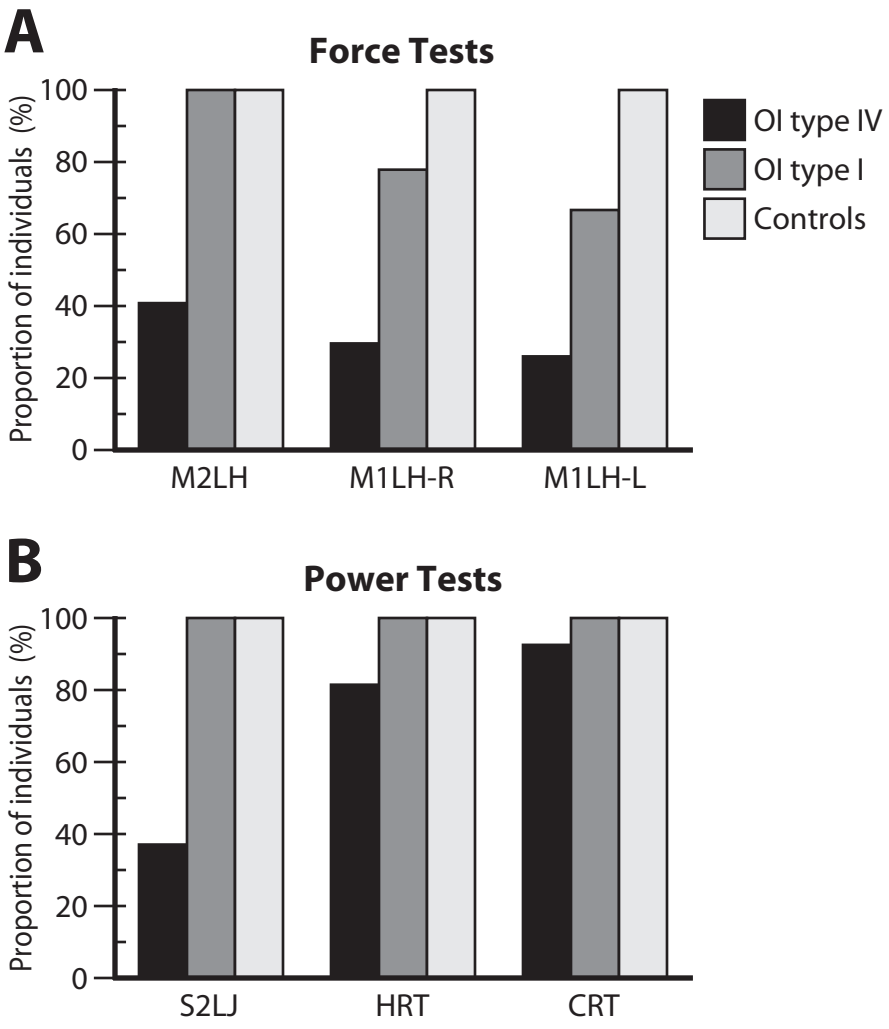
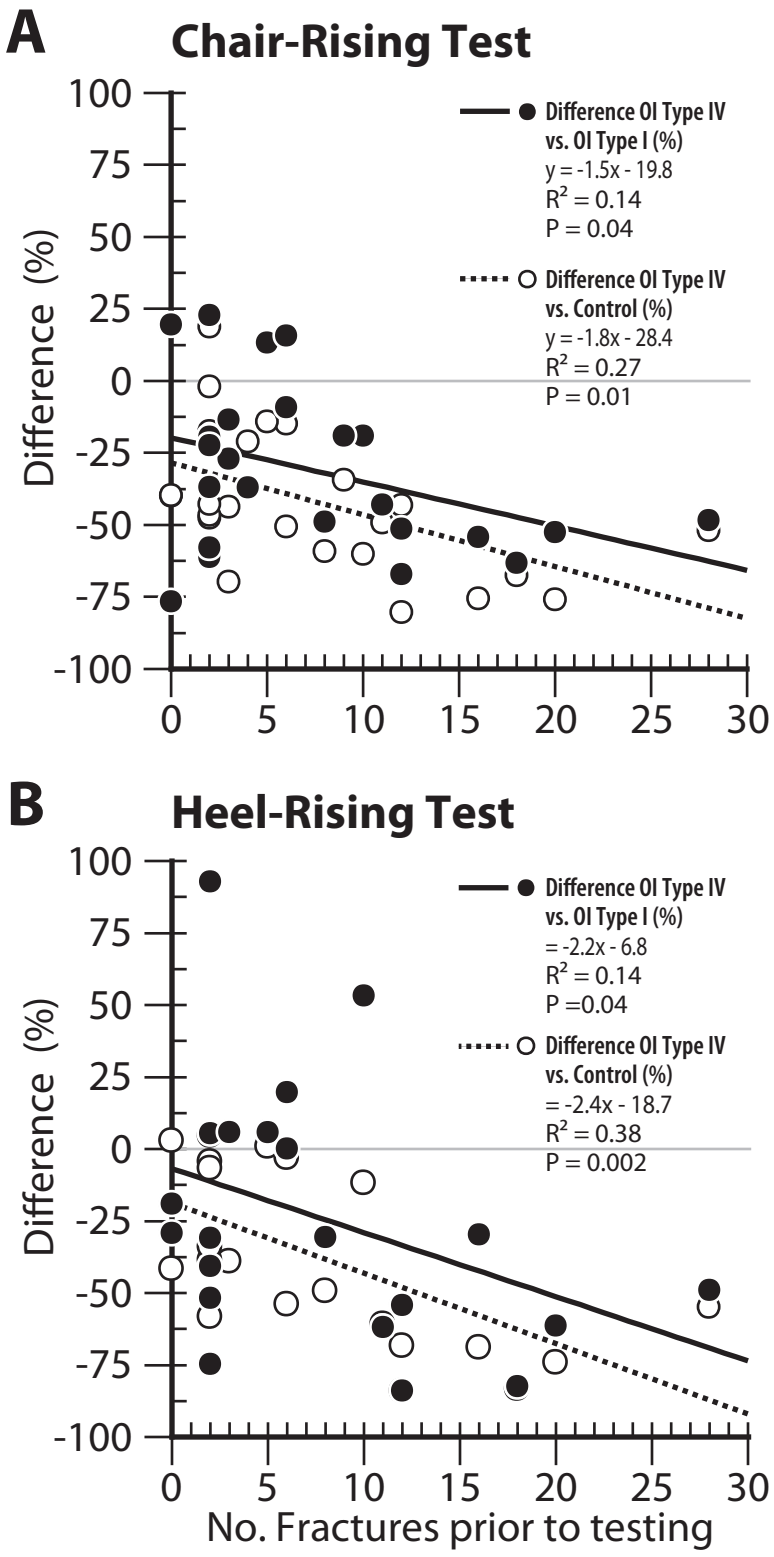


