Low bone mass in Pompe disease
Muscular strength as a predictor of bone mineral density

Linda E.M. van den Berg a,e, Adrienne A. Zandbergen b, Carine I. van Capelle a, Juna M. de Vries a,c, Wim C. Hop d, Johanna M. van den Hout a,c, Arnold J.J. Reuser f, M. Carola Zillikens b, Ans T. van der Ploeg a,*

a Department of Pediatrics, Division of Metabolic Diseases and Genetics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands
b Department of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands
c Department of Neurology, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands
d Department of Biostatistics, Erasmus MC, Rotterdam, The Netherlands
f Department of Clinical Genetics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands
* Corresponding author. Department of Pediatrics, Division of Metabolic Diseases and Genetics, Erasmus MC University Medical Center-Sophia Children’s Hospital, PO Box 2060, 3000 CB Rotterdam, The Netherlands. Fax: +31 10 7036800.
E-mail addresses: lvandenberg@erasmusmc.nl (L.E.M. van den Berg), adrienne_zandbergen@yahoo.com (A.A. Zandbergen), cvancapelle@erasmusmc.nl (C.J. van Capelle), jm.devries@erasmusmc.nl (J.M. de Vries), w.hop@erasmusmc.nl (W.C. Hop), lvandenhout@erasmusmc.nl (J.M. van den Hout), a.reuser@erasmusmc.nl (A.J. Reuser), m.zillikens@erasmusmc.nl (M.C. Zillikens), aw.vanderploeg@erasmusmc.nl (A.T. van der Ploeg).

A B S T R A C T

Pompe disease is an inherited metabolic myopathy caused by deficiency of acid alpha-glucosidase. The introduction of enzyme replacement therapy as treatment for the disease may change prospects for patients and may require that more attention be paid to co-morbidities such as osteoporosis.

Methods: Bone mineral status was assessed in children and adults with Pompe disease and compared with reference values by means of dual energy X-ray absorptiometry (DXA) technology (GE Lunar DPX, GE Health Care). Bone mineral density (BMD) of the total body and the lumbar spine (L2–L4) was measured in adults and children; BMD of the femoral neck was measured in adults only. Exclusion criteria were: age <4 years, severe contractures, and inability to transfer the patient.

Results: 46 patients were enrolled in the study; 36 adults and 10 children. The BMD was significantly lower in Pompe patients than in healthy individuals. Sixty-seven percent of patients had a BMD Z-score below −1, 26% were classified as osteoporosis/low bone mass for chronological age (T-score < −2.5 in adults or Z-score < −2 in children), 66% had a BMD Z-score below −1 of the femoral neck, and 34% had a BMD Z-score below −1 for the lumbar spine. Osteoporosis/low bone mass for chronological age was more frequent in patients who were wheelchair-bound, but was also observed in ambulant patients. We found a significant correlation between proximal muscle strength and total body BMD. Of the 10 children, 8 (all four patients with the classic infantile form) had a low BMD.

Conclusion: Low BMD is a frequent finding in patients with Pompe disease and may be causally related to decreased proximal muscle strength. BMD should be monitored at regular intervals. Children deserve specific attention.

© 2010 Published by Elsevier Inc.

Introduction

Pompe disease (glycogen storage disease type II, acid maltase deficiency) (OMIM #232300) is an inherited metabolic myopathy caused by deficiency of acid α-glucosidase [1]. Deficiency of this lysosomal enzyme leads to glycogen accumulating in a variety of tissues. The GAA gene is located on chromosome 17q25.3. More than 200 mutations have been detected in this gene [1,2]. Pompe disease presents as a broad clinical spectrum, ranging from the classic infantile form characterized by hypotonia, hypertrophic cardiomyopathy, and death within the first year of life [3,4], to more slowly progressive forms in children and adults with proximal muscle weakness and respiratory problems [5,6]. The most common genotype in children and adults with Pompe disease is the IVS1 c.-32-13T>C/null genotype [7,8], which gives rise to 10–30% residual alpha-glucosidase activity and explains the milder phenotype.

Though the prognosis of patients is poor, this may change with the introduction of enzyme replacement therapy. The therapy has led to increased survival and improved motor outcome in patients with the classic infantile form [9–11]. Data on enzyme replacement therapy in children and adults are still limited, but early results indicate that muscle and respiratory function may stabilize or improve [12,13]. These potential changes in outcome imply that better long-term clinical management programs will be needed for infants, children,
and adults with Pompe disease. These programs should also focus on co-morbidities.

