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Title: Static postural control in youth with osteogenesis imperfecta type I

Article Type: Original Research

Keywords: Osteogenesis Imperfecta; Postural control; Mechanography; Muscle function; Proprioception, Typically developping

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Abstract: Objective: The first objective of the current study was to assess static postural control in eyes-open and eyes-closed conditions in individuals with osteogenesis imperfecta (OI) type I as compared to typically developing (TD) individuals. The second aim was to explore the relation between postural control and lower-limbs muscle function. Design: This is a cross-sectional study. Settings: The study was carried out in the outpatient department of a pediatric orthopedic hospital. Participants: 22 individuals with OI type I (mean age [range]: 13.1 [6-21] years) and 16 typically developing (TD) individuals (mean age [range]: 13.1 [6-20] years) participated in the study. A convenience sample of participants was selected. Participants were eligible if they were between 6 and 21 years and if they did not have any fracture or surgery in the lower limb in the 12 months prior to testing. Main Outcomes Measures: Postural control was assessed through static balance tests and muscle function through mechanograhic tests, on a force plateform. Selected postural parameters were: path length and velocity, 90% confidence ellipse area and the ellipse's medio-lateral and antero-posterior axes length. Mechanographic parameters were peak force (kN) and peak power (kW) as measured in the Multiple Two-Legged Hopping and the Single Two-Legged jump, respectively. Results: OI type I had poorer postural control than TD as indicated by longer and faster displacements and a larger ellipse area. Muscle function was unrelated to postural control in the OI group. Removing visual information resulted in a larger increase in postural control parameters for the OI group compared to the TD group. Conclusions: A proprioceptive deficit is suggested to explain decreased postural control in individuals with OI type I.

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Pediatric Specialty Care

Montréal, January 19th 2017

Dear editor,

We hereby submit for publication as original article the **reviewed version** of the manuscript ARCHIVES-PMR-D-16-00933 entitled "**Static postural control in youth with osteogenesis imperfecta type I**".

". We appreciated the comments of the reviewers and performed the suggested modifications. We hope this revision is satisfactory to both you and the reviewers. Modifications of the manuscript are detailed in a separate document (response to reviewer) and have been highlighted throughout the whole manuscript.

We truly believe that the content of this manuscript is well suited for *Archives of Physical Medicine and Rehabilitation* and will interest the readers of the journal.

All authors contributed significantly to the present manuscript. Each of the authors has read and concurs with the content in the final manuscript. The material within has not been and will not be submitted for publication elsewhere. Written permission has been obtained from all persons named in the Acknowledgments and patient consent forms have been collected.

Best regards,

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***Detailed Response to Reviewers**

Reviewer #1:

TITLE

- the main idea of the study is clear
- Concise

ABSTRACT

1. Concise and specific
2. Coherent and readable
3. Structured format

Action: No change made.

4. The state about randomization does not appear later in the methods, thus further elaboration is required

Action: The state about randomization in the abstract was removed. A state mentioning that a convenience sample was used was added (see line 9).

INTRODUCTION

5. Previous pertinent literature cited, however it should be further discussed

Action: As suggested, the pertinent literature is now discussed (line 32 to 34)

6. Purpose/research hypotheses are not stated

Action: The research hypotheses were added to the manuscript (see line 44).

7. Conceptualization and rationale of study clearly apparent

Action: No change made.

METHODS

8. Study design appropriate to achieve study objective

Action: No change made.

9. Study population clearly and adequately described

Action: No change made.

10. Sampling procedures are not sufficiently described - was it a randomized sample?

Action: 10. The sample presented in this study is a convenience sample as described in the method section (lines 64 to 66).

11. Statistical analyses appropriate and used appropriately

Action: No change made.

RESULTS

12. Results clearly presented

Action: No change made.

13. The order of figure captions does not match the figures order presented later.
Action: The order of figure caption was modified to match the order of figure presentation.

14. There is a mistake in table 2 in male/female values; in addition it is not clear why they are two values bolded
Action: Bold was removed and in addition sex ratios were corrected.

DISCUSSION
15. Previous pertinent literature is poorly critiqued
Action: To our knowledge, there is no other study evaluating postural control in patients with OI. Even if few studies suggest a balance deficit, no direct measure of postural control was realised. However, we are now discussing the study of Dahan-Oliel et al (2016) on mobility (see line 201 to 205). Moreover, a statement about previous literature linking proprioceptive deficit and postural control was added (lines 215 to 216).

16. Similarities and differences to other studies are not noted
Action: See previous comment.

17. Theoretical and rehabilitation implications are not identified
Action: A statement was added about the implication of the results in rehabilitation (line 249 to 250)

18. Limitations of study noted
Action: No change made.

19. Avenues for future research are not provided
Action: The future research avenues were added to the manuscript in the conclusion section (see line 249 to 250).

CONCLUSIONS
20. Clearly stated

Reviewer #2:

Dear Authors
the paper is well-written and organized.

Only one question: could ancova adjusted also for sex?

Action: The ANCOVA was adjusted also for sex. No main effects or interaction were found as indicated by all Ps > 0.225. A statement was added to the manuscript (lines 172 to 174).

Reviewer #3:

Summary: Study assessed parameters of postural control using a force platform in kids with and without OI type I. Kids with OI did more poorly, especially when tested with eyes closed.

The following should be addressed and/or clarified:

1. In methods, it states kids are considered to have OI type I if there is a positive family history and blue sclerae or DI. However, people with types III and IV OI can have children who may also have blue sclerae and DI. The phenotype would be quite different, but this is potentially confusing.

Action: ''No lower limbs long bones deformities'' was added to the inclusion criterion (line 60 and 62). As the presence of leg deformity is a clinical sign for OI type IV and III, this added criterion differentiates OI type I from other types. In addition, according to Sillence (1978), blue sclerae is mainly observed in OI type I.

2. Also under methods, it states that there was one child with neg testing for COL1A1 or COL1A2. Ideally the data would have been presented with and without this child's info. Also, Table 1 lists 2 neg tests, not 1.

Action: The classification for OI type I are based on a clinical diagnosis as described in the inclusion/exclusion criterion section. The genotype/phenotype relationship has been found to be rather week i.e., that the observed mutation does not systematically lead to the prediction of a given OI type (Ben Amor et al, 2011). Nevertheless, we did the analysis without this patient. It was found that none of the reported main effects or interactions were significantly affected by the removal of this patient. Therefore we opted to leave the analyses as is. We added a line to clarify the situation (lines 78 to 81).

Table 1 was adjusted properly. A splice mutation in Col1A1 was found for one patient just prior to submission.

3. In discussion, Second paragraph, line 187, the word "control" seems to be missing after postural.

Action: The word control was added at line 207.

