Body Composition in Children and Adolescents with Osteogenesis Imperfecta

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Objective To use peripheral quantitative computed tomography to determine the cross-sectional area (CSA) of subcutaneous fat and muscle (fat CSA, muscle CSA) in transverse forearm scans in patients with osteogenesis imperfecta (OI).

Study design Fat and muscle CSA were quantified in 266 individuals (142 female) aged 5-20 years who had a diagnosis of OI type I, III, or IV and who had mutations in *COL1A1* or *COL1A2*. Results were compared with those of 255 healthy controls.

Results In a subgroup of 39 patients with OI type I, % fat CSA correlated closely with total body percentage fat mass as determined by dual-energy x-ray absorptiometry ($R^2 = 0.69$; $P < .001$). In the entire study cohort, muscle CSA adjusted for age, sex, and forearm length was lower in OI type I and III than in controls ($P < .05$ each), but fat CSA was similar between OI types and controls. No relationship between the type of disease-causing mutation in the *COL1A1* or *COL1A2* genes and fat CSA or muscle CSA was found.

Conclusions Children and adolescents with OI have low muscle size but a normal amount of subcutaneous fat at the forearm. *(J Pediatr 2016;169:232-7)*.

Osteogenesis imperfecta (OI) is usually caused by dominant mutations in *COL1A1* or *COL1A2*, the genes coding for collagen type I alpha chains.[1] Collagen type I consists of 2 alpha 1 chains and 1 alpha 2 chain that form a triple helical domain. The most common types of mutations associated with OI lead to substitutions of glycine in the triple helical domain and interfere with triple helix formation. Mutations that introduce premature termination codons in *COL1A1*, leading to haploinsufficiency, are also common. The consequence of these *COL1A1* or *COL1A2*, defects is alteration in bone matrix.[1]

The severity of these mutations is a continuum, but 4 OI types are recognized.[2] Type I represents the "mild" end of the spectrum and is often caused by haploinsufficiency mutations. Type II is the neonatal lethal form. Type III is the most severe type of OI in survivors, and type IV is intermediate in severity between types I and III. There is presently no cure, but bisphosphonates are given to decrease fracture rate.[3]

OI can also involve other tissues, either as a direct consequence of the collagen abnormalities or of other features such as decreased mobility. Thus, the effect of OI on fat and muscle is potentially important. Even though percentage body fat was low in a mouse model of dominant OI,[4] the opposite has been observed in 2 small studies on children with OI who had higher percent body fat than their healthy peers.[5,6] Apart from the negative consequences of high fat mass that apply to the general population, excess body weight can interfere with rehabilitation efforts in children with severe OI.[7] Increased body weight is a risk factor for loss in motor function, whereas low body weight facilitates improvements in mobility.[8]

Regarding muscle in OI, 1 mouse model of severe OI has impaired muscle function,[9] whereas no muscle function compromise was found in a mouse with a milder form of OI.[10] We recently reported that children with type I have slightly smaller calf muscles than healthy age- and sex-matched controls and generate less force during jumping tests.[11,12] In this group of mildly affected patients, these observations were not explained by lack of exercise, as physical activity was similar between children with type I and matched controls.[13] These studies were small and included no information about the muscle system in children with more severe OI types.

Metal implants, common in patients with OI, may interfere with measurements using dual-energy x-ray absorptiometry (DXA), the gold standard method for determining fat mass and lean mass. One way to circumvent this issue is to determine regional body composition at the forearm using peripheral quantitative computed tomography (pQCT). Few children with OI have permanent metal rods in forearm bones, making this limb segment suitable for analysis. Forearm pQCT can distinguish between fat, muscle, and bone and allows determining the cross-sectional area

BMI	Body mass index
CSA	Cross-sectional area
DXA	Dual-energy x-ray absorptiometry
fat CSA	CSA of subcutaneous fat
muscle CSA	CSA of muscle
OI	Osteogenesis imperfecta
pQCT	Peripheral quantitative computed tomography

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(CSA) of these tissues in transverse scan images of the limb.[14,15] In healthy children, the percentage of the forearm CSA taken up by fat correlates closely with percentage fat mass determined by total body DXA.[16]

We assessed fat and muscle mass in children and adolescents with OI by forearm pQCT. Our first objective was to verify that forearm pQCT reflects body composition of the whole body in OI, similar to what has been reported in healthy individuals. The second objective was to determine the effect of clinical OI types and of OI genotypes on fat and muscle mass.

