Evaluation of Body Composition in Paediatric Osteogenesis Imperfecta

Misha Gilani, Sheila Shepherd, Ben Nichols, Konstantinos Gerasimidis, Sze Choong Wong, and Avril Mason

Abstract

Background: Osteogenesis Imperfecta (OI) is a skeletal disorder characterised by a predisposition to recurrent fractures and bone deformities. Clinically OI is defined by features such as short stature, however, less is known regarding body composition.

Aim: Assess body composition, both lean mass and fat mass, in a paediatric OI population.

Methods: Children with OI attending the Bone service at the Royal Hospital for Children Glasgow were included; who had a dual-energy x-ray absorptiometry (DXA) scan performed 2015-2018. Height and body-mass-index (BMI) were converted to standard-deviation scores (SDS) using UK population references. DXA-derived lean mass and fat mass were used to generate lean-mass-index (LMI) and fat-mass-index (FMI) by dividing the covariates by height squared. LMI and FMI were converted to age-and-gender-adjusted SDS using DXA data from 198 local healthy children.

Results: 38 children (20 males) with median age 11.95 (range: 4.8, 18.3) years were included. Median height SDS was -1.08 (-3.64, 1.62) and was significantly lower than the healthy population ($p<0.0001$). Median BMI SDS was -0.10 (-2.31, 2.95), and not significantly different from the healthy population ($p=0.53$). Median LMI SDS was -2.52 (-6.94, 0.77), and significantly lower than healthy controls ($p<0.0001$); 61% (23/38) had an SDS below -2.0. Median FMI SDS was 0.69 (-0.45, 2.72), significantly higher than healthy controls ($p<0.0001$). BMI SDS cut-offs of -0.15 and 1.33, from ROC analysis, identified children with LMI SDS <-2, with a positive predictive value of 95% and a negative predictive value of 70%; and FMI SDS >2 with a positive predictive value of 44% and a negative predictive value of 100%.

Conclusions: A contemporary population of children with ranging severities of OI present with significant reduction in height and lean mass, and relatively high fat mass. Standard BMI SDS

cut-offs for identifying children with malnutrition and obesity have poor prognostic validity in OI.

Keywords: paediatric osteogenesis imperfecta, body composition assessment, fat mass, lean mass

Introduction

Osteogenesis Imperfecta (OI) is a clinically and genetically heterogeneous condition characterised by decreased bone mineral density (BMD) and a predisposition to recurrent fractures and bone deformities [1,2]. The mainstay treatment for children with OI involves the reduction and prevention of fractures and deformities as well as improving mobility. Bisphosphonate (BPN) therapy is commonly used to improve BMD and has been shown to have a positive effect on muscle force in OI through increased muscle function [3,4].

In addition to the disruption of bone architecture in OI, other tissues, including muscle and fat, are impacted by abnormal type-I collagen. Type-I collagen is present in the extracellular matrix of the connective tissue surrounding both muscle and fat as well as in the ligaments and tendons through which muscles transmit force [5]. Children with Type-I OI have slightly smaller calf muscles, on peripheral quantitative computed tomography (pQCT) scanning of lower limbs and generate less force during jumping tests than healthy age and sex matched controls [6].

Low muscle mass and strength contribute to adverse health outcomes in childhood and reduced bone parameters during growth [7]. The assessment of lean mass should be considered as part of routine clinical care along with bone density. Dual-energy X-ray absorptiometry (DXA) uses ionising radiation from two sources that traverse the body and measure absorption by the bone, giving a clear evaluation of BMD which remains the gold standard [8]. This also allows a convenient means of assessing lean mass (LM), which consists of water, muscle, connective tissue and internal organs; and fat mass (FM), which is fat tissue;

and is accessible to the majority of paediatric bone services [9,10]. Although used interchangeably and as a surrogate marker, LM is critically different to muscle mass. LM is total body weight minus fat mass whereas muscle mass is defined simply by muscle itself [10]. The aim of this study was to characterise body composition in children with all types of OI relative to a healthy population using DXA.

Methods and Measurements

Study Population and Measures

Children and adolescents with a clinical diagnosis of OI evaluated at the Complex Bone Clinic at The Royal Hospital for Children in Glasgow; who had a DXA scan performed between 2015 and 2018 were included. DXA scans, for children with OI, were obtained on Lunar iDXA driven by Encore Software Version 15.0 (GE, Wisconsin, USA). The Sillence classification, using clinical findings, was used to categorise subjects into OI types I-IV [11]. Values for LM and FM were obtained from DXA scan results. Anthropometric data of height and weight were taken from the case record corresponding to the date of the scan. Height (cm) to the nearest 0.1cm was measured on a wall-mounted stadiometer (SECA, Germany). Weight (kg) to the nearest 0.1kg was measured in light clothing on a SECA balance.