4. Line 199, consider adding comma after muscles.

Action: A comma was added after muscles at line 219.

5. Final sentence under section Postural control tests is missing a period.

Action: A period was added to the sentence at line 129.

6. Figure 2 is apparently mislabeled figure 3 and I found it very confusing. Graph needs better labeling and explanation.

Action: The mislabelling of all figures was addressed. Further explanation of the figures was added into figure caption Also, the values presented in the graph relates to velocity and not path length. This has been modified in Figure 3's caption.

7. Figure 3 (apparently incorrectly labeled Figure 2) is confusing. Clarification of the p values within the graphs would be very helpful.
Action: Figure 3 is now labeled as Figure 3.The p values were clarified in the figure's caption.

8. Should address the possibility that effort in kids with OI was limited in jumping and hopping activities because of fear of fracture.
Action: A statement about this possible limitation was added to the manuscript (see line 239 to 242).

9. Could mention that another limitation was comparing kids with different sizes, which could explain part of the difference in strength.
Answer: In a previous study in OI type I and typically developed children, it has been demonstrated that force and power generation were not related to leg length (Veilleux et al, 2014). Furthermore, a previous study demonstrated a close link between age-related gain in muscle function during growth and increased height (Rauch et al, 2000). The result of force and power were normalized per body weight and body mass respectively as an attempt to control for the wide range of participants sizes.

***Title page with author details**

Running head: Postural Control in Osteogenesis Imperfecta

Static postural control in youth with osteogenesis imperfecta type I

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Preliminary results of this study were presented at the 2016 Scientific Day of the Quebec Rehabilitation Research Network (REPAR) on May 17th at Laval University in Québec city.

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Conflict of Interests: The authors declare no conflicts of interest.

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- Postural control deficits are reported in youth with OI type I;
- Poorer postural control was not associated with muscle function deficits;
- Proprioceptive deficits could explain poorer postural control in OI type I.

Static postural control in youth with osteogenesis imperfecta type I

Abstract

Objective: The first objective of the current study was to assess static postural control in eyes-open and eyes-closed conditions in individuals with osteogenesis imperfecta (OI) type I as compared to typically developing (TD) individuals. The second aim was to explore the relation between postural control and lower-limbs muscle function. **Design:** This is a cross-sectional study. **Settings:** The study was carried out in the outpatient department of a pediatric orthopedic hospital. **Participants:** 22 individuals with OI type I (mean age [range]: 13.1 [6-21] years) and 16 typically developing (TD) individuals (mean age [range]: 13.1 [6-20] years) participated in the study. A convenience sample of participants was selected. Participants were eligible if they were between 6 and 21 years and if they did not have any fracture or surgery in the lower limb in the 12 months prior to testing. **Main Outcomes Measures:** Postural control was assessed through static balance tests and muscle function through mechanograhic tests, on a force plateform. Selected postural parameters were: path length and velocity, 90% confidence ellipse area and the ellipse's medio-lateral and antero-posterior axes length. Mechanographic parameters were peak force (kN) and peak power (kW) as measured in the Multiple Two-Legged Hopping and the Single Two-Legged jump, respectively. **Results:** OI type I had poorer postural control than TD as indicated by longer and faster displacements and a larger ellipse area. Muscle function was unrelated to postural control in the OI group. Removing visual information resulted in a larger increase in postural control parameters for the OI group compared to the TD group. **Conclusions:** A proprioceptive deficit is suggested to explain decreased postural control in individuals with OI type I.

Key Words: Osteogenesis Imperfecta; Postural control; Mechanography; Muscle function; Proprioception, Typically developing

Abbreviations: TD: Typically developing; OI: Osteogenesis imperfecta ; CoF: Center of Force

Osteogenesis imperfecta (OI) is a congenital disorder characterized by increased bone fragility. Several types of the disorder are distinguished on the basis of clinical features and genetic findings, but OI type I is the most common type of OI [1]. OI type I is typically associated with a relatively mild phenotype with normal or near-normal height and absence of bone deformities [2]. OI type I is caused by mutations in one of the two genes that code for collagen type I alpha chains, *COL1A1* and *COL1A2* [1].

Previous studies have shown that individuals with OI type I, although generally fully mobile, may nevertheless experience limitations during walking, running and daily living activities [3, 4]. Specifically, the duration of the double support phase is lengthened in children with OI type I compared to typically developing children [5]. Increasing the duration of the double support phase may help children with OI to overcome postural control difficulties. In addition to those limitations, we have recently shown that muscle weakness was present in 80% of patients with a confirmed *COL1A1/COL1A2* mutation and an OI type I phenotype [6, 7]. In pediatric populations with muscle weaknesses, previous studies have shown that deficits in muscle function was associated poorer postural control [8, 9]. Based on these results, it can be hypothesized that the muscle weakness frequently observed in OI type I leads to decreased postural control in this population.

The goal of the current study was twofold: (1) to determine whether postural control was normal in individuals with OI type I as compared to typically developping children and (2) to determine whether the previously reported deficits in muscle function are related to postural control in youth with OI type I. We hypothesis that postural control is affected in individual with OI type I as compared to typically developing children and muscle function are related to postural control in youth with OI type I.

Methods

Study population

The study population comprised individuals with a clinical diagnosis of OI type I who were followed in the outpatients department at the Shriners Hospital for Children-Canada between February 2012 and July 2013. Patients were classified as having OI type I if they fulfilled one of the following criteria:

1. In the presence of a family history of OI: presence of blue sclerae or dentinogenesis imperfecta and no lower limbs long bones deformities.
2. In the absence of a positive family history: presence of at least one fracture and either blue sclerae or dentinogenesis imperfecta and no lower limbs long bones deformities.

Because the assessments require substantial cooperation, children under 6 years of age can usually not be assessed. Participants were not eligible for the study if they had any fracture or surgery in the lower limb in the 12 months prior to testing.

The current research was part of an exploratory aim of a larger research project[6, 10] and participation to the postural control tasks was done on a voluntary basis. Sample size was defined by the participants who volunteered to take part in the postural control study.

Twenty-two individuals were recruited to participate (mean age [SD]: 13.1 [4.2] years; 14 females). Genetic testing for mutations in *COL1A1* or *COL1A2* had been performed in all individuals. In 21 patients, genetic testing had revealed a disease-causing mutation in *COL1A1* or *COL1A2*. No disease-causing mutation was found in one individual, even though he presented typical clinical signs of mild OI (Table 1). Statistical analyses have been run with and without this individual. Results remained the same with or without this individual's data and we therefore opted to keep his results in our analyses. The main reason for this is that individuals

with OI are generally classified based on a clinical diagnosis rather than a genetic one. Sixteen typically developing individuals (TD) were also recruited as controls (mean age [SD]: 12.6 [4.1] years; 10 females). The control group was comprised of children of employees and general population. All participants were between 6 and 21 years of age.