Methods

The study population comprised individuals with a diagnosis of OI who were evaluated at the Shriners Hospital for Children in Montreal between January 2003 and April 2014. Data were obtained by retrospective chart review. Starting in 2003, pQCT scans at the forearm were performed in children and adolescents with OI as part of their care. The study was approved by the Institutional Review Board of McGill University. As this study was a retrospective chart review, informed consent was not required.

The following inclusion criteria were applied: (1) a clinical diagnosis of type I, III, or IV, as assessed by one of the authors; (2) presence of a known mutation in either *COL1A1* or *COL1A2*; (3) age between 5 and 20 years, as pQCT is usually not feasible in children below 5 years of age because of lack of cooperation, and 20 years is the upper age limit for receiving clinical care at the institution where patients were followed; and (4) availability of data from at least one pQCT scan at the 65% site of the forearm.

Of the 298 patients meeting these criteria, 32 did not have a valid pQCT (reasons included one or more of the following: arms too short or deformed for positioning in the pQCT device; presence of metal implants in both forearms; movement artefacts during the scan). The data from the remaining 266 patients (142 female, 124 male; age range: 5.4-20.9 years; *COL1A1* mutation, n = 179; *COL1A2* mutation, n = 87) were included in the present analysis.

Results in the OI group were compared with those of 255 healthy controls (181 female, 74 male; age range: 5.8-20.3 years). These were participants of a nutritional study on healthy children and adolescents that used forearm pQCT to assess local body composition, as described.[14,15] For the purpose of the present analysis, data sets were selected from the results of this previous study to match the age-distribution of the OI cohort.

Subgroups were selected from the OI cohort in order to address the specific study questions: (1) To assess the relationship between the percentage of the forearm cross-section taken up by subcutaneous fat (% CSA of subcutaneous fat [fat CSA]) and percentage fat mass in total body DXA (total body % fat mass), as well as the relationship between forearm % CSA of muscle (muscle CSA) and total body % lean mass, we evaluated results of patients who had undergone forearm pQCT and total body DXA during the same clinic visit. Additional selection criteria were diagnosis of type I (in order to minimize the influence of skeletal deformity on DXA results) and no prior exposure to bisphosphonates (as it was deemed a priori possible that bisphosphonates might affect results). A total of 39 patients were identified and included in this substudy; and (2) To compare fat and muscle pQCT results between controls and the 266 patients with types I, III, and IV, the result of the first valid forearm pQCT scan at the 65% forearm site of each individual was included.

Height, weight, and body mass index (BMI) were converted to age- and sex-specific z-scores on the basis of reference data published by the Centers for Disease Control and Prevention.[17]

A pQCT scan (XCT-2000; Stratec Inc, Pforzheim, Germany) was obtained at the forearm (65% site), as described previously.[18] From this scan, muscle and bone were separated from fat using a density threshold of 40 mg/cm^3, and muscle was further separated from bone using a density threshold of 280 mg/cm^3. After this separation procedure, the muscle and bone CSAs (the combined areas encircled by the periosteal perimeters of radius and ulna) was determined. The fat, muscle, bone CSAs, and of the entire forearm cross-section were expressed as absolute values (mm^2).

