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Fractures on bisphosphonates in osteoporosis pseudoglioma syndrome (OPPG): pQCT shows poor bone density and structure

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Abstract

Osteoporosis pseudoglioma syndrome (OPPG) is a rare autosomal recessive disorder of childhood osteoporosis and blindness due to inactivating mutations in LDL receptor-like protein 5 (LRP5). We and others have reported improvement in areal bone mineral density (aBMD) by DXA in OPPG on short term bisphosphonates. Long-term data on bisphosphonate use in OPPG and measures of volumetric BMD (vBMD) and cortical structure are not available. In addition, no long-term DXA data on untreated OPPG is available. The aims of this study were to: (1) record low trauma fractures and longitudinal aBMD by DXA in 5 OPPG patients on chronic bisphosphonate treatment, and in 4 OPPG patients never treated (2) to perform tibia peripheral quantitative CT (pQCT) to evaluate volumetric bone mineral density (vBMD), cortical structure and calf muscle area in 6 OPPG patients and 14 unaffected first degree family members. pQCT results were converted to sex-specific Z-scores for age and adjusted for tibia length based on data in >700 reference participants. We observed 4 fractures (3 femoral shafts) in 3 OPPG patients while on bisphosphonates, after each achieved significant improvement in aBMD. OPPG participants had significantly lower mean trabecular vBMD (−1.51 vs. 0.17, $p = 0.002$), cortical area (−2.36 vs. 0.37; $p < 0.001$) and periosteal circumference (−1.86 vs. −0.31, $p = 0.001$) Z-scores, compared with unaffected participants and had a trend toward lower muscle area Z-score (−0.69 vs. 0.47, $p = 0.12$). These data demonstrate substantial bone fragility despite improvements in aBMD. The pQCT data provide insight into the fragility with substantial deficits in trabecular vBMD and cortical dimensions, consistent with OPPG effects on bone formation. Treatment that improves bone quality is needed to reduce fractures in OPPG.

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Disclosures

All authors state that they have no conflicts of interest.

Keywords

Osteoporosis pseudoglioma syndrome; OPPG; pQCT; Bone mineral density; Atypical femur fracture

Introduction

Osteoporosis pseudoglioma syndrome (OPPG) is a rare autosomal recessive disorder characterized by childhood osteoporosis with recurrent fragility fractures, congenital blindness, and in some, behavioral and cognitive abnormalities, due to inactivating mutations in LDL receptor-like protein 5 (*LRP5*) [1–5]. *LRP5* stimulates bone formation via activation of the canonical Wnt pathway [2]. OPPG is considered to be primarily a disorder of reduced bone formation, due to reduced *LRP5* production. We [4] and others [6–8] have shown that bisphosphonate treatment for several years improves DXA areal bone mineral density (aBMD) in OPPG. However, there have been no reports of aBMD or fractures with more long term use of bisphosphonates in OPPG. In addition, there are no longitudinal data available on untreated patients or on aBMD after discontinuation of bisphosphonates.

Skeletal development is characterized by age- and sex-specific increases in trabecular volumetric bone mineral density (vBMD), cortical dimensions and muscle mass [9]. Activation of the canonical Wnt signaling pathway is also critical for myogenesis and muscle repair [10], and there is some evidence that *LRP5* is important for muscle development [11]. However, muscle mass has not been studied in patients with inactivating *LRP5* mutations. Therefore, the structural underpinnings of the skeletal fragility in OPPG have not been well characterized, and the associations between cortical structure and muscle mass have not been addressed.

The goals of this study were twofold, to: (1) record low trauma fractures and DXA-derived aBMD in OPPG patients on chronic bisphosphonates and in untreated patients, (2) evaluate tibia trabecular vBMD, cortical structure, and calf muscle area by pQCT in OPPG patients compared to unaffected first degree relatives.