This study was approved by the Institutional Review Board of the Faculty of Medicine of McGill University. Informed consent was provided by participants or, in minors, by their parents. Assent was provided by participants aged between 7 to 17 years.

Test procedures

After weight and height measurements, postural control test and muscle function was assessed using a vertical ground reaction measuring force plate (Leonardo Mechanograph® Ground Reaction Force Plate; Novotec Medical Inc, Pforzheim, Germany).

The force plate was connected to a laptop computer and force measurements were sampled at a frequency of 800 Hz. As described in detail elsewhere, all 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 [b]) [11].

Anthropometric measurements

Height was measured using a Harpenden stadiometer [a]. Body mass was determined using the Leonardo Mechanograph® GRFP [b] for all participants. Height and weight were converted to age- and sex-specific z-scores on the basis of reference data published by the Centers for Disease Control and Prevention [12].

Postural control tests

Postural control tests were done on a force platform without shoes. Feet were placed by the experimenter at hip width in a natural position with arms at their sides. Participants were asked to maintain a quiet upright standing posture and remain as stable as possible for the duration of each trial.

Three trials of 40 seconds were performed in each of two visual conditions: eyes-open and eyes-closed. These two conditions were selected to evaluate the importance of visual and proprioceptive inputs on postural control [13]. A one minute rest period was given to the participant between conditions. The order of presentation of the visual conditions was counterbalanced within each experimental group.

The first and last 5 seconds of data acquisition were trimmed with the GRFP software. This allowed removal of stabilisation that could occur just after the beginning of the test and at the end of it, due to the transient nature of these phases [14, 15]. Therefore, a 30 second time frame was left for analysis which is sufficient to produce reliable measurements [16]. The three trials were averaged and the mean value was used for statistical analysis.

Three postural control parameters were selected to quantify the individual's (in)stability performance (Figure 1): (1) Path length is the distance travelled by the center of force (CoF); (2) Velocity is defined as the ratio between path length and the total duration of the test (30s) and is recognize as one of the most sensitive [17] and reproducible [18] measure to assess postural control. (3) The 90% confidence ellipse is defined as the ellipse that contains the center of the points of the CoF with a 90% probability [19]. Three variables are computed from the ellipse: the ellipse area which defined as being the surface covered by the 90% confidence ellipse [20], the medio-lateral ellipse axis length and the antero-posterior ellipse axis length (see Figure 1 for

details). Whereas the area provides a general measure of performance (the smaller the better), the axes length allows a better understanding of the direction in which the instability is more important [21].

Mechanography

Muscle function was assessed by two different tests: (1) multiple two-legged hopping, representing vertical hopping on both forefeet (similar to rope-skipping). The aim of this hopping tests is to achieve maximal ground reaction forces during eccentric muscle contraction [22]. (2) Single two-legged jump, a vertical countermovement jump to achieve maximum jump height during a stretch-shortening cycle movement.

Each test was repeated three times and the 'best' result was retained as the participant's test result. The definition of 'best' result was: (1) Highest peak force for a given hop in the multiple two-legged hopping; (2) highest peak power of the take-off phase during a single two-legged jump [11]. For the multiple one- and two-legged hopping, the main outcome parameter was peak force and peak force relative to body weight, whereas for the single two-legged jump, the main outcome parameter was peak power and peak power relative to body mass.

Statistical Analysis

Results are presented as mean (SD) and a P value < 0.05 was considered significant. The groups' sex ratios (Male vs Female) and anthropometrics (height, body mass and age) were compared with Chi-square and independent sample t-tests, respectively. One sample t-tests were used to determine whether height and body mass z-scores were different from zero.

Normality of the postural control parameter distributions were examined with the Shapiro-Wilk test. Analyses of postural control parameters were performed with repeated measure

ANCOVAs. Covariates were standing sex (male = 0; female =1), height (cm) and age (years), as these factors influence balance performance [23, 24]. Therefore all five posturographic parameters were analysed independently with a 2 groups (OI; TD) X 2 visual conditions (eyes open; eyes closed) with repeated measure on the last factor.

In order to determine whether there was a relationship between lower limb muscle function and postural control, simple bivariate correlations were performed. Specifically, peak force as measured during the multiple two-legged hopping, and peak power as measured during single two-legged jump were assessed independently with all five posturographic parameters.

All calculations were performed using IBM SPSS Statistics 20® [c].

Results

The majority of the study participants with OI had a history of femur and/or tibia fracture (Table 1), but these fractures had occurred more than 12 months prior to testing. More than half of individuals in the OI group had received intravenous bisphosphonate treatment. The OI group had lower mean z-scores for height and body mass than the TD group (Table 2).

Posturographic testing revealed poorer performance in the OI group for each of the five parameters (Table 3). No significant interactions involving the sex and height as covariates were found (all $P > 0.22$), whereas Age was found to interact significantly with velocity ($P = 0.04$) and ellipse's length of the medio-lateral axis ($P = 0.05$). Corrected values at age = 13.0 were used. Figure 3 illustrates the interaction between the experimental groups and the visual conditions. For the ellipse's related parameters, there was a main effect of visual conditions indicating that removing visual information resulted in a larger increase in length of the medio-lateral axis ($p = 0.04$), whereas a main effect of group showed that the ellipse's area was larger and both

ellipse's axes longer in the OI group than in the TD group ($p = 0.04$; $p = 0.06$; $p = 0.03$, respectively for the ellipse's area, the antero-posterior axis and medio-lateral axis).

Mechanographic testing showed that lower limbs peak muscle force (kN) and relative peak force (multiples of body weight) during multiple two-legged hopping were lower in the OI group than in the TD group (Table 4). Group differences in lower limbs peak muscle power (kW) and relative peak power (W/kg) during the single two-legged jump did not reach significance.

Independent correlation analyses for the OI type I group revealed no significant relationship between lower limb muscle force/power and posturographic performance variables (All P values > 0.09) whereas for the TD group, lower limb peak muscle force was significantly related to average velocity (Figure 3 A-C) and path length. A tendency for lower limbs peak muscle power to be related to velocity (Figure 3 B-D) and path length was observed in both visual conditions.

Discussion

The present results showed that individuals with OI type I had poorer postural control than typically developing individuals and that this was not associated with muscle weakness. The most interesting results of the study comes from the observation of increased reliance on visual input in the OI group compared to the TD group, suggesting proprioceptive postural control deficits.