Total body DXA was performed in some patients with type I. These measurements were obtained between 2003 and 2005 using a Hologic QDR Discovery device (Hologic Inc, Waltham, Massachusetts). Both the staff operating the device (2 radiology technicians) and the device hardware remained unchanged during the study period. Total body % fat mass was calculated as the ratio between fat mass and total body mass and the total body % lean mass was calculated as the ratio between lean mass and total body mass. Coefficients of variation were <2% for fat mass and <1% for lean mass measurements.

Collagen Type I Mutation Analysis

Sequence analyses of *COL1A1* and *COL1A2* were performed in genomic DNA, either by Sanger sequencing (Applied Biosystems 3100 DNA sequencer; Applied Biosystems, Foster City, California) after polymerase chain reaction amplification of all exons of *COL1A1* and *COL1A2*, or by semiconductor-based next-generation sequencing using an Ion Torrent PGM device (Life Technologies, Carlsbad, California), as described.[19] Results were compared with RefSeq sequences NM_000088.3 for *COL1A1* and NM_000089.3 for *COL1A2*. Mutations in *COL1A1* that introduce stop codons or lead to frameshifts were classified as haploinsufficiency mutations. Small indel mutations leading to the in-frame addition or deletion of amino acids were considered in-frame mutations. Mutations in either *COL1A1* or *COL1A2* that lead to glycine substitutions in the triple helical domains of the collagen type I alpha 1 or alpha 2 chains were regarded as glycine substitutions. Mutations close to exon/intron boundaries that were predicted or proven to affect splicing were considered splice mutations. Mutations affecting the C-propeptide of either the alpha 1 or the alpha 2 chain of collagen type I were classified as C-propeptide mutations.

Statistical Analyses

Differences between 2 groups were tested for significance using unpaired *t* tests. Group differences in dichotomous variables were tested for significance using the χ^2 test. ANOVA was used to examine differences between more than 2 groups, and Bonferroni adjustment was used for post-hoc analyses. For the comparisons of pQCT body composition variables between groups (controls, type I, type III, type IV in the phenotype analysis; haploinsufficiency, glycine substitution, splice site mutation, C-propeptide mutation in the genotype analysis), results were adjusted for age, sex distribution, and forearm length to account for group differences in these potential confounders. Pearson correlations were used to explore the relationship between 2 measurements. Nonnormally distributed data were log-transformed prior to analysis. All tests were 2-tailed, and throughout the study *P* values of <.05 were considered significant. Calculations were performed using SPSS software (v 22.0; SPSS Inc, Chicago, Illinois).

Results

The study population comprised 266 children and adolescents with OI and 255 healthy controls (Table I). Close to one-half of the population with OI had a diagnosis of type I, 38% were diagnosed with type IV, and 13% with type III. Sixty percent of the cohort with OI had a history of bisphosphonate treatment. As expected, height was very low in type III and IV and closer to controls in type I. Forearm length was also lower in types III and IV than in controls and in type I. The mean BMI z-score was significantly higher in type III than in the other groups.

The relationship between pQCT- and DXA-based indicators of body composition was assessed in 39 individuals with type I who did not have a history of bisphosphonate treatment (18 female, 21 male; age range: 5.3-19.2 years; mean height z-score −0.6 [SD 0.9]; mean weight z-score −0.2 [SD 1.1]). Forearm % fat CSA determined by pQCT (mean 30.7%; SD: 9.4) and total body % fat mass assessed by DXA (mean 26.1%; SD 7.2) correlated closely (Figure 1, A). Forearm % muscle CSA measured by pQCT (mean 65.4%, SD 8.9) correlated with DXA-derived total body % lean mass (mean 71.2%, SD 7.2) (Figure 1, B).