Lean mass index (LMI), fat mass index (FMI) and body mass index (BMI) were calculated by adjusting the given variable by height squared. Values of height and BMI were converted to standard deviation scores (SDS) using 1990 British childhood standards [12]. LMI, and FMI were compared to a local population of healthy children (n=198) as age and sex matched controls. For the purpose of this study, centile charts were plotted for the data on healthy children, upon which SDS were calculated for children with OI. This control group consisted of school children (94 males and 103 females) recruited for a previous study on bone health [13]. DXA scans were obtained on healthy control subjects using narrow fan beam technology on a Lunar Prodigy scanner driven by Encore Software Version 13.0 (GE, Wisconsin, USA). SDS were used for all subsequent analyses to allow population-based assessments. We considered it justifiable to use the two different machines with two versions of software (Lunar iDXA and Lunar Prodigy), as there are strong linear relationships between GE scanners and software when applying the basic analysis (r=0.990 and r=0.986 for total FMI and LMI respectively) [13].

Other information such as age, sex, history of lower limb fracture within the last 12 months, ambulant status and history of surgical rodding were obtained from electronic case records. In addition, history of BPN use was obtained and subjects were categorised according to previous/current BPN users or non-users (BPN naïve).

Inclusion criteria were subjects with a confirmed clinical or genetic diagnosis of OI with a DXA scan performed within 2015 to 2018. Exclusion criteria included non-ambulant status and children with metal insertions in the long bones or spine, as the presence of metal can significantly impair results from DXA [14]. Non-ambulant status was excluded due to added difficulties of measuring height in these patients as well as any confounding factors with

estimation of muscle and fat mass [15]. This retrospective review did not require ethics approval or informed consent as it was conducted as part of healthcare evaluation of routine clinical practice and according to national guidance [16].

Statistical Analysis

All statistical tests were performed using IBM SPSS Statistics v. 24. The data did not follow a normal distribution therefore non-parametric tests were used for any comparisons. Mann-Whitney was used to compare SDS for different variables between the subtypes. For anthropometric and body composition variables, SDS were calculated using LMS parameters and computed using R v.4.0.2 and the GAMLSS package v.5.2-0 [17]. Spearman correlation tests were performed to evaluate potential relationships between covariates (age, height, BMI, LMI and FMI) with OI subtypes. Receiver Operating Characteristic (ROC) curves were produced using MedCalc v.19.6.1 to compare sensitivity, specificity, positive and negative predictive values of using BMI to identify body composition extremes. The optimal cut-off value was determined by calculating the Youden Index (sensitivity + specificity – 1). Statistical significance was deemed at a p-value < 0.05 and all tests were 2-tailed.

Results

Forty-eight children were identified with a diagnosis of OI in whom a DXA had been performed. Thirty-eight children fulfilled the inclusion criteria for the study. Nine children were excluded: metal insertions (n=5), non-ambulant (n=1), and both non-ambulant and metal insertions (n=3). Thirty-one children were classed as Type-I and seven as Type-IV based on Sillence classification. Since there was only one child classed as Type-III, their data was excluded. Clinical characteristics are shown in Table 1, as well as a quantitative summary of the findings. No child, included in the study, had suffered a lower limb fracture in a 12-month period prior to the DXA. For all variables investigated there were no significant differences observed between the two subgroups.

Height SDS

Median height SDS in all children was -1.08 (range: -3.64, 1.62), ($p<0.0001$ as compared with reference population) as shown in Table 1. Seven children (18.4%) had a height SDS below -2.0, with no difference between subtypes ($p=1.00$). No difference in height SDS was seen in individuals with a history of BPN use and no BPN use ($p=0.98$), as shown in Table 2.

BMI SDS

Median BMI SDS in all children was -0.10 (range: -2.31, 2.95), ($p=0.53$) shown in Table 1. Three individuals (7.9%) had a BMI SDS below -2.0 and four (10.5%) had a BMI SDS above +2.0. (Table 1). Within Type-I, three out of thirty-one (9.7%) had a BMI SDS below -2.0 and none with Type-IV had a BMI SDS below -2.0. Within Type-I, three out of thirty-one (9.7%) had a

BMI SDS above +2.0; whereas for Type-IV, one individual (14.3%) had a BMI SDS above +2.0 (p=1.00). No effect of BPN use on BMI SDS was seen (p=0.60), shown in Table 2.