To the best of our knowledge, this study is the first to evaluate static postural control in youth with OI type I. Limitations in daily life activities and mobility have been previously described by questionnaire suggesting postural control impairment [25]. However, even if balance is a major component of mobility, it was not known whether postural control is affected in youth with OI

Based on previous literature related to pediatric disorders with muscle weaknesses [8, 9], it was hypothesised that muscle function deficits [5-7] would be related to poorer postural control in OI as compared to typically developing individuals. The absence of significant correlation between muscle function parameters and postural control parameters suggests that the apparent muscle function deficit reported in OI type I was not important enough to impact postural control other factors might be more important to account for it.

To this end, one potential factor to explain the poorer postural control observed in OI might be linked to altered proprioception as it has been reported in other pediatric populations with altered proprioception [26, 27]. In the current study, it was shown that removing visual information resulted in a more important performance decrement for the OI than for the TD group, indicating greater reliance on visual information and deficits in proprioceptive information processing. There are many factors in OI that are susceptible to affect haptic and proprioceptive sensory information most of which are linked to collagen type I, the defective protein in OI. Collagen type I is a major component of skin, tendon, ligaments and muscles, the properties of which have been shown to be affected in OI either in mouse models [28-30] or in human [31]. In turn, muscles [9], tendons [32], ligaments [33] and skin [34] all have been shown to have an impact on postural control. Although speculative at this point, it could be suggested that joint hypermobility due to hyperlaxity of the ligaments, a clinical feature frequently reported in OI [35], contributes to poorer postural control through ankle joint instability [36]. In the same vein, a loss in elasticity at the skin level or changes in tendon properties are both likely to affect the perception of a perturbation that would require a postural adjustment [37].

Study limitations

One study limitation was that the control group was not matched for age and sex. However,

231 statistical analyses revealed that both groups were equivalent with regard to these two
232 parameters. Another study limitation is that dynamic tests (requiring eccentric and concentric
233 muscle contractions) were used to assess the relationship between muscle function and static
234 postural control (requiring isometric contractions). It is suggested that there is only a weak
235 association between these two types of muscle functions [38] and this may have limited the
236 chances of observing a significant association between postural control and muscle function in
237 the OI population. However, the fact that a significant association was found between these two
238 factors in the TD group casts some doubts on this interpretation. Nevertheless, it is suggested
239 that it may be more appropriate to use isometric muscle function tests to assess the relationship
240 with static postural control and dynamic function test for dynamic postural control. The fear of
241 fracture reported in this population in previous study [39] may have limited the effort of participants
242 in the jumping and hopping task and again may have limited the chances of observing a
243 significant association between postural control and muscle function.
244
245 **Conclusion**
246 The data of the current study showed poorer postural control in individuals with OI type I
247 compared to typically developing individuals and further indicated that this might be associated
248 to a proprioceptive deficit. Due to the importance of postural control in fall risks, it can be
249 hypothesized that young individual with OI are more at risks for falls than typically developing
250 young individuals. Therapies aimed at improving postural control might reduce falls risk and
251 fracture frequency in children and adolescents with OI type I.
252

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Figure Captions

Figure 1. Plot of a typical center of force recordings over a 30s period. (1) path length (grey irregular line): path of variation of position of the force vector entering the platform (center of force; CoF); (2) 90% confidence ellipse (cm^2; black plain line), the ellipse's area is the area defined by the ellipse countour; (3) Ellipse's medio-lateral axis length (black doted line); (4) Ellipse's antero-posterior axis length (black dashed line)

Figure 2. Relative performance decrement (in %) when contrasting the eyes closed to the eyes open condition (i.e by how much in % balance performance decreased when vision was removed). The ANCOVA revealed a group x visual condition interaction for path length ($p = 0.006$) and velocity ($p = 0.001$), indicating that removing visual information resulted in performance deterioration for both groups and for both parameters but that this deterioration was significantly more important for the OI group than for the TD group. OI: osteogenesis imperfecta; TD: typically developing.

Figure 3 A-D. Independent bivariate correlation analyses between average velocity (mm/s) posturographic parameters and lower limb peak force (A-B) and peak power (C-D) in the eyes closed (A-C) and eyes open conditions (B-D). R= coefficient of correlation; P = P values are indicating whether there was a significant correlation between muscle function (peak force and power) and average velocity. OI: osteogenesis imperfecta; TD: typically developing.

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Static postural control in youth with osteogenesis imperfecta type I

Abstract

Objective: The first objective of the current study was to assess static postural control in eyes-open and eyes-closed conditions in individuals with osteogenesis imperfecta (OI) type I as compared to typically developing (TD) individuals. The second aim was to explore the relation between postural control and lower-limbs muscle function. **Design:** This is a cross-sectional study. **Settings:** The study was carried out in the outpatient department of a pediatric orthopedic hospital. **Participants:** 22 individuals with OI type I (mean age [range]: 13.1 [6-21] years) and 16 typically developing (TD) individuals (mean age [range]: 13.1 [6-20] years) participated in the study. A convenience sample of participants was selected. Participants were eligible if they were between 6 and 21 years and if they did not have any fracture or surgery in the lower limb in the 12 months prior to testing. **Main Outcomes Measures:** Postural control was assessed through static balance tests and muscle function through mechanograhic tests, on a force plateform. Selected postural parameters were: path length and velocity, 90% confidence ellipse area and the ellipse's medio-lateral and antero-posterior axes length. Mechanographic parameters were peak force (kN) and peak power (kW) as measured in the Multiple Two-Legged Hopping and the Single Two-Legged jump, respectively. **Results:** OI type I had poorer postural control than TD as indicated by longer and faster displacements and a larger ellipse area. Muscle function was unrelated to postural control in the OI group. Removing visual information resulted in a larger increase in postural control parameters for the OI group compared to the TD group. **Conclusions:** A proprioceptive deficit is suggested to explain decreased postural control in individuals with OI type I.

Key Words: Osteogenesis Imperfecta; Postural control; Mechanography; Muscle function; Proprioception, Typically developing

Abbreviations: TD: Typically developing; OI: Osteogenesis imperfecta ; CoF: Center of Force

Osteogenesis imperfecta (OI) is a congenital disorder characterized by increased bone fragility. Several types of the disorder are distinguished on the basis of clinical features and genetic findings, but OI type I is the most common type of OI [1]. OI type I is typically associated with a relatively mild phenotype with normal or near-normal height and absence of bone deformities [2]. OI type I is caused by mutations in one of the two genes that code for collagen type I alpha chains, *COL1A1* and *COL1A2* [1].