To evaluate the effect of phenotypic OI type on body composition, we compared the fat, muscle, and bone CSAs, and the entire arm cross-section between OI types and healthy controls after adjustment for age, sex, and forearm length (Figure 2). Arm and fat CSA did not differ significantly between OI types and controls. Compared with controls, forearm muscle CSA was 8% lower in type I and 14% lower in type III. Mean muscle CSA was also 8% lower in type IV than in controls, but in contrast to type I the difference to controls did not achieve statistical significance. No significant differences in muscle CSA were found between OI types. Bone CSA was between 34% and 37% smaller in OI types than in controls, but was similar between OI types.

We next compared body composition between OI genotypes by analyzing the OI cohort according to the type of underlying *COL1A1/COL1A2* mutation (Table II). Two patients with in-frame deletions were excluded from this analysis, as this type of mutation was too rare for meaningful statistical evaluation. In the other 264 patients, we found that the haploinsufficiency group had higher height z-scores and weight z-scores than any other group and also had lower BMI z-scores than the glycine substitution group. However, after adjustment for age, sex, and forearm length, no group differences were observed in the fat, muscle, and bone CSAs, and the entire arm cross-section (Figure 3). To assess the effect of bisphosphonate treatment on body composition, bisphosphonate treatment history (no prior treatment = 0; history of prior treatment = 1) was included in the model but was not a significant predictor of fat, muscle, or bone CSAs in either the OI phenotype of the genotype analysis (data not shown).

Discussion

In this study, we found that forearm pQCT at the 65% site provides a reasonable estimate of total body fat and muscle

Table I. Demographic and anthropometric data in healthy controls and according to clinical OI type

	Control	OI type I	OI type III	OI type IV	*P*
N (male/female)*	255 (74/181)	126 (57/69)	37 (20/17)	103 (47/56)	<.001
Age (y)	12.1 (11.7-12.6)†,‡	11.0 (10.3-11.7)§	12.8 (11.5-14.0)‡	10.8 (10.0-11.5)§,¶	.001
Height (z-score)	0.7 (0.6-0.9)†,‡,¶	−0.9 (−1.2 to −0.8)‡,§,¶	−7.0 (−7.6 to −6.4)†,‡,§	−3.8 (−4.2 to −3.5)†,§,¶	<.001
Weight (z-score)	0.4 (0.3-0.5)†, ‡,¶	−0.4 (−0.7 to −0.2)‡,§,¶	−4.1 (−5.3 to −2.8)†,‡,§	−2.1 (−2.7 to −1.6)†,§,¶	<.001
BMI (z-score)	0.1 (−0.1 to 0.2)‡,¶	0.1 (−0.1 to 0.3)¶	1.3 (0.8-1.7)†,‡,§	0.5 (0.2-0.7)§,¶	<.001
Forearm length (cm)	23.6 (23.2-23.9)†,‡,¶	21.7 (20.9-22.4)‡,§,¶	18.5 (17.4-19.6)†,§	19.3 (18.6-20.1)†,§	<.001
Bisphosphonate Tx (yes/no)*	0/255	47/79	32/5	87/16	<.001**

Bisphosphonate Tx, history of bisphosphonate treatment.
Results are given as n or mean (95% CI).
P values indicate the significance of the difference between groups, calculated by χ^2 test (for *P* values indicated by an asterisk *) or by ANOVA (for all other *P* values).
The results of post-hoc analyses (Bonferroni adjustment) are shown by footnotes.
†Significant difference to OI type I.
‡Significant difference to OI type IV.
§Significant difference ($P < .05$) to control group.
¶Significant difference to OI type III.
**Comparison only between OI types.