Methods

Participants

The OPPG and unaffected participants in this study were all members of the Old Order Mennonite (OOM) community in Pennsylvania, consisting of three nuclear families, all sharing common ancestors. As shown in Fig. 1, our cohort currently includes 15 patients with OPPG; this report includes data on 9 of them. The OPPG participants and their unaffected family members belong to 3 nuclear families, who also share common ancestors. The OPPG patients in two of the nuclear families (Families A and C) had the same homozygous W425X mutation in *LRP5* (a severe mutation in exon six which codes for a stop codon, referred here-to-for as the AA genotype). The OPPG patients in the third nuclear family (Family B) were compound heterozygotes for the W425X mutation and a T409 mutation (predicted to be less deleterious, resulting in some *LRP5* protein being formed, here-to-for called the AB genotype). This report includes DXA aBMD data on five patients

with OPPG (A1–3, C1–2), and pQCT data on two of these individuals (A2, A3) and four others with OPPG (B1–4). Of the 14 unaffected first-degree relatives who completed pQCT scans, 11 were *LRP5* mutation heterozygotes (here-to-for called hets) and the rest had no *LRP5* mutation.

For the tibial pQCT, of the six OPPG patients included, four (B1–4) had never been on bisphosphonates (or any other bone active drug). Two OPPG participants (A2, A3) were on bisphosphonates (A2, for 7 years; A3, for 4 years, shown in Fig. 2), that were stopped six months before the pQCT was done. At the time of the study, no participants were on routine prescription medications of any kind. Participants were studied in the University of Maryland Amish Research Clinic in Lancaster, PA with pQCT scans performed at the Children's Hospital of Philadelphia (CHOP). All clinically unaffected first-degree relatives of patients with OPPG were genotyped for the two exon six *LRP5* mutations present in our kindred, W425X and T409A [4].

The study was approved by IRBs at both the University of Maryland School of Medicine and CHOP. Written, informed consent was obtained from all study participants over age 18, assent from those 13–18 years of age, and parental consent from those under age 13.

Peripheral quantitative computed tomography (pQCT)

Scans were obtained in the left tibia using a Stratec XCT2000 device (Orthometrix, White Plains, NY) with a 12 detector unit, voxel size 0.4 mm, slice thickness 2.3 mm and scan speed 25 mm/s at CHOP, as previously described in children and adults [9,12]. A scout view was obtained to place the reference line at the proximal border of the distal tibia growth plate in participants with open growth plates and at the distal endplate in those with fused growth plates. Bone measurements were obtained 3% proximal to the reference line for trabecular vBMD (mg/cm^3) and at the 38% diaphysis for periosteal and endosteal circumferences (mm), and cortical area (mm^2). An in vivo study demonstrated that pQCT trabecular vBMD ($R^2 = 0.56$) and diaphyseal cortical area ($R^2 = 0.86$) were highly correlated with fracture load [13]. Muscle and fat cross-sectional area (mm^3) were assessed at the 66% site. The manufacturer's hydroxyapatite phantom was scanned daily. In our laboratory, the CV ranged from 0.5 to 1.6% for these pQCT outcomes.

Statistical analyses

Age- and sex-specific height and BMI Z-scores were generated using national reference data [14]. For participants greater than 20 years of age (the upper limit of the national reference data), height Z-scores were generated relative to age 20, and BMI Z-scores were not generated. pQCT outcomes were converted to race- and sex-specific Z-scores using the LMS (lambda mu sigma) method (Chartmaker Program version 2.3) based on over 700 healthy reference participants enrolled in prior studies at CHOP and scanned on the same pQCT machine as the study participants here [12,15]. The LMS method accounts for the non-linearity, heteroscedasticity and skew of bone data with age in children and adults. The trabecular vBMD outcomes were assessed relative to age. The cortical geometry outcomes and muscle and fat area were highly correlated with tibia length (all $p < 0.0001$); therefore,

Z-scores for these parameters were generated relative to age and further adjusted for tibia length for age Z-scores, as previously described [16,17].

Continuous variables were expressed as means $\pm$ SD or median (range). Group differences in pQCT Z-scores according to genotype were assessed using Student's t-test or the rank-sum test if skewed. All analyses were performed using SAS 9.2 (Cary, North Carolina).