Previous studies have shown that individuals with OI type I, although generally fully mobile, may nevertheless experience limitations during walking, running and daily living activities [3, 4]. Specifically, the duration of the double support phase is lengthened in children with OI type I compared to typically developing children [5]. Increasing the duration of the double support phase may help children with OI to overcome postural control difficulties. In addition to those limitations, we have recently shown that muscle weakness was present in 80% of patients with a confirmed *COL1A1/COL1A2* mutation and an OI type I phenotype [6, 7]. In pediatric populations with muscle weaknesses, previous studies have shown that deficits in muscle function was associated poorer postural control [8, 9]. Based on these results, it can be hypothesized that the muscle weakness frequently observed in OI type I leads to decreased postural control in this population.

The goal of the current study was twofold: (1) to determine whether postural control was normal in individuals with OI type I as compared to typically developping children and (2) to determine whether the previously reported deficits in muscle function are related to postural control in youth with OI type I. We hypothesis that postural control is affected in individual with OI type I as compared to typically developing children and muscle function are related to postural control in youth with OI type I.

Methods

Study population

The study population comprised individuals with a clinical diagnosis of OI type I who were followed in the outpatients department at the Shriners Hospital for Children-Canada between February 2012 and July 2013. Patients were classified as having OI type I if they fulfilled one of the following criteria:

1. In the presence of a family history of OI: presence of blue sclerae or dentinogenesis imperfecta and no lower limbs long bones deformities.
2. In the absence of a positive family history: presence of at least one fracture and either blue sclerae or dentinogenesis imperfecta and no lower limbs long bones deformities.

Because the assessments require substantial cooperation, children under 6 years of age can usually not be assessed. Participants were not eligible for the study if they had any fracture or surgery in the lower limb in the 12 months prior to testing.

The current research was part of an exploratory aim of a larger research project[6, 10] and participation to the postural control tasks was done on a voluntary basis. Sample size was defined by the participants who volunteered to take part in the postural control study.

Twenty-two individuals were recruited to participate (mean age [SD]: 13.1 [4.2] years; 14 females). Genetic testing for mutations in *COL1A1* or *COL1A2* had been performed in all individuals. In 21 patients, genetic testing had revealed a disease-causing mutation in *COL1A1* or *COL1A2*. No disease-causing mutation was found in one individual, even though he presented typical clinical signs of mild OI (Table 1). Statistical analyses have been run with and without this individual. Results remained the same with or without this individual's data and we therefore opted to keep his results in our analyses. The main reason for this is that individuals

with OI are generally classified based on a clinical diagnosis rather than a genetic one. Sixteen typically developing individuals (TD) were also recruited as controls (mean age [SD]: 12.6 [4.1] years; 10 females). The control group was comprised of children of employees and general population. All participants were between 6 and 21 years of age.

This study was approved by the Institutional Review Board of the Faculty of Medicine of McGill University. Informed consent was provided by participants or, in minors, by their parents. Assent was provided by participants aged between 7 to 17 years.

Test procedures

After weight and height measurements, postural control test and muscle function was assessed using a vertical ground reaction measuring force plate (Leonardo Mechanograph® Ground Reaction Force Plate; Novotec Medical Inc, Pforzheim, Germany).

The force plate was connected to a laptop computer and force measurements were sampled at a frequency of 800 Hz. As described in detail elsewhere, all 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 [b]) [11].

Anthropometric measurements

Height was measured using a Harpenden stadiometer [a]. Body mass was determined using the Leonardo Mechanograph® GRFP [b] for all participants. Height and weight were converted to age- and sex-specific z-scores on the basis of reference data published by the Centers for Disease Control and Prevention [12].

Postural control tests

Postural control tests were done on a force platform without shoes. Feet were placed by the experimenter at hip width in a natural position with arms at their sides. Participants were asked to maintain a quiet upright standing posture and remain as stable as possible for the duration of each trial.

Three trials of 40 seconds were performed in each of two visual conditions: eyes-open and eyes-closed. These two conditions were selected to evaluate the importance of visual and proprioceptive inputs on postural control [13]. A one minute rest period was given to the participant between conditions. The order of presentation of the visual conditions was counterbalanced within each experimental group.

The first and last 5 seconds of data acquisition were trimmed with the GRFP software. This allowed removal of stabilisation that could occur just after the beginning of the test and at the end of it, due to the transient nature of these phases [14, 15]. Therefore, a 30 second time frame was left for analysis which is sufficient to produce reliable measurements [16]. The three trials were averaged and the mean value was used for statistical analysis.

Three postural control parameters were selected to quantify the individual's (in)stability performance (Figure 1): (1) Path length is the distance travelled by the center of force (CoF); (2) Velocity is defined as the ratio between path length and the total duration of the test (30s) and is recognize as one of the most sensitive [17] and reproducible [18] measure to assess postural control. (3) The 90% confidence ellipse is defined as the ellipse that contains the center of the points of the CoF with a 90% probability [19]. Three variables are computed from the ellipse: the ellipse area which defined as being the surface covered by the 90% confidence ellipse [20], the medio-lateral ellipse axis length and the antero-posterior ellipse axis length (see Figure 1 for

details). Whereas the area provides a general measure of performance (the smaller the better), the axes length allows a better understanding of the direction in which the instability is more important [21].

Mechanography

Muscle function was assessed by two different tests: (1) multiple two-legged hopping, representing vertical hopping on both forefeet (similar to rope-skipping). The aim of this hopping tests is to achieve maximal ground reaction forces during eccentric muscle contraction [22]. (2) Single two-legged jump, a vertical countermovement jump to achieve maximum jump height during a stretch-shortening cycle movement.

Each test was repeated three times and the 'best' result was retained as the participant's test result. The definition of 'best' result was: (1) Highest peak force for a given hop in the multiple two-legged hopping; (2) highest peak power of the take-off phase during a single two-legged jump [11]. For the multiple one- and two-legged hopping, the main outcome parameter was peak force and peak force relative to body weight, whereas for the single two-legged jump, the main outcome parameter was peak power and peak power relative to body mass.

Statistical Analysis

Results are presented as mean (SD) and a P value < 0.05 was considered significant. The groups' sex ratios (Male vs Female) and anthropometrics (height, body mass and age) were compared with Chi-square and independent sample t-tests, respectively. One sample t-tests were used to determine whether height and body mass z-scores were different from zero.

Normality of the postural control parameter distributions were examined with the Shapiro-Wilk test. Analyses of postural control parameters were performed with repeated measure

ANCOVAs. Covariates were standing sex (male = 0; female =1), height (cm) and age (years), as these factors influence balance performance [23, 24]. Therefore all five posturographic parameters were analysed independently with a 2 groups (OI; TD) X 2 visual conditions (eyes open; eyes closed) with repeated measure on the last factor.

In order to determine whether there was a relationship between lower limb muscle function and postural control, simple bivariate correlations were performed. Specifically, peak force as measured during the multiple two-legged hopping, and peak power as measured during single two-legged jump were assessed independently with all five posturographic parameters.