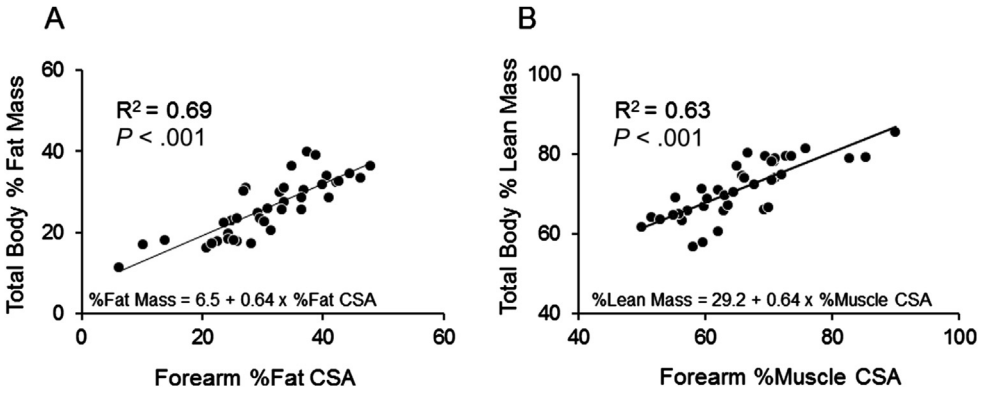

Figure 1. Relationship in OI type I (n = 39) between forearm pQCT measures of **A,** fat and **B,** muscle CSAs and DXA-derived total body results for fat and lean mass.

mass in individuals with OI. Surprisingly, fat CSA was similar between individuals with OI and healthy controls when differences in forearm length were taken into account. In contrast, muscle CSA was significantly lower in patients with types I and III than in healthy controls.

In a methodological subanalysis using data from individuals with type I, we compared percentages of body composition as measured by pQCT and by total body DXA. This showed that pQCT variables of body composition were closely associated with DXA results, mirroring previous observations in healthy prepubertal children.[16] Thus, our data indicate that body composition at the 65% forearm site provides an estimate of the composition of the total body also in children and adolescents with OI.

In the entire study population, we found that fat CSA was similar in individuals with OI and in controls and also similar between OI types. In light of the previous literature, this is somewhat surprising. Mouse studies had shown abnormally low fat mass in a model of severe OI.[4] OI is characterized by a disturbance in osteoblast function, and osteoblasts are implicated in the control of energy metabolism.[20] It has been reported that children with OI are in a state of "hypermetabolism,"[21] which would be expected to lead to low body fat stores. However, it is currently not known whether the endocrine function of osteoblasts is affected by mutations causing OI. In any case, the previously published evidence from 2 smaller clinical studies (on 26 and 63 children with OI) had pointed toward increased, not