Decreased bone mineral density (BMD) and increased incidence of fractures have been observed in several myopathies [14–16] and lysosomal storage diseases [17,18]. It seems likely that patients with Pompe disease are at a greater risk of acquiring osteoporosis—a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture [19]. There is evidence to suggest that bone fractures occur more frequently in infants and children with Pompe disease, especially in those who are immobile and bedridden [20]. However, no BMD data are available for child, adolescent, or adult Pompe disease patients. The goal of this study was therefore to systematically assess the bone mineral status in a cohort of forty-six patients with Pompe disease (children, adolescents, and adults) via dual-energy X-ray absorptiometry (DXA) technology, to ascertain the prevalence of osteoporosis/low bone mass for chronological age and to identify candidate causes of possible decreased BMD in this patient group.

Patients and methods

This study on bone mineral density was performed at the Erasmus MC University Medical Center in Rotterdam, the Netherlands, which is the Dutch national referral center and international expert center for patients with Pompe disease. The Ethical Committee of the Erasmus MC University Medical Center approved the research protocol. Written informed consent was obtained from all patients or their parents.

Exclusion criteria comprised age < 4 years, severe contractures and inability to transfer the patient to the DXA table. Forty-six patients were enrolled in this project since 1995. The diagnosis of Pompe disease was confirmed in all patients through mutation analysis and measurement of decreased acid α-glucosidase activity in leukocytes or fibroblasts. The distinction between classic infantile and milder variants with Pompe disease is made on the basis of clinical presentation, residual alpha-glucosidase activity, and severity of the mutations in the GAA gene.

The DXA scan was performed on the adults just before or within 34 weeks after the start of enzyme replacement therapy (mean 11 weeks; range 0–34 weeks). At the time of their DXA scan, all but one of the children/adolescents had been undergoing enzyme replacement therapy for longer (mean 3.7 years; range 0–8 years).

Anthropometrics

Body weight with indoor clothing without shoes was measured on a digital scale (ServoBalans type KA-20-1505, Servo Berkel Prior B.V.) to the nearest 0.1 kg. The height of ambulant patients was measured barefoot standing (Ulmer Stadiometer, Prof. E. Heinze); wheelchair-dependent patients were measured while lying in bed. The Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Bone densitometry scanning

Bone densitometry was performed by using DXA technology (GE Lunar DPX, GE Health Care). In adults, the BMD of the total body, the lumbar spine (L2–L4), and femoral neck was measured. In children/adolescents (age ≤ 20 years) only the BMD of the total body and lumbar spine (L2–L4) were measured, because reference values were available from a study of 444 healthy white volunteers aged between 4 and 20 years in the Netherlands [21]. The BMD results were expressed as Z-scores, which are the number of standard deviations above or below the mean reference values for healthy persons matched for age, sex, height, weight, and ethnic group.

To identify osteoporosis in the adults, the T-score was used. A T-score for total body, lumbar spine or femoral neck T-score of less than or equal to −2.5 SD was defined as indicating osteoporosis. In children/adolescents, the term “low bone mass for chronological age” is preferred when the Z-score is less than or equal to −2 SD [22].

The reference values used in the DPX software are from studies of reference populations in university medical centers and clinics in the US, England and Northern Europe.

Daily quality assurance tests were performed with a calibration block supplied by the manufacturer. Repeated measurements on the calibration block had coefficients of variation < 0.5%. In addition, a calibration aluminium phantom was measured weekly; the coefficients of variation were < 0.5%.

Laboratory analysis

We analyzed non-fasting blood samples for serum concentrations of calcium (normal values: 2.10 to 2.60 mmol/L in children and 2.20 to 2.65 mmol/L in adults) and phosphate (normal values: 1.00 to 1.80 mmol/L in children and 0.80 to 1.40 mmol/L in adults), 25-hydroxyvitamin D (normal values: 50–136 nmol/L), and parathyroid hormone (normal values: 1.4 to 7.3 pmol/L). As markers of bone turnover we assessed the bone formation marker alkaline phosphatase and the bone resorption marker ICTx (normal values are shown in Table 4). ICTx concentrations were determined using an electrochemiluminescence immunoassay (ECLIA) following the manufacturer’s instructions (ICTx/CrossLaps/serum, Cobas®, Roche Diagnostics, Mannheim, Germany).