All calculations were performed using IBM SPSS Statistics 20® [c].

Results

The majority of the study participants with OI had a history of femur and/or tibia fracture (Table 1), but these fractures had occurred more than 12 months prior to testing. More than half of individuals in the OI group had received intravenous bisphosphonate treatment. The OI group had lower mean z-scores for height and body mass than the TD group (Table 2).

Posturographic testing revealed poorer performance in the OI group for each of the five parameters (Table 3). No significant interactions involving the sex and height as covariates were found (all P > 0.22), whereas Age was found to interact significantly with velocity (P = 0.04) and ellipse's length of the medio-lateral axis (P = 0.05). Corrected values at age = 13.0 were used. Figure 3 illustrates the interaction between the experimental groups and the visual conditions. For the ellipse's related parameters, there was a main effect of visual conditions indicating that removing visual information resulted in a larger increase in length of the medio-lateral axis (p = 0.04), whereas a main effect of group showed that the ellipse's area was larger and both

ellipse's axes longer in the OI group than in the TD group ($p = 0.04$; $p = 0.06$; $p = 0.03$, respectively for the ellipse's area, the antero-posterior axis and medio-lateral axis).

Mechanographic testing showed that lower limbs peak muscle force (kN) and relative peak force (multiples of body weight) during multiple two-legged hopping were lower in the OI group than in the TD group (Table 4). Group differences in lower limbs peak muscle power (kW) and relative peak power (W/kg) during the single two-legged jump did not reach significance.

Independent correlation analyses for the OI type I group revealed no significant relationship between lower limb muscle force/power and posturographic performance variables (All P values > 0.09) whereas for the TD group, lower limb peak muscle force was significantly related to average velocity (Figure 3 A-C) and path length. A tendency for lower limbs peak muscle power to be related to velocity (Figure 3 B-D) and path length was observed in both visual conditions.

Discussion

The present results showed that individuals with OI type I had poorer postural control than typically developing individuals and that this was not associated with muscle weakness. The most interesting results of the study comes from the observation of increased reliance on visual input in the OI group compared to the TD group, suggesting proprioceptive postural control deficits.

To the best of our knowledge, this study is the first to evaluate static postural control in youth with OI type I. Limitations in daily life activities and mobility have been previously described by questionnaire suggesting postural control impairment [25]. However, even if balance is a major component of mobility, it was not known whether postural control is affected in youth with OI

Based on previous literature related to pediatric disorders with muscle weaknesses [8, 9], it was hypothesised that muscle function deficits [5-7] would be related to poorer postural control in OI as compared to typically developing individuals. The absence of significant correlation between muscle function parameters and postural control parameters suggests that the apparent muscle function deficit reported in OI type I was not important enough to impact postural control other factors might be more important to account for it.

To this end, one potential factor to explain the poorer postural control observed in OI might be linked to altered proprioception as it has been reported in other pediatric populations with altered proprioception [26, 27]. In the current study, it was shown that removing visual information resulted in a more important performance decrement for the OI than for the TD group, indicating greater reliance on visual information and deficits in proprioceptive information processing. There are many factors in OI that are susceptible to affect haptic and proprioceptive sensory information most of which are linked to collagen type I, the defective protein in OI. Collagen type I is a major component of skin, tendon, ligaments and muscles, the properties of which have been shown to be affected in OI either in mouse models [28-30] or in human [31]. In turn, muscles [9], tendons [32], ligaments [33] and skin [34] all have been shown to have an impact on postural control. Although speculative at this point, it could be suggested that joint hypermobility due to hyperlaxity of the ligaments, a clinical feature frequently reported in OI [35], contributes to poorer postural control through ankle joint instability [36]. In the same vein, a loss in elasticity at the skin level or changes in tendon properties are both likely to affect the perception of a perturbation that would require a postural adjustment [37].

Study limitations

One study limitation was that the control group was not matched for age and sex. However,

231 statistical analyses revealed that both groups were equivalent with regard to these two
232 parameters. Another study limitation is that dynamic tests (requiring eccentric and concentric
233 muscle contractions) were used to assess the relationship between muscle function and static
234 postural control (requiring isometric contractions). It is suggested that there is only a weak
235 association between these two types of muscle functions [38] and this may have limited the
236 chances of observing a significant association between postural control and muscle function in
237 the OI population. However, the fact that a significant association was found between these two
238 factors in the TD group casts some doubts on this interpretation. Nevertheless, it is suggested
239 that it may be more appropriate to use isometric muscle function tests to assess the relationship
240 with static postural control and dynamic function test for dynamic postural control. The fear of
241 fracture reported in this population in previous study [39] may have limited the effort of participants
242 in the jumping and hopping task and again may have limited the chances of observing a
243 significant association between postural control and muscle function.
244
245 **Conclusion**
246 The data of the current study showed poorer postural control in individuals with OI type I
247 compared to typically developing individuals and further indicated that this might be associated
248 to a proprioceptive deficit. Due to the importance of postural control in fall risks, it can be
249 hypothesized that young individual with OI are more at risks for falls than typically developing
250 young individuals. Therapies aimed at improving postural control might reduce falls risk and
251 fracture frequency in children and adolescents with OI type I.
252

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Figure Captions

Figure 1. Plot of a typical center of force recordings over a 30s period. (1) path length (grey irregular line): path of variation of position of the force vector entering the platform (center of force; CoF); (2) 90% confidence ellipse (cm^2; black plain line), the ellipse's area is the area defined by the ellipse countour; (3) Ellipse's medio-lateral axis length (black doted line); (4) Ellipse's antero-posterior axis length (black dashed line)

Figure 2. Relative performance decrement (in %) when contrasting the eyes closed to the eyes open condition (i.e by how much in % balance performance decreased when vision was removed). The ANCOVA revealed a group x visual condition interaction for path length ($p = 0.006$) and velocity ($p = 0.001$), indicating that removing visual information resulted in performance deterioration for both groups and for both parameters but that this deterioration was significantly more important for the OI group than for the TD group. OI: osteogenesis imperfecta; TD: typically developing.

Figure 3 A-D. Independent bivariate correlation analyses between average velocity (mm/s) posturographic parameters and lower limb peak force (A-B) and peak power (C-D) in the eyes closed (A-C) and eyes open conditions (B-D). R= coefficient of correlation; P = P values are indicating whether there was a significant correlation between muscle function (peak force and power) and average velocity. OI: osteogenesis imperfecta; TD: typically developing.

