Osteopenia: a common aspect of Fabry disease. Predictors of bone mineral density

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Purpose: We investigated the bone mineral status in patients with untreated Fabry disease (FD). **Methods:** Descriptive, cross-sectional study in 53 patients with FD investigating bone mineral density (BMD)/content (dual energy x-ray absorptiometry scan), bone metabolism (parathyroid hormone, osteocalcin, and insulin-like growth factor I), and renal function (ethylene diamine tetraacetic acid clearance). **Results:** Mean BMD *z* score at the lumbar spine and femoral neck were -0.05 ± 1.46 SD and -0.37 ± 1.02 SD, respectively. Approximately 50% had osteopenia in the hip or lumbar spine and additionally four had osteoporosis. Multivariate analysis including body weight, impaired renal function, and genotype overall explained 48% of the variance in lumbar spine BMD ($P < 0.001$), whereas body weight, impaired renal function, and menopausal status in the female population accounted for more than 50% of the variation in BMD of both the lumbar spine and femoral neck (both $P < 0.001$). Twenty percent of patients had hyperparathyroidism. Although the level of parathyroid hormone was significantly associated with impaired renal function, osteocalcin levels were significantly higher in patients with lumbar spine osteopenia or osteoporosis than in those with normal BMD. **Conclusions:** Osteopenia was present in approximately 50% of patients with untreated FD. Whether BMD and bone metabolism will improve after enzyme replacement therapy remains to be established. *Genet Med* 2007:9(12):812–818.

Key Words: Fabry disease, bone mineral density, parathyroid hormone, osteoporosis, osteopenia, dexa-scan

Fabry disease (FD) is a rare X-linked metabolic glycosphingolipid storage disease caused by deficiency of the lysosomal enzyme α-galactosidase A (α-gal A).[1] With increasing age of the patient, globotriaosylceramide (Gb₃) progressively accumulates in vulnerable cells and organs. Affected cell types include endothelial cells, pericytes, smooth muscle cells of the vascular system, renal epithelial cells, myocardial cells, and dorsal ganglia neuronal cells.[2,3] FD is associated with high levels of premature morbidity and mortality. Death usually occurs during the fourth or fifth decade of life from cardiovascular, cerebrovascular, or end-stage renal disease (ESRD).[4]

The successful introduction of enzyme replacement therapy (ERT) may reverse the situation[5–8]: data from the National Institute of Health[8] revealed improved cardiac conduction af-

ter treatment, yet the long-term effect on morbidity and mortality is unclear. The potential improvement in the clinical course necessitates increased knowledge of FD and awareness of comorbidities such as osteoporosis, as more patients may live to have disease-related complications. Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and increased fracture risk. The amount of bone mineral present in the skeleton is primarily a function of the amount gained during the phase of skeletal development and maturation. Normal bone development with achievement of peak bone mass is influenced by several factors: genetics, nutritional status, hormones, exercise, and other physical factors. Skeletal manifestations of Gaucher disease, another glycosphingolipid storage disease, can severely impair the mobility of patients with considerable impact on the quality of life. Patients with FD are characterized by weight loss[9] and low body mass index (BMI),[10] the cause being unknown. In addition, progression of renal impairment may further reduce bone mineralization and contribute to the development of osteoporosis in this population. A recent letter reports an increased risk of reduced bone mineral density (BMD) in hemizygous men with FD.[11]

This study was undertaken to assess the bone mineral status in patients with untreated FD and to identify patients at risk for development of osteoporosis.

PATIENTS AND METHODS

Design

The study was a cross-sectional, descriptive study of patients with FD. The investigations included assessment of height, body weight, body composition, BMD, bone mineral content (BMC), genotype, renal function and analyses of parathyroid hormone (PTH), osteocalcin (OC) and insulin-like growth factor (IGF)-I.

Human studies

The study was approved by the regional ethical committees in Denmark (registration number KF 01-075/01) and Sweden (registration number S 194-01), respectively. Written informed consent was obtained from all patients.