Lung function

Pulmonary function (FVC) was measured with spirometry. Historical data were used for comparison.

Muscle strength

The muscle strength of twelve muscle groups was measured in Newtons with a hand-held dynamometer (dynamometer type CT3001-C.L.T. Technics). Maximum isometric contraction values were assessed with the break technique, in which the examiner applies adequate force to overcome the examinee, thereby producing an eccentric contraction. The values obtained for the different muscle groups were expressed as percentages of age- and sex-matched reference values. We used summed scores for total muscle force (neck flexors, neck extensors, shoulder abductors, elbow flexors, elbow extensors, wrist extensors, hip flexors, hip abductors, knee flexors, knee extensors, foot dorsiflexors, and foot plantiflexors), muscle force of the neck region (neck flexion and extension), proximal muscle force of the upper extremities (shoulder abductors, elbow flexors, and extensors), distal muscle force of the upper extremities (wrist extensors), proximal muscle force of the lower extremities (hip flexors and abductors, knee flexors, and extensors) and distal muscle force of the lower extremities (foot dorsiflexors and plantiflexors). All muscle groups were assigned equal weight. The values obtained for children could not be incorporated in the analyses since insufficient age-matched reference values were available for the various muscle groups [23].

Statistical analysis

Descriptive statistics are presented as mean ± SD. All variables were analyzed to evaluate their normality (Shapiro–Wilk test), and then the appropriate statistical tests were chosen. Student’s t-test was used for the comparison of the means, after validating the normality assumptions. The one-sample t-test was used to compare mean Z-scores with zero within groups. The nonparametric tests for independent samples
(Mann–Whitney test and Kruskal–Wallis test) were used for the other variables.

Pearson correlation coefficients were calculated in order to ascertain the relationships between muscle strength and BMD. Multiple regression analysis was used to evaluate various factors simultaneously in relation to BMD Z-scores. All the analyses were performed using SPSS for Windows (version 15.0, SPSS Inc. Chicago, IL, USA). Two-sided P-values less than 0.05 were considered significant.

Results

Patients

Forty-six patients (23 males, 23 females) were enrolled in this study. Thirty-six were adults and ten were children/adolescents. The most common genotype c.-32–13T>G (IVS1-13T>G) mutation was present in 84% of the patients. The patient characteristics are summarized in Table 1.

DXA scanning

Table 2 shows the BMD Z-scores of the children/adolescents and adults compared with the reference values of healthy individuals. The Z-scores for total body and femoral neck were significantly lower in the Pompe patients. The mean Z-scores of lumbar spine were not significantly different from zero. The patients’ TB and FN BMD scores are plotted against reference values for healthy individuals in Fig. 1.

Of all patients, 31 (67%) had a BMD Z-score below −1 and 12 (26%) of them were classified as osteoporosis/low bone mass for chronological age (T-score < −2.5 in adults or Z-score < −2 in children). A BMD Z-score below −1 was found at the femoral neck in 66% of the patients. Fewer (34%) had this score at the lumbar spine.

The characteristics of the 12 patients with osteoporosis/low bone mass for chronological age are given in Table 3. Four of these patients were children/adolescents; three of them had the classic infantile form of Pompe disease. In this group of twelve patients, seven (58%) were wheelchair-bound compared with 12 (23%) in the total group.

Eight of the 10 children had a BMD Z-score below −1. No significant differences were found between ambulant patients and non-ambulant patients, or between ventilated and non-ventilated patients. No correlation was found between the Z-score of total body BMD and disease duration. There were no significant differences for age and years of symptoms between the group of twelve patients with a T-score < −2.5 or Z-score < −2 and the total group. No significant correlations emerged from the multivariate analysis of total body Z-score in relation to age, ventilation dependency, and years of symptoms.

We found Z-scores below −1 and even below −2, and T-scores below −2.5 in both patients with an IVS1 c.-32–13T>G/null genotype and patients with other mutations. None of the patients with classic infantile or juvenile onset disease and low bone mass for chronological age had an IVS1 c.-32–13T>G/null genotype.