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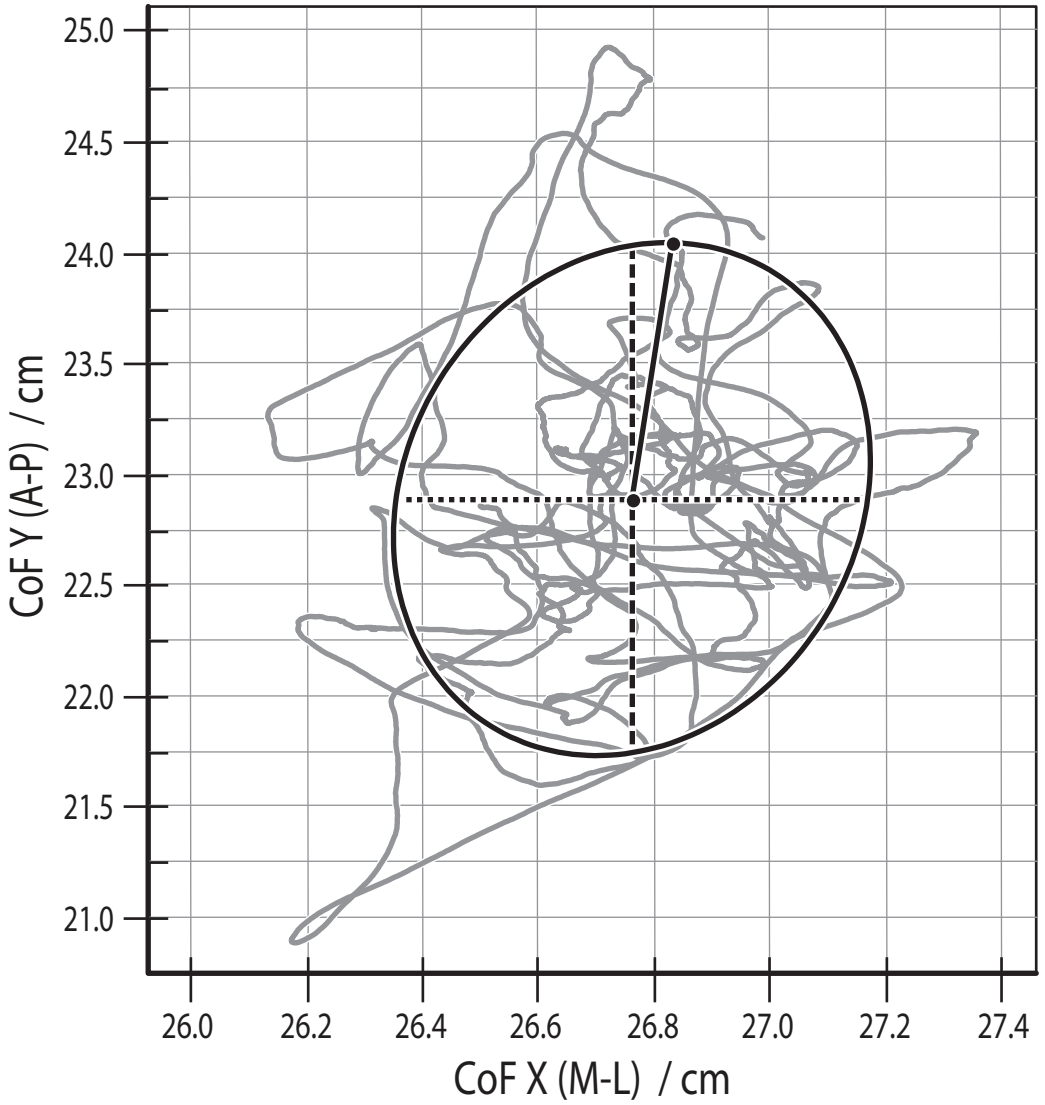
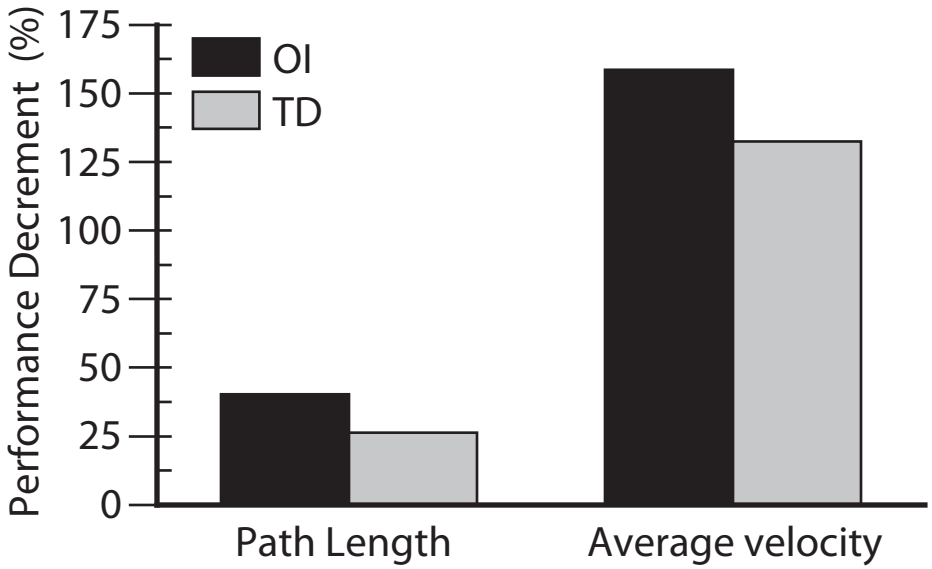
Figure 01