Lean Mass Index SDS

Median LMI SDS in all children was -2.52 (range: -6.94, 0.77), (p<0.0001) shown in Table 1. Twenty-three individuals (60.5%) had a LMI SDS below -2.0, Figure 1(A) and 1(B). Within Type-I, eighteen out of thirty-one (58.1%) had a LMI SDS below -2.0; whereas for Type-IV, six out of seven (85.7%) had a LMI SDS below -2.0 (p=1.00). No effect of BPN use on LMI SDS was seen (p=0.87), shown in Table 2.

Fat Mass Index SDS

Median FMI SDS in all children was 0.69 (range: -0.45, 2.72), (p<0.0001) shown in table 1. Four individuals (10.5%) had a FMI SDS above +2.0, Figure 1(C) and 1(D). Within Type-I, three out of thirty-one (9.7%) had a FMI SDS above +2.0; whereas for Type-IV, one individual (14.3%) had a FMI SDS above +2.0 (p=1.00). No effect of BPN use on FMI SDS was seen (p=0.74) as shown in Table 2.

Comparisons of BMI with Body Composition Parameters

BMI was compared with each of the body composition parameters to interpret how measurement of body mass relates to composition. BMI SDS was positively associated with FMI SDS (r=0.838 p<0.0001). Out of three subjects who had a FMI SDS greater than +2SD; two also had a BMI SDS greater than +2SD. LMI SDS was positively associated with BMI SDS (r=0.570 p<0.0001). From the 17 subjects who had a LMI SDS of lower than -2SD; only two had a BMI SDS also lower than -2SD.

ROC analysis was used to explore the use of BMI SDS in predicting both LMI SDS and FMI SDS, Table 3A and 3B respectively, and propose new optimal thresholds. A BMI SDS of <-0.15, has a sensitivity of 75% and a specificity of 93% to identify children with a low LMI (<-2 SDS). The positive predictive value for BMI <-0.15 SDS to identify LMI <-2 SDS is 95% and the negative predictive value is 70%. A cut-off BMI SDS of >1.33 has a sensitivity of 100% and a specificity of 85.7% to identify children with a high FMI (>2.0 SDS). The positive predictive value of BMI >1.33 SDS to identify FMI >2.0 SDS is 44% and the negative predictive value is 100%.

Discussion

Osteogenesis Imperfecta is a heterogenous condition affecting musculoskeletal growth and development. We describe a cross-sectional analysis of DXA-derived body composition in 38 children and adolescents with variable clinical severity of OI. We found altered body composition – both lean mass and fat mass in Type-I and Type-IV OI. To the best of our knowledge, this is the first study to assess body composition parameters using DXA in a paediatric population with OI. We also highlight that performance of universally accepted definitions of obesity and slimness do not perform well in this population and we propose new optimal cut-offs.

Low lean mass has previously been reported as a risk factor for fracture in children with OI[18]. Both OI types in our cohort had significantly lower lean mass index compared to a healthy age and sex matched control population. Children with OI Type-I have previously been shown to have lower calf muscle cross-sectional area, measured using tibial pQCT, and generate less force through lower limbs, using mechanography, compared to healthy age and sex matched controls [6,19]. Children with OI Type-I and Type-III have additionally been shown to have significantly reduced forearm muscle cross-sectional area, measured using radial pQCT [5]. It has long been considered that reduced lean mass in OI is related to muscle atrophy from reduced physical activity. Whilst it might be assumed that children with OI Type-III would have difficulty with physical activity due to limb deformity and recurrent fracture; children with milder OI phenotypes report similar levels of activity to healthy controls, and therefore reduced lean mass cannot be fully explained by reduced physical activity in all children with all severities of OI [6,19,20].

Alternative theories to explain reduced lean mass in OI include direct and indirect effects of abnormal type-I collagen. Collagen is present in abundance in the extra-cellular matrix surrounding muscle fibres, tendons and ligaments such that abnormal type-I collagen can result in abnormal transmission of muscle force [20]. Indirectly there is both biomechanical and biochemical cross-talk between muscle and bone [20,21]. The mechanostat theory of the relationship of bone-muscle states that bone adapts to the largest physiological load placed upon it [21]. Muscle force and tibial length are both positively related to bone strength, therefore a weakness in the muscle would contribute to a decrease in bone strength [22]. Biochemically there may be a negative effect of bone matrix and muscle itself on muscle via endocrine and paracrine effects, respectively, through circulating osteokines and myokines. Previous mouse-model studies have highlighted increased expression of TGF-beta (tumour growth factor) signalling in OI. Overexpression of TGF-beta is known to drive bone and extra-skeletal abnormalities, consequently leading to decreased muscle mass [20,23].