Results

DXA-derived aBMD and fractures in OPPG patients during bisphosphonate treatment and after treatment discontinuation

The six OPPG patients shown in Fig. 2A all have the AA genotype. After achieving improvements in Z-scores to zero in the spine and in the setting of Z-scores better than -2.0 in the hip, three of these patients (A2, A3, C1) suffered four fractures, including femoral shaft fractures in each patient. All fractures were confirmed by review of radiographs and, when surgery occurred, hospital records were reviewed. These fractures occurred within the 2 years after our report in 2008, in which we showed improved aBMD by DXA with bisphosphonates [4] and prompted our discontinuation of bisphosphonates in all, with later resumption in two (C1, C2).

After discontinuation of bisphosphonates in A1–3, aBMD decreased in all 3. Two of these patients (A1, A2) have not had any additional fractures since stopping bisphosphonates. In the other, (A3), three years after bisphosphonate discontinuation, a lateral right subtrochanteric stress fracture was noted when she complained of thigh pain and progressed to a complete fracture that required surgery. Because this fracture location was suspicious for a bisphosphonate-associated atypical femur fracture, A3 has remained off bisphosphonates since this fracture. C1 and C2 each had fractures after stopping bisphosphonates. Because of their relatively young ages and shorter duration of bisphosphonate use (compared to the older A1–3), bisphosphonates were later resumed in C1 and C2 as shown in Fig. 2A.

DXA-derived aBMD in OPPG patients never treated pharmacologically

DXA data from 4 OPPG patients with the less severe AB genotype are shown in Fig. 2B. These patients, never treated with bisphosphonates or any other bone active medication, appear to have less gain in spine BMD over time than in hip.

pQCT substudy

The characteristics for the 20 participants in the pQCT substudy are summarized in Table 1. Participants were six OPPG patients, including A2 and A3 (who also had longitudinal DXA studies, shown in Fig. 2A), and B1–4 (whose longitudinal DXA studies are shown in Fig. 2B) and 14 unaffected first-degree relatives (11 hets, three with no mutation). Participants A2 and A3 had previously been treated with bisphosphonates; B1–4 had no prior treatment with any bone active drug. Tibial pQCT was not performed in OPPG patient A1 (because of the presence of tibial surgical hardware), C1 (unable to cooperate with the study) or C2 (leg was too short to do pQCT).

Trabecular vBMD and cortical dimensions were markedly lower in OPPG affected participants compared with unaffected participants and there was a trend toward lower height in OPPG affected participants (Table 1). Fig. 3A demonstrates the normal trabecular vBMD, cortical area, and periosteal circumference Z-scores in the unaffected participants (compared with the reference median Z-score of 0), and the significantly lower trabecular vBMD ($p = 0.002$), cortical area ($p < 0.001$) and periosteal circumference ($p = 0.001$) Z-scores in the OPPG participants. Of note, one OPPG participant (A2) had exceptionally low cortical area and periosteal circumference Z-scores of -9.27 and -6.98 , respectively. The pQCT images at the trabecular (3%) and cortical (38%) sites in this 14 year old male are shown in Fig. 4, in comparison with a reference participant of the same age, sex and tibia length. The lower trabecular vBMD and cortical dimensions in OPPG are evident. The statistical significance of the group differences was unchanged in analyses excluding this participant.

The differences in endosteal circumference, muscle area and fat area are shown in Fig. 3B. Although the data suggest lower endocortical circumference, lower muscle area, and greater fat area in OPPG compared with controls, the results did not reach statistical significance. Mean muscle area Z-scores were 1.16 lower in the OPPG participants, compared with controls. The lack of statistical significance for the clinically significant difference in muscle area Z-scores between OPPG and controls is likely related to the limited power.

Discussion

OPPG is a rare disease, with no controlled trials available to guide treatment. Given the morbidity of fractures in children, particularly in those with blindness as in OPPG, these patients have generally been treated clinically. Bisphosphonates have been shown by us [4] and others [6–8] to improve DXA-derived aBMD in OPPG after a few years of use. However, there have been no reports on long term bisphosphonate use in OPPG. Additional gaps in available knowledge about OPPG include the absence of longitudinal DXA data after bisphosphonate discontinuation, data on untreated patients and the absence of data on bone quality. We now report our experience with 5 OPPG patients treated with bisphosphonates for 3–9 years, aBMD changes after stopping bisphosphonates in these patients and bone structural measures derived by pQCT in 6 OPPG patients compared to 14 unaffected first degree relatives. In addition, we report longitudinal data over >10 years in 4 OPPG patients who have never been treated.