Patients

We examined 53 patients (21 hemizygous men, 32 heterozygous women) before initiation of ERT. Mean (range) age was 40 (15–63) years. The patients originated from 14 different families, all of European (white) descent and resident in Denmark (33 patients) or Sweden (20 patients). The diagnosis of FD was verified by mutation analysis. All 14 families represented a private mutation. No patients had previously experienced vertebral crush fractures; hip fractures or Colles fracture of the distal forearm and none had known osteoporosis. Three patients were prescribed calcium/vitamin D, but two of these were on maintenance hemodialysis because of ESRD. All men had testosterone levels within the normal range. A total of 13 women were postmenopausal and 19 were premenopausal (confirmed by menstrual status and hormone analyses). None were pregnant or lactating. A total of four women of postmenopausal age and two of premenopausal age received sex steroid replacement therapy. No other osteoporosis prophylactic precautions were administered. Oral corticosteroids were used by two patients (prednisolone 5–25 mg). Data on regular milk consumption, alcohol intake, food composition, or smoking status were not available.

Operational definitions

The definition recommended by the European Foundation for Osteoporosis and Bone Disease, The National Osteoporosis Foundation of the United States, and The World Health Organization 1994[12] was used to categorize regional and/or total BMD into (1) normal: a T score above -1.0 SD; (2) osteopenia: a T score between -1.0 and -2.5 SD; and (3) osteoporosis: a T score below -2.5 SD. An adult white population provided by the manufacturer were applied as reference. Obesity status was classified according to World Health Organization's definitions based on BMI, which was calculated as weight in kilograms divided by height in meters squared: patients with a BMI below 18.5 kg/m^2 were considered underweight, patients with a BMI between 18.5 and 24.9 kg/m^2 were considered normal weight, patients with a BMI between 25.0 and 29.9 kg/m^2 were considered overweight, and patients with a BMI above 30 kg/m^2 were considered obese.

Anthropometrics, body composition, and bone mineral status

Body weight was measured in indoor clothing without shoes, on a decimal scale to the nearest 0.1 kg (type M4, Bisco, Farum, Denmark and System 31, The advanced weighting Co Ltd., Newhaven, East Sussex, Great Britain). Height was measured barefoot to the nearest 0.5 cm.

Regional BMD and BMC were measured at the lumbar spine L2-L4 and the left femoral neck using dual energy x-ray absorptiometry (model XP-26, Norland Medical Systems, Fort Atkinson, and Lunar Prodigy, MEC, Minster, OH). In addition, whole body scans were performed with separate assessment of the three compartments: total BMC, total fat mass, and total lean body mass. The sum of these provided the total body weight. During the study period the scanner was calibrated daily against a phantom provided from the manufacturer.

Laboratory analyses

Blood samples were obtained after an overnight fasting of at least 10 hours and stored frozen at $-20°C$, until thawed for analyses. IGF-I was determined by competitive radioimmunoassay (RIA) using polyclonal rabbit anti-IGF-I antiserum as described by Juul.[13] Intra- and interassay coefficients of variation (CV) were 3.1% and 10.0%, respectively (at a concentration of 202 μg/L). Assay-specific reference values were used to calculate the IGF-I standard deviation scores (SDS) based on the SD from an age- and gender-adjusted mean. SDS = z scores = $[\sqrt{(IGF\text{-}I)} - \sqrt{mean}]/\sqrt{SD}$. PTH was analyzed on 150 μL ethylene diamine tetraacetic acid (EDTA) plasma samples by chemiluminescence immunoassay utilizing polyclonal goat antibodies (Nichols Institute Diagnostika, Bad Neuheim, Germany). Intra-assay CV was 12.5% and 4.1% at a concentration of 1.96 pg/mL and 17.1 pg/mL, respectively. The serum concentration of OC was measured by a double antibody RIA (Biointernational CIS, Gif-sur Yvette, Cedex, France) with intra-assay CV of 8.2%, 5.6%, and 5.4% at serum concentrations of 3.6, 10.3, and 22.3 μg/L, respectively. The assay-specific normal reference ranges of PTH and OC were: 1.1–6.9 pmol/L and 0.9–18.0 μg/L, respectively.