Low muscle mass is an important finding and has various clinical implications – showing associations with reduced bone parameters during growth and increased risk of osteoporosis in older age [7]. Type of OI and total muscle strength have been found to predict both level of ambulation and dependence on support for daily activities [24]. Adolescents within the general population with low muscle mass seem to be at a significantly increased risk of metabolic syndrome and, when combined with obesity, results show an adverse cardio-metabolic risk profile [25,26]. Persistently high fat mass during adolescence has been associated with increased arterial stiffness, which is an early marker of atherosclerotic disease [27]. Although this evidence demonstrates only a general health principal for the paediatric population and

cannot be confidently extrapolated to explain adverse future outcomes in OI; it highlights the importance of considering body composition when assessing metabolic risk in children with OI. A 13-week exercise programme for overweight/obese normal children showed improved function and global muscular strength [28]. These improvements can potentially prevent musculoskeletal disorders and have been shown to improve quality of life in children [28]. Abnormalities outlined above are considered strong predictors of morbidity and mortality in adults and therefore when recognised early, interventions should be put in place in order to improve these [29].

Fat mass index was significantly higher in children with OI, and at all levels of severity, than healthy controls. Interestingly, mouse models have shown an abnormally low FM with severe OI [30]. BMI was not significantly different in our children with OI relative to the healthy population and was not a useful screening parameter to identify those children with high FMI. We would recommend the use of fat mass index as a more accurate measure of adiposity than BMI in OI, or percentage body-fat; as in the latter two methods the measurement of fat mass is not independent of lean mass, such that a high %BF may reflect low lean mass rather than high fat mass and a normal BMI may mask a high FMI in the context of low LMI [5,31]. In addition, we would propose the use of a healthy BMI SDS range of -0.15 to 1.33 SDS in children with OI to identify those with either low LMI or high FMI. A child with OI with BMI SDS of < -0.15 will have a 95% probability of having LMI <-2.0 SDS; in addition, a child with OI with BMI SDS of >1.33 will have a 44% probability of having FMI >2.0 SDS.

This study did not find any association of any variable with BPN therapy. There were no significant differences between subjects on current or previous BPN therapy and those who were BPN naïve. Considering that the mechanism of action of BPNs works specifically on bone, these findings were not very surprising. In contrast, a recent study has demonstrated a rapid increase in grip force after a single infusion cycle of pamidronate [4]. However, this positive outcome, within 4 months, was most likely due to an increase in muscle function through decreased skeletal pain rather than an effect on muscle mass itself. An alternative theory discusses how bisphosphonates might exert a positive effect on muscle function through the inhibition of TGF-Beta released from the bone matrix [20]. Other studies are more in keeping with our findings and have concluded no significant change in gross motor function and muscle strength during the treatment phases or change in muscle size respectively [5,32]. There were no children in our clinic cohort receiving treatment with receptor activator of Nfkb ligand (RANKL) inhibition, Denosumab; which has been shown to improve muscle strength in osteoporotic mice and humans and therefore could have therapeutic benefits beyond those seen with BPN therapy alone [33].

We are the first to report no differences in body composition using DXA between a relatively mild and more severe phenotype of OI. These results are similar to a recent study which used pQCT to determine cross-sectional forearm fat and muscle in children with OI; and found no significant differences in either category between subtypes [5]. Although our median height SDS is also similar to height SDS in this study and the wider OI literature, the range seen in our sample is higher. A possible explanation for our results could be the exclusion of severely affected patients, (individuals who were non-ambulant and had femoral rodding or spinal surgery) most of whom were classified as Type-III. This can be deemed a possible limitation

of this study as well as in the clinical applicability of DXA for measurement of body composition in all patients. Although with LMI, LM is adjusted to the height; a certain dependence on the height remains [34]. Therefore, the likely small size of the children included in this sample may contribute to the low LMI values and underestimate the FMI.