After our report of improved aBMD in four patients with OPPG in 2008 [4], we observed fractures in three of these previously reported children while on alendronate (A2, A3, C1), after DXA Z-scores had improved significantly in all (to zero in the spine and better than -2.0 in the hip in all). In light of their improved Z-scores, the fractures were surprising and prompted us to study bone structure in OPPG by pQCT. Furthermore, OPPG is associated with substantial impairments in growth, and short stature results in significant underestimates of aBMD for age [21]. Therefore, the DXA aBMD Z-scores summarized in Fig. 2 may be artificially low. In two of the OPPG patients reported in 2008 and included in the current study (A2, A3), pQCT and DXA were done simultaneously. Although the DXA Z-scores in the spine suggested normal trabecular BMD, by pQCT, their trabecular vBMD

was clearly reduced in the tibia. This discrepancy highlights the limitations of DXA in predicting fracture in this population.

Among the fractures seen in our OPPG patients, the lateral cortical subtrochanteric stress fracture that progressed to a complete fracture that occurred in one patient (A3) is of particular interest. This fracture occurred three years after A3 had discontinued bisphosphonate treatment and was similar to a fracture reported in another OPPG patient, described as an atypical femur fracture in a patient who had not been treated with any anti-resorptive therapy [18]. This prior report brings into question whether the subtrochanteric femur fracture in our case was associated with her prior bisphosphonate treatment or with the underlying disease itself.

By pQCT, we found that bone structure was poor in OPPG, in both untreated patients ($n = 4$) and those previously on bisphosphonates ($n = 2$), compared to 14 unaffected first degree family members. Trabecular vBMD, periosteal circumference and cortical area were lower in OPPG, and the cortical structure Z-scores were far lower than observed in our prior studies in multiple pediatric diseases associated with muscle deficits [16,17]. Therefore, we believe that the Z-scores in OPPG were lower than what can be attributed to relatively low physical activity due to their blindness. Our findings of reduced trabecular vBMD, lower cortical area and periosteal circumference without endocortical expansions are consistent with the proposed pathogenesis of OPPG, reduction in bone formation. In this study, there were insufficient numbers of participants to determine if pQCT results differed according to OPPG genotype (AA vs. AB). Given that the A mutation codes for a stop codon, whereas the B mutation is predicted to result in some LRP5 protein being produced, additional studies are needed to compare these mutations.

The trend toward lower muscle area in OPPG found in this study was not statistically significant, possibly due to the small number of participants. Additional studies will be needed to determine if reduced muscle mass is present in OPPG. Wnt signaling, for which LRP5 is a cofactor, is known to be important for muscle development [10,11,19].

Our results are strengthened by the large reference database of pQCT phenotypes in children and adults, and by the ability to adjust cortical dimensions and muscle area for tibia length. This is important given the strong correlations between cortical dimensions and tibia length, and the impaired growth in many children with OPPG. The OPPG participants had a mean height Z-score of -1.25 (equivalent to the 10th percentile for age and sex) and the adjustment for tibia length confirmed that the markedly smaller cortical dimensions persisted after adjustment for the shorter tibia length.

The inclusion of Old Order Mennonite (OOM) controls is an additional strength of the study. The controls for pQCT were all first degree relatives of OPPG patients, who could be expected to have higher muscle mass (than the CHOP reference participants recruited for the greater Philadelphia area) because of their simple lifestyle (no electricity or cars) which involves more physical activity (e.g. farming, hand washing clothes, bicycle use for transportation). Limitations of this study include the relatively small number of participants and limited longitudinal DXA data for OPPG patients never treated with bisphosphonates.