Figure 03



e.LNV.fig03-2_b ©¶[cs5].ai

Table 1. Anthropometric description of the study population

	OI type IV	OI type I	Control
N (Male/Female)	27 (15/12)	27 (15/12)	27 (15/12)
Age (years)	13.2 (4.1)	13.1 (4.1)	13.1 (4.3)
Height (m)	1.34 (0.19)[a, b]	1.48 (0.18)	1.53 (0.21)
Height (z-scores)	**-3.1 (-2.9)** [c]	**-0.7 (-0.9)** [c]	-0.2 (-0.4)
Body Mass (kg)	39.2 (16.8) [a, b]	42.1 (13.6)	47.2 (19.5)
Body Mass (z-scores)	**-1.2 (-1.1)** [a, c]	**-0.9 (-1.1)** [a, b, c]	-0.5 (-0.7)

Results are mean (SD).

[a] significant difference from controls ($p < 0.05$); [b] significant difference from OI type I ($p < 0.05$) ;

[c] significant difference from 0 ($p < 0.05$)

Table 2. Clinical data for the patients with OI type IV

Molecular Diagnosis	
Gene involved (*COL1A1*/*COL1A2*)	11/16
Type of Mutation (Glycine/C-Propeptide/Splice-site)	21/4/2
Bisphosphonate Treatment	
Received bisphosphonates (yes/no)	26/1
Age at start (years)	4.0 (3.8)
Time under treatment (years)	9.2 (2.7)
Lower Limbs Roddings	
Time since last surgery (years)	3.4 (3.0)
Femur rodding done (Patient N)	24
Femur rodding segments (Unilateral/Bilateral)	6/18
Tibia rodding done (Patient N)	14
Tibia rodding segments (Unilateral/Bilateral)	2/12
Fractures	
History of tibia and/or femur fractures (yes/no)	25/2
Time since last fracture (years)	3.4 (2.8)
Number of fractures prior to testing	8.6 (6.7)

Results are given as N or mean (SD)

Table 3. Mechanographic test results.

	OI type IV	OI type I	Control
Power tests			
Single Two-Legged Jump (n = 10/27)	4.0 (2.0) [a, b]	5.6 (1.7) [a]	6.6 (1.9)
Heel-Rising Test (n = 22/27)	7.3 (3.1) [a, b]	11.0 (2.4)	13.4 (4.2)
Chair-Rising Test (n = 25/27)	18.9 (12.1) [a, b]	39.6 (13.0)	47.9 (12.7)
Force tests			
Multiple Two-Legged Hopping (n = 11/27)	2.4 (0.4) [a]	2.5 (0.2) [a]	3.4 (0.6)
Multiple One-Legged Hopping-Right (n = 7/27)	2.7 (0.5)	2.6 (0.3) [a]	3.4 (0.4)
Multiple One-Legged Hopping-Left (n = 8/27)	3.5 (1.1) [a]	3.9 (0.6) [a]	5.2 (0.8)

Results are given as mean (SD)

[a] significant difference from controls ($p < 0.05$); [b] significant difference from OI type I ($p < 0.05$)

Table 4. Groups' Z-scores for Force (M1LH) and Power (S2LJ) mechanographic tests

	OI type IV		OI type I		Control	
	Age related z-scores	Weight related z-scores	Age related z-scores	Weight related z-scores	Age related z-scores	Weight related z-scores
M1LH (n=8)	-2.4 (1.5) [a, b]	-1.8 (1.1) [a, b]	-2.2 (1.1) [a, b]	-2.1 (1.0) [a, b]	1.3 (1.4)	0.6 (0.8)
S2LJ (n=11)	-2.0 (1.6) [a, b]	-1.1 (1.4)	-0.6 (0.9) [b]	-0.2 (1.0)	0.6 (0.5) [a]	0.8 (0.7) [a]

Results are given as mean (SD)

[a] significant difference from “0” ($p < 0.05$); [b] significant difference from controls ($p < 0.05$)

Table 5. Univariate Logistic Regression Analysis

Mecanographic tests	Predictor	Odds Ratio [CI]	P-Value
S2LJ	number of fracture prior to testing	2.1 [1.2,3.7]	< 0.001
M2LH	number of fracture prior to testing	1.4 [1.1,1.8]	0.001
M1LH-Right	number of fracture prior to testing	1.1 [0.9,1.3]	0.359
M1LH-Left	number of fracture prior to testing	1.5 [1.0,2.3]	0.002

S2LJ: Single Two-Legged Jump; M2LH: Multiple Two-Legged Hopping; M1LH: Multiple One-Legged Hopping; [CI]: 95% confidence intervals