Body Composition in Children and Adolescents with Osteogenesis Imperfecta

Telma Palomo, MD, Francis H. Glorieux, MD, PhD, Eckhard Schoenau, MD, and Frank Rauch, MD

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

From the Shriners Hospital for Children and McGill University, Montreal, Quebec, Canada

Supported by the Shriners of North America and the Fonds de recherche du Québec - Santé. F.R. received support from the Chercheur-Boursier Clinicien program of the Fonds de Recherche Québec - Santé. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.10.058

(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.