Our experience with long-term bisphosphonate treatment in OPPG has demonstrated that normal DXA-derived aBMD Z-scores can be achieved in the spine. Since this was not a controlled trial, we cannot determine how many fractures might have been prevented by bisphosphonate treatment. However, the occurrence of fractures in three of our OPPG patients with low normal hip aBMD indicates that bisphosphonates are not an ideal treatment for OPPG. An adult with OPPG was reported to have improved BMD from teriparatide [20], but this drug is not FDA approved for children. In our one patient treated with teriparatide, he had no fractures after teriparatide was given but this coincided with his puberty which we feel is a more important reason for his fracture cessation as we have seen no fractures in our cohort after puberty. Additional treatments are needed to treat the severe bony fragility in OPPG. Given the pathogenesis of reduced bone formation in OPPG, an anabolic agent would be an ideal treatment. Although this was not a controlled trial, our observation in 4 untreated OPPG patients was that BMD gains over time appeared to be worse in the spine than in the hip.

In summary, we have found that DXA-derived aBMD can be normalized in the spine in OPPG and improved to low normal in the hip but that all fractures are not necessarily prevented and that QCT-derived trabecular vBMD, periosteal circumference and cortical area were lower in OPPG than in controls, in a pattern consistent with reduced bone formation. These results suggest that DXA may be an inadequate method for the assessment of treatment response and for the prediction of fracture in OPPG. Additional studies on bone structure and quality in OPPG are needed to better define the bone response to treatment and to determine if muscle mass is reduced.

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Fig. 1.
OPPG pedigree — Study participants are indicated by *.

Fig. 2.

Longitudinal bone mineral density by DXA in OPPG patients. Fractures are indicated by arrows. 2A. Five OPPG patients with AA genotype treated with bisphosphonates. Fractures included femoral shaft, tibia and fibula fractures. Treatment is indicated by solid bars. BP = bisphosphonates. TER = teriparatide. Patient A1 was treated with risedronate from age 8.5–11 years, pamidronate from 11–14.5 years and alendronate from 16–19.5 years. Patient A2 was treated with risedronate from age 5–8.5 years, pamidronate from 8.5–9.5 years and alendronate from 10–12 years and 13.5–14 years. In patients A2 and A3, the pQCT was

done when they were ages 14.5 and 8.5 years. pQCT was not performed in A1, C1, C2. 2B. Four OPPG patients with AB genotype never treated pharmacologically. pQCT scans on these participants were 3 years prior to the last DXA.

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A) Trabecular vBMD, cortical area and periosteal circumference Z-scores were significantly lower in the OPPG participants

B) Endosteal circumference, muscle area and fat area Z-scores

Fig. 3. pQCT Z-scores in 6 OPPG and 14 unaffected participants. (A). Trabecular vBMD, cortical area and periosteal circumference Z-scores were significantly lower in the OPPG participants.

Fig. 4. pQCT images in a 14 year old male OPPG participant and an age-, sex-, and tibia length-matched reference participant. The markedly greater cortical area and periosteal circumference at the 38% cortical diaphysis is evident in the reference participant (A) compared with the OPPG (B) participant. The greater trabecular BMD at the 3% metaphysis site is shown in the reference (C) compared with the OPPG (D) participant.

Table 1

Participant characteristics and pQCT results in the pQCT substudy.

	OPPG affected	Unaffected	p-Value
n	6	14	
Age, years ^a	14.5 (8.5–22.6)	22.8 (5.7–51.3)	
Sex, n (% male)	3 (50%)	6 (43%)	
Height Z-score	−1.25 ± 1.03	−0.50 ± 0.66	0.07
Trabecular BMD Z-score	−1.57 ± 1.43	0.22 ± 0.73	0.002
Cortical area Z-score	−2.19 ± 1.29	0.04 ± 0.80	0.0003
Periosteal circumference Z-score	−2.07 ± 1.08	−0.30 ± 0.88	0.001
Endosteal circumference Z-score	−1.35 ± 1.47	−0.59 ± 0.82	0.17
Muscle area Z-score	−0.69 ± 1.78	0.47 ± 1.28	0.12
Fat area Z-score	1.32 ± 1.32	0.55 ± 1.14	0.21

Results presented as median (range) or mean ± SD.

Ages of OPPG affected were: 22.6, 17.3, 14.5, 13.0, 11.2, and 8.5; unaffected: 51.3, 48.7, 41.0, 40.9, 30.0, 29.1, 15.4, 13.1, 11.7, 9.7, 8.2, 7.6, 6.3, and 5.7.

^aUnaffected group was older than affected group because six were parents of affected participants.