Laboratory analysis

Analysis of the blood samples obtained from 44 patients revealed that seven patients had elevated serum concentrations of parathyroid hormone (7.6–14.4 μg/L, normal values 1.4–7.3 μg/L) and eight patients had lowered serum concentrations of 25-hydroxyvitamin D (13–47 nmol/L, normal values 50–136 nmol/L). Three of these patients had signs of secondary hyperparathyroidism, as evidenced by lowered concentrations of 25-hydroxyvitamin D in combination with an elevated serum concentration of parathyroid hormone. Only one of them had osteopenia (T-score < −1).

All patients had normal serum concentrations of the bone turnover markers alkaline phosphatase and β-CtX (Table 4).

No significant differences were found between the group with a T-score < −2.5 or Z-score < −2 and the other Pompe patients for the bone turnover markers and the serum concentrations of calcium, parathyroid hormone, and 25-hydroxyvitamin D.

Bone mineral density and lung function

We did not find significant correlations between the BMD Z-scores of any region and lung function (forced vital capacity).

Bone mineral density and muscle strength

Table 5 summarizes the correlations between BMD Z-score of the total body and muscle strength of several regions of the body in 32 adults. Four adults were excluded from the analysis because reliable data could not be obtained for some muscle groups. A significant correlation was found between total body BMD and total body muscle strength (Fig. 2). This relation remained significant after adjustment for age, ventilation dependency, and years of symptoms (P = 0.025). Significant correlations were also found between the total body BMD and muscle strength of the neck region, and the proximal muscles of the upper and lower extremities; no correlations were found between total body BMD and distal muscle strength. The correlation between the strength of the proximal muscles of the lower extremities and BMD of the femoral neck showed a trend (r = 0.34), but did not reach statistical significance (P = 0.06). There were no significant correlations between muscle strength of any of the muscle groups and BMD of the femoral and lumbar spine.

Discussion

With the changing perspectives on Pompe disease patients, supportive care and prevention of co-morbidities such as osteoporosis are becoming more important. The results of the current study show that low bone mineral density, a possible indicator of the co-morbidity osteoporosis, is a common feature in patients with Pompe disease. Thirty-one of the forty-six patients (67%), that we investigated had a

---

**Table 1**

Patient characteristics.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI (g/cm²)</th>
<th>Disease duration (years)</th>
<th>Mobility</th>
<th>Ventilation</th>
<th>Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Adults</td>
<td>17</td>
<td>19</td>
<td>52±11</td>
<td>174±10</td>
<td>73±14</td>
<td>24±4</td>
<td>17±10</td>
<td>25</td>
</tr>
<tr>
<td>Children/adolescents</td>
<td>6</td>
<td>4</td>
<td>11±6</td>
<td>161±15</td>
<td>47±15</td>
<td>19±3</td>
<td>6±4</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>23</td>
<td>43±20</td>
<td>172±12</td>
<td>69±17</td>
<td>23±4</td>
<td>15±10</td>
<td>33</td>
</tr>
</tbody>
</table>

* All ambulant patients. In parentheses: the number of patients who were ambulant, but with aids.

---

Please cite this article as: van den Berg LEM, et al, Low bone mass in Pompe disease, Bone (2010), doi:10.1016/j.bone.2010.06.021
Fig. 1. Total body bone mineral density for individual patients for men (A), women (B), boys (C) and girls (D) and femoral neck bone mineral density for men (E) and women (F). Reference values are plotted for comparison. Lowest curve: $Z = -2$ next curve up: $Z = -1$; middle curve: $Z = 0$; next curve up: $Z = +1$ uppermost curve: $Z = +2$. 

Please cite this article as: van den Berg LEM, et al, Low bone mass in Pompe disease, Bone (2010), doi:10.1016/j.bone.2010.06.021
BMD Z-score below −1. Remarkably, this group included eight of the 10 participating children/adolescents. The eight included all four patients with the classic infantile form of Pompe disease. Three of those four had a low bone mass for chronological age (Z-score < −2).

Low BMD increases the risk of fractures. A recent article reported the occurrence of fractures in children with an infantile onset of Pompe disease, mostly in the long bones (femur and humerus) of patients with a lack of weight-bearing [20]. It is unlikely that patients with a decreased bone mineral density in childhood will attain a normal peak bone mass [24]. This puts them at even greater risk of fractures later in life.