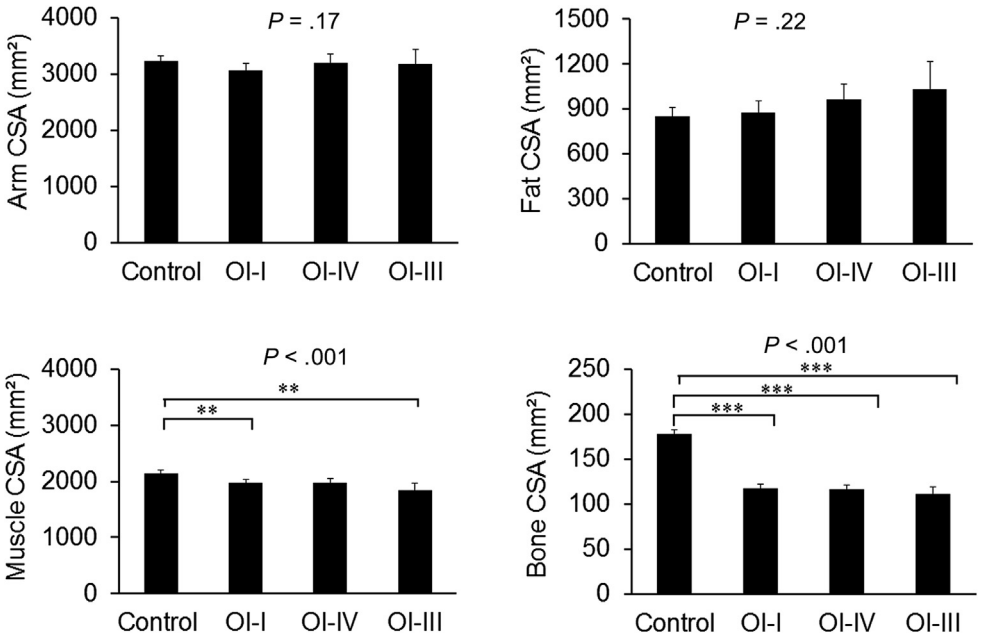

Figure 2. Results of pQCT analyses at the 65% forearm site in healthy controls and in individuals with OI grouped according to clinical OI types. The results of post-hoc analyses (Bonferroni adjustment) are shown as asterisks: $^{**}P < .01$; $^{***}P < .001$.

Table II. Demographic and anthropometric data in OI according to the type of *COL1A1/COL1A2* mutation

	COL1A1, Haploinsufficiency	*COL1A1/COL1A2*, Glycine substitution	*COL1A1/COL1A2*, Splice site	*COL1A1/COL1A2*, C-propeptide	*P*
N (male/female)*	65 (25/40)	135 (68/67)	50 (24/26)	14 (5/9)	.36
Age (y)	11.0 (10.1-11.9)	11.4 (10.7-12.1)	10.6 (9.4-11.9)	11.2 (8.4-14.1)	.70
Height (z-score)	−0.9 (−1.1 to −0.6)†,‡,§	−4.2 (−4.6 to −3.7)‡,¶	−2.1 (−2.7 to −1.5)†,¶	−2.8 (−4.5 to −1.1)¶	<.001
Weight (z-score)	−0.4 (−0.8 to −0.1)†	−2.2 (−2.8 to −1.7)¶	−1.1 (−1.6 to −0.5)	−2.1 (−3.7 to −0.6)	<.001
BMI (z-score)	0.1 (−0.2 to 0.4)†	0.7 (0.5-0.1)§,¶	0.2 (−0.1 to 0.6)	−0.4 (−1.5 to 0.6)†	<.001
Forearm length (cm)	21.7 (20.9-22.6)†	19.7 (19.0-20.3)¶	20.6 (19.2-21.9)	19.5 (17.2-21.8)	.009
Bisphosphonate Tx (yes/no)*	22/43†,§	107/28‡,¶	24/26†	12/2‡,¶	<.001

Results are given as n or mean (95% CI). *P* values indicate the significance of the difference between groups, calculated by χ^2 test (for *P* values indicated by an asterisk, *) or by ANOVA (for all other *P* values).
The results of post-hoc analyses (Bonferroni adjustment) are shown by footnotes.
†Significant difference to glycine substitution group.
‡Significant difference to splice mutation group.
§Significant difference to C-propeptide mutation group.
¶Significant difference ($P < .05$) to haploinsufficiency group.

decreased DXA-derived total body %fat mass in children with severe OI.[5,6] However, this data is not entirely conclusive, as total body %fat mass can simply reflect low %lean mass and, therefore, is not necessarily a sign of increased adiposity. In the present study, we assessed forearm fat CSA not as a percentage of the limb cross-section but rather adjusted the absolute fat CSA by forearm length to account for body size differences. Therefore, the fat CSA results presented in the present study are not mathematically influenced by variations in muscle CSA.

Our data also highlight that the use of BMI is problematic in individuals with lower extremity deformities or scoliosis, such as children with type III. Compared with healthy controls, this group had significantly elevated BMI z-scores but pQCT analysis revealed normal forearm fat CSA and low muscle CSA. This apparent discrepancy may be explained by the fact that BMI is a body height-related measure and, therefore, is influenced by height loss due to leg deformities or scoliosis. For example, loss of 10% in body height because of leg deformities will, other things being equal, increase BMI by 23.5%. Thus, the increased BMI z-score in type III may reflect short legs rather than increased adiposity.