Other groups have used pQCT to describe muscle cross-sectional area in either upper or lower limbs; however not all centres have access to pQCT. Appendicular LMI, rather than total, has been used in children with cerebral palsy to quantify muscle mass, and can be considered a closer surrogate for muscle mass in a population where LM is severely affected [35]. However, there is often observed a discrepancy in OI between muscle mass and function of the lower and upper limbs, such that measuring one does not reflect total body composition [5]. In our mild-moderate cohort of ambulant children with OI we made the assumption that abnormalities in collagen, as opposed to inactivity, would have greatest impact on muscle and would be best represented by measuring total LM [6,19,20]. In a cohort of severe OI, who might be expected to have lower participation in physical activity or be non-ambulant, appendicular LM should be considered. Despite the small sample size and with exclusion of severe phenotypes; variables of height and LMI SDS remained significantly lower than the healthy population. Our findings, in a cohort of largely milder phenotypes, indicate the possible extent of associated skeletal morbidity in OI may be more profound and that our findings may underestimate the difference if more severe phenotypes had been included. Our sample group was gathered from a real clinical setting and we therefore had no information on activity levels or include any measures of muscle function, which could add information to the phenotype described.

Our findings would suggest a need to implement treatment with the aim of improving muscle mass including exercise or whole-body vibration. A 12-week exercise program in children with OI, has been shown to improve muscle force and peak oxygen consumption [36]. In addition, whole-body vibration therapy has potential to improve mobility and increase total lean mass in children with OI [37,38]. Improvements in muscle strength and function have direct benefits on bone strength, as well as improve cardiovascular and metabolic health in these patients, leading to an improvement in long term health and quality of life.

Conclusion and Future Directions

We have shown altered body composition in children with OI attending a clinical bone service compared to the normal population; lower lean mass and higher fat mass. We have extended the clinical utility of DXA in OI to provide independent information of lean mass and fat mass and propose new BMI SDS cut-offs to identify those children with extreme measures of body composition. Longitudinal studies would allow us to look at changes in body composition with growth and pubertal development as well as response to treatment.

References

1. Glorieux, F H. 2008 Osteogenesis imperfecta. *Best Practice & Research Clinical Rheumatology*. 22:85–100

2. Rauch, F and Glorieux, F H. 2004 Osteogenesis imperfecta. *Lancet*. 363:1377–85

3. Bains, J S, Carter, E M, Citron, K P, et al. 2018 A Multicenter Observational Cohort Study to Evaluate the Effects of Bisphosphonate Exposure on Bone Mineral Density and Other Health Outcomes in Osteogenesis Imperfecta. *JBMR Plus*. 3:101-18

4. Montpetit, K, Plotkin, H, Rauch, F, Bilodeau, N, Cloutier, S, Rabzel, M and Glorieux, F H. 2003 Rapid increase in grip force after start of pamidronate therapy in children and adolescents with severe osteogenesis imperfecta. *Pediatrics*. 111:601-603

5. Palomo, T, Glorieux, F H, Schoenau, E and Rauch, F. 2016 Body Composition in Children and Adolescents with Osteogenesis Imperfecta. *The Journal of Pediatrics*. 169:232–7

6. Veilleux, L-N, Lemay, M, Pouliot-Laforte, A, Cheung, M S, Glorieux, F H and Rauch, F. 2014 Muscle Anatomy and Dynamic Muscle Function in Osteogenesis Imperfecta Type I. *J Clin Endocrinol Metab*. 99:356–62

7. Orsso, C E, et al. 2019 Low muscle mass and strength in pediatrics patients: Why should we care? *Clinical Nutrition*. 38:2002–15

8. Berger, A. 2002. Bone mineral density scans. *BMJ*. 325:484

9. Zambrano, M B, Félix, T M and de Mello, E D. 2018 Difference between Methods for Estimation of Basal Metabolic Rate and Body Composition in Pediatric Patients with Osteogenesis Imperfecta. *Annals of Nutrition and Metabolism*. 72:21–9

10. Wells, J C K. 2005 Measuring body composition. *Archives of Disease in Childhood*. 91:612–7

11. Sillence, D O, Senn, A and Danks, D M. 1979 Genetic heterogeneity in osteogenesis imperfecta. *J. Med. Genet.* 16:101–16

12. Freeman, J V, Cole, T J, Chinn, S, Jones, P R, White, E M and Preece, M A. 1995 Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child*. 73:17–24

13. Crabtree, N J, et al. 2017 Amalgamated Reference Data for Size-Adjusted Bone Densitometry Measurements in 3598 Children and Young Adults-the ALPHABET Study. *J. Bone Miner. Res.* 32:172–80

14. Giangregorio, L M and Webber, C E. 2003 Effects of metal implants on whole-body dual-energy x-ray absorptiometry measurements of bone mineral content and body composition. *Can Assoc Radiol J*. 54:305–9

15. Lund, A M, Muller, J and Skovby, F. 1999 Anthropometry of patients with osteogenesis imperfecta. *Archives of Disease in Childhood*. 80:524–8.