Twelve of the 46 patients were classified as osteoporosis/low bone mass for chronological age (T-score < −2.5 in adults or Z-score < −2 in children). In this group of twelve, more patients were wheelchair-bound and ventilation-dependent than in the total group of patients. This may be explained by the fact that prolonged inactivity and immobilization are important risk factors for osteoporosis [25,26]. A noteworthy finding was that there was osteoporosis/low bone mass for chronological age in five ambulant patients: this indicates that factors other than inactivity and immobilization also play a role. Muscle strength is one such factor: we found that BMD was correlated with proximal muscle strength.

The mechanostat theory postulates that muscle strength is a predictor of BMD in the non-diseased population [27–29]. Our study indicates that this theory may be extended to populations with neuromuscular diseases as well. We therefore recommend that all patients with impaired muscular strength are screened for decreased BMD. Screening should not be limited to inactive and immobile patients but should also include those who are ambulant. Skeletal muscle weakness is expected to have the greatest impact in children/adolescents, since the capacity of bone to increase its strength in response to mechanical forces is greatest during growth [30–32].

The notion that muscle strength and weight-bearing affect BMD in patients with Pompe disease is further supported by the greater involvement of the femoral neck compared to the lumbar spine. Trabecular bone (e.g. lumbar spine) is mainly influenced by general, systemic factors, such as hormone status and [30]. Cortical bone (the femur), however, is more subject to regional, mechanical influences, such as gravity, muscle mass, and muscle strength [30].

When treating osteoporosis/low bone mass for chronological age in Pompe disease it is important first to reduce or eliminate all the known risk factors for low bone mass. Effective control of the underlying disease is the best approach to prevent secondary osteoporosis. In 2006, enzyme therapy for Pompe disease was registered as a causative treatment for the disease. The possible long-term effects of enzyme replacement therapy on BMD are unknown, but positive effects might be seen when muscle strength increases. Physical activity is essential to increase BMD, not only in healthy individuals but also in persons with various pathological conditions [33]. On the basis of our finding that a decreased BMD is partly due to skeletal muscle weakness, we recommend exercise training for Pompe disease patients, because besides the possible positive effects on disease progression and daily life, such training may also prevent and ameliorate this long-term complication of Pompe disease. On the basis of their findings, Slonim et al. advised a combination of high protein diet and exercise for Pompe disease patients [34].

With regard to therapeutic interventions with drugs for osteoporosis/low bone mass for chronological age, one should begin with the simplest and safest ones, such as calcium and vitamin D supplementation in case of deficiency [33]. Anti-resorptive drugs such as bisphosphonates have been shown to increase BMD, relieve pain, increase mobility, and reduce fragility fractures in osteogenesis imperfecta, corticosteroid-induced osteoporosis, and osteoporosis due to cerebral palsy [33]. In children, the most commonly used are intravenous cyclical pamidronate.
or oral alendronate [35–37]. Although the long-term safety of bisphosphonates is uncertain, the original concerns, such as reduced healing of fractures and altered onset and course of puberty, have not been confirmed in over ten years of pediatric use [33]. Remarkably, in our patients the bone turnover markers were not increased. It is not known whether medical therapy in the form of bisphosphonates is effective in patients with Pompe disease and low BMD.

In summary, our study demonstrates for the first time that patients with Pompe disease often have a decreased BMD (Z-score < -1) and are at risk of osteoporosis/low bone mass for chronological age. At particular risk are patients who are wheelchair-bound and ventilator-dependent. However, in ambulant patients we also found Z-scores below -1 and even below -2, and T-scores below -2.5. We found that the low BMD of Pompe patients correlated with a decreased proximal muscle strength. For detection of decreased BMD we recommend screening all affected children, wheelchair-bound and ventilator-dependent adults, and all patients with decreasing muscle strength. Prospective studies are needed to evaluate the effect of enzyme replacement therapy and exercise training on muscle strength and BMD in patients with Pompe disease.

Acknowledgments

We thank the patients for participating in this study as well as all who have given their support: J.F. Hardon, H.A. Nelisse, J.P. Sluimer.

The Research on Pompe disease at Erasmus MC was financially supported by the Princes Beatrix Fonds (Grant OP07-08), the 7th Frame Program “EUCLYD-a European Consortium for Lysosomal Storage Diseases” [58] grant agreement 201678], ZonMW-Dutch Organization for Healthcare Research and Innovation of Care [Grant 152001005], and Genzyme.

The authors’ editor was J. Burrough.

References


Please cite this article as: van den Berg LEM, et al, Low bone mass in Pompe disease, Bone (2010), doi:10.1016/j.bone.2010.06.021