Regarding muscle mass, our results are in accordance with our previous studies in OI type I, where we had observed 7% lower calf muscle CSA than in healthy age- and sex-matched controls.[11] In the present study, the difference in forearm muscle CSA between type I and controls was 8%. However, it is possible that the muscle function deficit in OI is larger than the deficit in muscle mass. For example, we noted that muscle force per unit area of calf muscle cross-section was

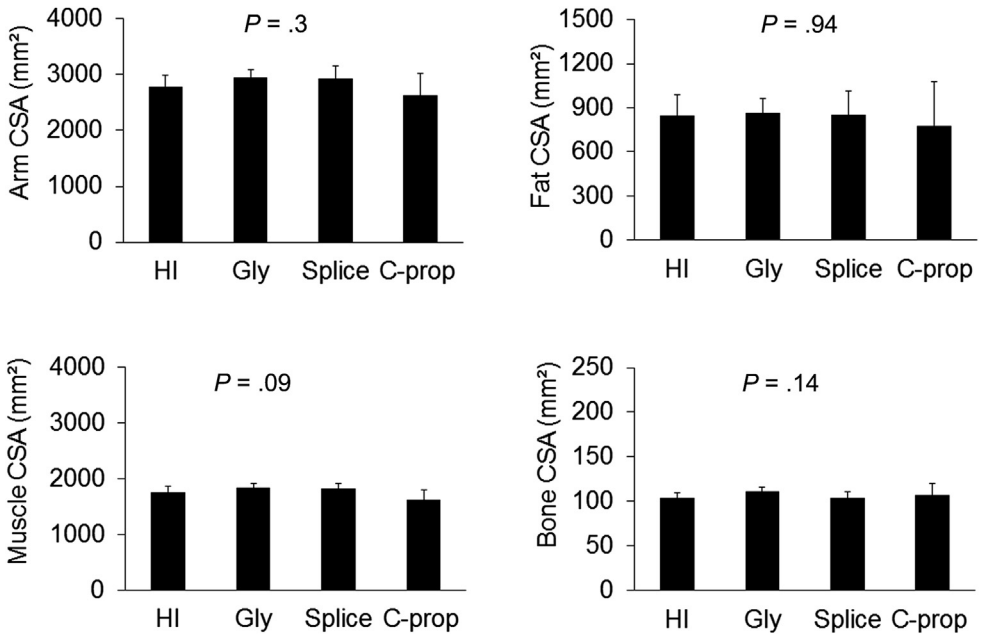

Figure 3. Results of pQCT analyses at the 65% forearm site in individuals with OI grouped according to the type of disease-causing *COL1A1/COL1A2* mutation. *C-prop*, C-propeptide mutation; *Gly*, glycine substitution; *HI*, haploinsufficiency; *Splice*, splice site mutation.

lower in type I than in controls.[11] We are not aware of any data on muscle size in children with type III and IV. It may come as a surprise that we did not detect differences in muscle CSA between OI types, as the disease severity and overall level of mobility is dramatically different between type I and III. However, many individuals with severe OI and reduced mobility use their arms for propelling wheelchairs or for using walkers. The increased use of arms for mobility may have a beneficial effect on arm muscle mass.

The present study has several limitations that stem from the fact that the data were obtained by retrospective chart review. There was no information on pubertal status, energy intake, and on physical activity levels which could affect muscle and fat mass. Also, subjects with severe OI are likely to have less physical activity than healthy children and adolescents, affecting body composition. Finally, levels of osteocalcin or other hormones thought to be involved in the fat-bone axis were not available. Prospective studies are, therefore, needed to elucidate the factors that determine fat and muscle mass in children and adolescents with OI.

In conclusion, the present study shows that pQCT scans at the forearm can be used to assess adiposity and muscle mass in OI. We found that children and adolescents with OI had decreased muscle mass. This was related to clinical disease severity rather than the type of disease-causing mutation in *COL1A1/COL1A2*. ■

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