16. Medical Research Council and NHS Health Research Authority. Is my study research? *HRA Decision Tools.* Available at: http://www.hra-decisiontools.org.uk/research/. Accessed September 23, 2020.

17. Rigby, R A and Stasinopoulos, D M. 2005 Generalized additive models for location, scale and shape. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*. 54:507–54

18. Chagas, C E A, Roque, J P, Santarosa Emo Peters, B, Lazaretti-Castro, M and Martini, L A. 2012 Do patients with osteogenesis imperfecta need individualized nutritional support? *Nutrition*. 28:138–42

19. Pouliot-Laforte, A, Veilleux, L-N, Rauch, F and Lemay, M. 2015 Physical activity in youth with osteogenesis imperfecta type I. *J Musculoskelet Neuronal Interact*. 15:171–6

20. Veilleux, L-N, Trejo, P and Rauch, F. 2017 Muscle abnormalities in osteogenesis imperfecta. 17:1-7

21. Frost, H M and Schönau, E. 2000 The "muscle-bone unit" in children and adolescents: a 2000 overview. *J. Pediatr. Endocrinol. Metab.* 13:571–90

22. Veilleux, L-N, Pouliot-Laforte, A, Lemay, M, Cheung, M S, Glorieux, F H and Rauch, F. 2015 The functional muscle–bone unit in patients with osteogenesis imperfecta type I. *Bone*. 79:52–7

23. Grafe, I, Yang, T, Alexander, S, et al. 2014 Excessive transforming growth factor-β signaling is a common mechanism in osteogenesis imperfecta. *Nat. Med.* 20:670–5

24. Engelbert, R H, Uiterwaal, C S, Gerver, W-J, van der Net, J-J, Pruijs, H E and Helders, P J. 2004 Osteogenesis imperfecta in childhood: impairment and disability. A prospective study with 4-year follow-up. *Arch Phys Med Rehabil*. 85:772–8

25. Kim, J-H and Park, Y S. 2016 Low muscle mass is associated with metabolic syndrome in Korean adolescents: the Korea National Health and Nutrition Examination Survey 2009-2011. *Nutrition Research*. 36:1423–8

26. Burrows, R, Correa-Burrows, P, Reyes, M, Blanco, E, Albala, C and Gahagan, S. 2017 Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: A cross-sectional study in a Chilean birth cohort. *Pediatric Diabetes*. 18:895–902

27. Dangardt, F, et al. 2019 Association between fat mass through adolescence and arterial stiffness: a population-based study from The Avon Longitudinal Study of Parents and Children. *The Lancet Child & Adolescent Health*. Elsevier. 3:474–81

28. Molina-Garcia, P, Mora-Gonzalez, J, Migueles, J H, et al. 2020 Effects of Exercise on Body Posture, Functional Movement, and Physical Fitness in Children With Overweight/Obesity. *J Strength Cond Res*. 34:2146–55

29. Prado, C M, Purcell, S A, Alish, C, et al. 2018 Implications of Low Muscle Mass across the Continuum of Care: A Narrative Review. *Ann Med*. 50:675–93

30. Chen, F, Guo, R, Itoh, S, et al. 2014 First Mouse Model for Combined Osteogenesis Imperfecta and Ehlers-Danlos Syndrome. *Journal of Bone and Mineral Research*. 29:1412–23

31. Weber, D R, Moore, R H, Leonard, M B and Zemel, B S. 2013 Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. *The American Journal of Clinical Nutrition*. 98:49–56

32. Letocha, A D, Cintas, H L, Troendle, J F, et al. 2005 Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. *J. Bone Miner. Res.* 20:977–86

33. Bonnet, N, Bourgoin, L, Biver, E, Douni, E and Ferrari, S. 2019 RANKL inhibition improves muscle strength and insulin sensitivity and restores bone mass. *J. Clin. Invest.* 129:3214–23

34. Fan, B, Shepherd, J A, Levine, M A, et al. 2014 National Health and Nutrition Examination Survey Whole-Body Dual-Energy X-Ray Absorptiometry Reference Data for GE Lunar Systems. *Journal of Clinical Densitometry*. 17:344–77