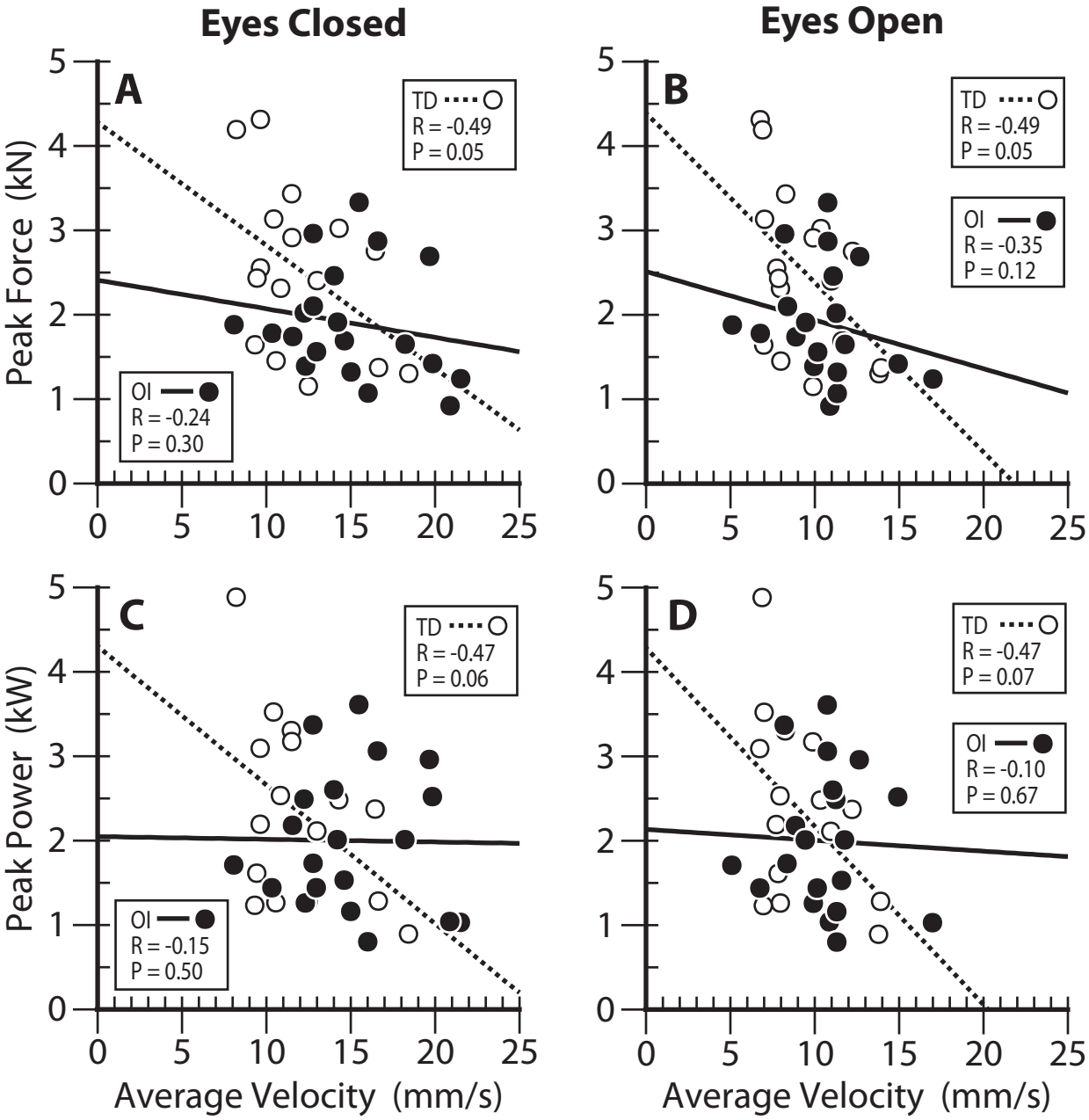
g.LNV. fig01b ß¶[cs5].ai

Figure 02



g.LNV.fig03c ß¶[cs5].ai

Figure 03



g.LNV.fig02-2d ß¶[cs5].ai

Table 1

Table 1. Clinical data for the patients with mild OI

Molecular Diagnosis	
Gene involved (*COL1A1*/*COL1A2*/Negative)	18/3/1
Type of Mutation (Haploinsufiency/Others/Negative)	11/10/1
Bisphosphonate Treatment	
Received bisphosphonates (yes/no)	12/10
Time under treatment (years)	5.7 (2.8)
Lower Limbs Roddings	
Time since last surgery (years)	6.0 (2.8)
Femur rodding done (Patient N)	1
Tibia rodding done (Patient N)	3
Fractures	
History of Femur fractures (yes/no)	3/18
Time since last Femur fracture (years)	11.9 (3.6)
Number of Femur fractures prior to testing	2.0 (1.0)
History of tibia fractures (yes/no)	15/7
Time since last tibia fracture (years)	3.4 (2.8)
Number of tibia fractures prior to testing	2.7 (1.7)

Results are given as N or mean (SD)

Table 2

Table 2. Anthropometric description of the study populations

	OI type I	Control
N (Male/Female)	22 (8/14)	16 (6/10)
Age (years)	13.1 (4.1)	13.1 (4.3)
Height (m)	1.50 (0.21)	1.56 (0.21)
Height (z-scores)	-0.4 (1.5)	0.9 (0.8) [a]
Body Mass (kg)	45 (18)	52 (18)
Body Mass (z-scores)	-0.4 (1.6)	0.8 (0.7) [a]

Results are mean (SD).

[a] Z-scores significantly different from 0 ($p < 0.05$); no other significant difference were observed

Table 3

Table 3. Posturographic data parameters

	Eyes Opened		% diff.	Eyes Closed		% diff.
	OI	TD		OI	TD	
Path Length (mm)	329 (83)	279 (72)	18	461 (112)	352 (90)	31
Average velocity (mm/s)	6 (2)	5 (2)	20	15 (4)	12 (3)	25
95% Standard Ellipse						
Area (cm^2)	1.48 (0.90)	0.93 (0.51)	59	2.39 (1.66)	1.43 (1.21)	67
Antero-posterior axis length (cm)	1.83 (0.48)	1.62 (0.60)	13	2.42 (0.84)	1.88 (0.69)	29
Medio-lateral axis length (cm)	1.09 (0.51)	0.79 (0.27)	38	1.24 (0.53)	0.94 (0.43)	32

Results are mean (SD)

Covariates appearing in the model are evaluated at the following values: Age = 13.0, Height = 141.4.

Table 4

Table 4. Mechanographic data parameters

	OI	TD	ANCOVA
Multiple Two-Legged Hopping (Force test)			
Peak force (kN)	1.84 (0.71)	2.52 (0.98)	F(1, 33) = 30.09, p < 0.001
Relative Peak Force (multiples of body weight)	4.03 (0.56)	4.99 (0.64)	F(1, 33) = 21.83, p < 0.001
Single Two-Legged Jump (Power test)			
Peak Power (kW)	2.03 (0.82)	2.32 (1.08)	F(1, 33) = 3.82, p = 0.06
Relative Peak Power (W/kg)	40 (6)	42 (10)	F(1, 33) = 1.95, p = 0.17

Results are mean (SD)

Covariates appearing in the model are evaluated at the following values: Age = 13.2, Height = 142.2.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	X
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	X
Methods			
Study design	4	Present key elements of study design early in the paper	X
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X
Bias	9	Describe any efforts to address potential sources of bias	X
Study size	10	Explain how the study size was arrived at	X
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	X
		(*b*) Describe any methods used to examine subgroups and interactions	X
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NX
		(*e*) Describe any sensitivity analyses	X
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X
		(b) Indicate number of participants with missing data for each variable of interest	X
Outcome data	15*	Report numbers of outcome events or summary measures	X
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

Discussion			
Key results	18	Summarise key results with reference to study objectives	X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X
Generalisability	21	Discuss the generalisability (external validity) of the study results	X
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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