35. Duran, I, Martakis, K, Rehberg, M, Stark, C, Koy, A and Schoenau, E. 2019 The Appendicular Lean Mass Index Is a Suitable Surrogate for Muscle Mass in Children with Cerebral Palsy. *The Journal of Nutrition*. 149:1863–8

36. Van Brussel, M, Takken, T, Uiterwaal, C S P M, et al. 2008 Physical training in children with osteogenesis imperfecta. *J. Pediatr.* 152:111–6, 116.e1

37. Sá-Caputo, D C, Dionello, C da F, Frederico, E H F F, et al. 2017 Whole-body vibration exercise improves functional parameters in patients with osteogenesis imperfecta: a systematic review with a suitable approach. *Afr J Tradit Complement Altern Med*. 14:199–208

38. Högler, W, Scott, J, Bishop, N, et al. 2017 The Effect of Whole Body Vibration Training on Bone and Muscle Function in Children With Osteogenesis Imperfecta. *J Clin Endocrinol Metab*. Oxford Academic. 102:2734–43

BMI SDS CRITERION	SENSITIVITY	SPECIFICITY	+PV	-PV
< -2.31	0.00	100.00		39.5
≤ -1	43.48	100.00	100.0	53.6
≤ -0.81	43.48	93.33	90.9	51.9
≤ -0.15	73.91	93.33	94.4	70.0
≤ -0.14	73.91	86.67	89.5	68.4
≤ -0.07	78.26	86.67	90.0	72.2
≤ 0.01	78.26	80.00	85.7	70.6
≤ 0.11	82.61	80.00	86.4	75.0
≤ 0.75	82.61	53.33	73.1	66.7
≤ 0.78	86.96	53.33	74.1	72.7
≤ 1.33	86.96	40.00	69.0	66.7
≤ 1.35	95.65	40.00	71.0	85.7
≤ 1.52	95.65	26.67	66.7	80.0
≤ 1.85	100.00	26.67	67.6	100.0
≤ 2.95	100.00	0.00	60.5	

Table 3A: Diagnostic performance of BMI to predict LMI SDS < -2 with selected criterions/cut-offs. The table describes respective sensitivity, specificity, positive predictive value (+PV) and negative predictive value (-PV) for each BMI criterion.

BMI SDS CRITERION	SENSITIVITY	SPECIFICITY	+PV	-PV
≥ -2.31	100.00	0.00	10.5	
> 1.33	100.00	85.29	44.4	100.0
> 1.34	75.00	85.29	37.5	96.7
> 2.24	75.00	100.00	100.00	97.1
> 2.95	0.00	100.00		89.5

Table 3B: Diagnostic performance of BMI to predict FMI SDS > 2 with selected criterions/cut-offs. The table describes respective sensitivity, specificity, positive predictive value (+PV) and negative predictive value (-PV) for each BMI criterion.

	All		OI Type I		OI Type IV		p-value
Number	38		31	(79.5)	7	(20.5)	
Males, number	21	(55.3)	16	(51.6)	4	(57.1)	0.79
Age (years)	11.95	(4.80, 18.30)	12.20	(4.80, 18.30)	9.90	(6.20, 13.80)	0.24
Height SDS	-1.08	(-3.64, 1.62)	-1.06	(-3.64, 1.62)	-1.18	(-2.54, -0.30)	0.46
BMI SDS	-0.10	(-2.31, 2.95)	-0.70	(-2.31, 2.81)	-0.25	(-1.62, 2.95)	0.72
FMI SDS	0.69	(-0.45, 2.72)	0.60	(-0.45, 2.36)	0.98	(0.46, 2.72)	0.06
LMI SDS	-2.52	(-6.94, 0.77)	-2.45	(-6.94, 0.32)	-2.83	(-4.72, 0.77)	0.64

Values: median (range) or number (percentage frequency)

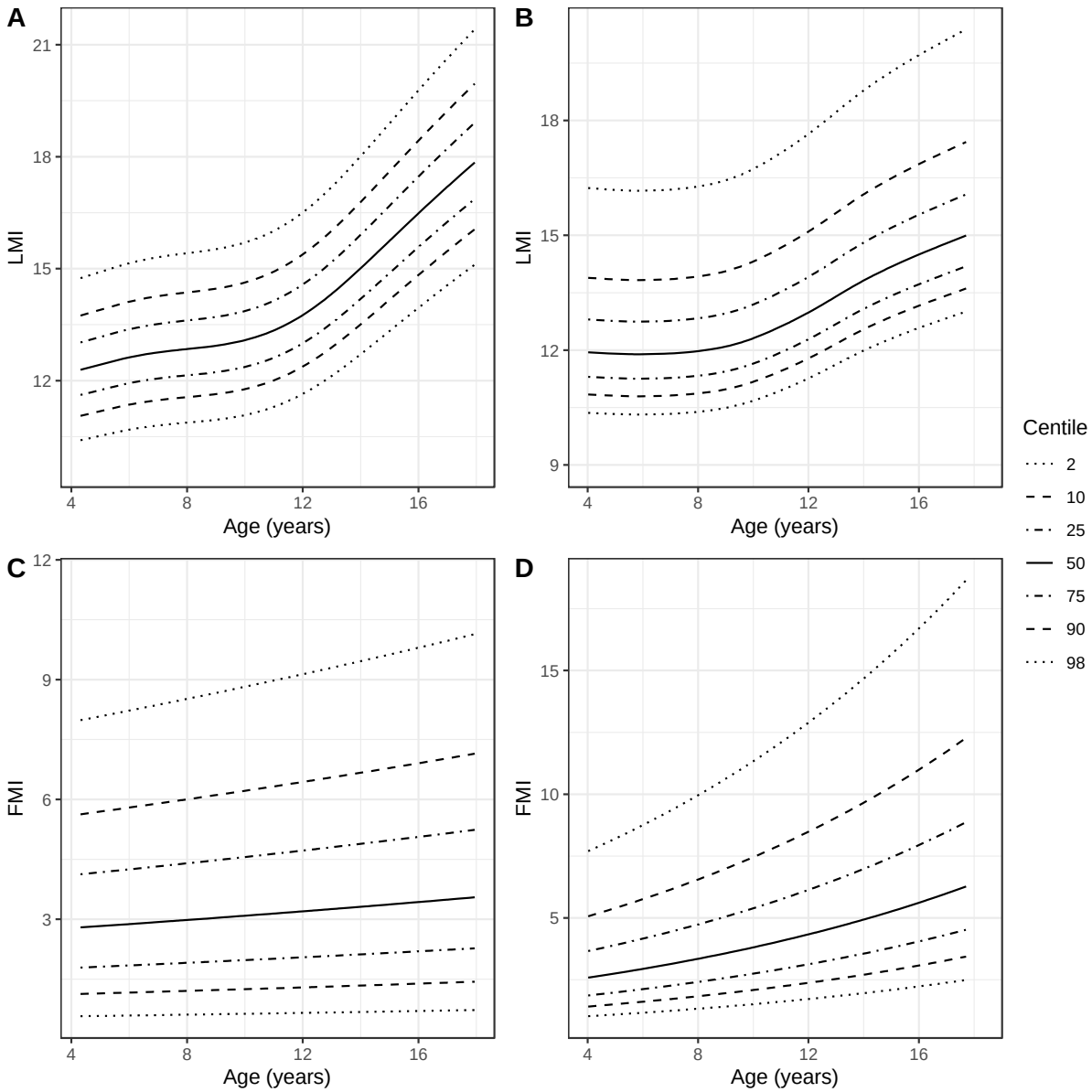
Table 1: Characteristics of children with OI: Height and indices of body composition (BMI, FMI and LMI) expressed as standard deviation scores. P-values denoted are of comparison of each variable between subtypes of OI.

	Bisphosphonate use (previous or current)		No Bisphosphonate use		P-values
Number	29	(76.3)	9	(23.7)	
Height SDS	-1.10	(-3.16, 1.62)	-0.57	(-3.64, 0.22)	0.98
BMI SDS	-0.15	(-2.31, 2.95)	0.52	(-2.28, 2.69)	0.60
FMI SDS	0.70	(-0.45, 2.72)	0.56	(-0.33, 2.30)	0.74
LMI SDS	-2.51	(-6.94, 0.77)	-2.57	(-5.74, 0.33)	0.87

Values: median (range) or number (percentage frequency)

Table 2. Characteristics of children with OI treated and not treated with Bisphosphonate Therapy: Height and indices of body composition (BMI, FMI and LMI) expressed as standard deviation scores. P-values denoted are of comparisons of each variable between those who have been treated with bisphosphonate and those that are bisphosphonate naive. No differences were seen between OI Type-I and Types-III/IV in number of individuals who have received bisphosphonate therapy.

Fig.1. ***Relationship of (A) LMI in males, (B) LMI in females, (C) FMI in males, (D) FMI in females with Age in OI, presented on centile charts.***



447
448