Renal function

Renal function was investigated by assessment of glomerular filtration rate (GFR) using EDTA clearance. GFR was considered to be low, when EDTA clearance was below 80 mL/min (for patients at age 15–30 years), 75 mL/min (for patients at age 30–50 years), and 60 mL/min (for patients at age 50–70 years). Urinary excretion of albumin and protein was measured by 24-hour urine sampling. Micro and macroalbuminuria was defined by excretion of 30–300 mg/24 hr and more than 300 mg/24 hr albumin, respectively. Proteinuria was defined by excretion of over 0.1 g/24 hr protein.

Statistics

All measured variables were normally distributed, except for PTH. A symmetric distribution of PTH was obtained by log

transformation of data. The PTH results are presented in geometric means (2.5–97.5 percentile). All other data are presented in means ± SD. Group differences were evaluated by analysis of variance (ANOVA) followed Bonferroni correction for multiple comparisons. Univariate and multivariate regressions were performed by forward stepwise regression and presented with R^2 values and P values for the last determinant added. The level of statistical significance was set at 0.05. All statistical analyses were performed by Statistica version 6.0 (StatSoft Inc., Tulsa, OK).

RESULTS

Renal function

Twenty-three percent ($n = 12$) had impaired renal function with low GFR evaluated by EDTA clearance, whereas 77% ($n = 40$) had preserved renal function. Fifty-one percent ($n = 27$) had some degree of renal affection including presence of microalbuminuria ($n = 7$), macroalbuminuria ($n = 8$), proteinuria ($n = 23$), or low GFR ($n = 12$).

Anthropometry and body composition

Mean body weight and BMI were 70.8 ± 14.7 kg and 24.1 ± 4.3 kg/m², respectively (Table 1). Mean relative fat mass was 32.4 ± 11.2% (Table 1). Fifteen percent ($n = 8$) of the Fabry patients revealed a BMI below 20 kg/m², and 9% ($n = 5$) were underweight. Twenty-six percent ($n = 14$) and 9% ($n = 5$) presented with overweight or obesity, respectively.

Bone mineral status

Results on bone mineral status are summarized in Table 1. Mean z score at the lumbar spine was −0.05 ± 1.46 SD. At the femoral neck the corresponding value was −0.37 ± 1.02 SD. Men had lower total BMD z score and hip z score than premenopausal female patients (both $P < 0.05$), whereas no apparent differences between male patients and postmenopausal female patients were found. Patients with known risk factors ($n = 8$) including ESRD, sex steroid replacement therapy in postmenopausal women, calcium/vitamin D therapy, or steroid therapy had significantly lower regional BMD than patients with no known risk factors ($n = 45$). Overall 49% and 63% of the patients presented with negative BMD z scores of

Table 1
Anthropometry, body composition; total and regional bone mineral content (BMC) and bone mineral density (BMD) assessed by DEXA

	All patients ($n = 53$)	Postmenopausal women ($n = 13$)	Premenopausal women ($n = 19$)	Low GFR ($n = 12$)	Normal GFR ($n = 40$)
Body weight (kg)	70.8 ± 14.7	66.8 ± 14.0	68.9 ± 15.8	70.2 ± 8.3	71.2 ± 16.3
Height (m)	1.71 ± 0.1	1.64 ± 0.0	1.68 ± 0.1	1.75 ± 0.1	1.70 ± 0.09
Body mass index (kg/m²)	24.1 ± 4.3	24.8 ± 5.1	24.2 ± 4.4	23.2 ± 2.6	24.5 ± 4.7
Relative fat mass (%)	32.4 ± 11.2	40.7 ± 9.4	37.1 ± 6.1	28.1 ± 16.7	34.0 ± 8.7
Total BMD (g/cm²)	1.08 ± 0.17	0.98 ± 1.16	1.11 ± 0.19	1.02 ± 0.17	1.10 ± 0.17
Total BMC (g)	2778 ± 460	2406 ± 340[a]	2810 ± 509	2731 ± 419	2784 ± 478
Total BMD T score (SD)	−0.05 ± 1.35	−0.51 ± 1.23[a]	0.65 ± 1.61	−0.73 ± 0.73[b]	0.17 ± 1.44
Total BMD z score (SD)	−0.05 ± 1.27	−0.08 ± 1.35	0.44 ± 1.48	−0.55 ± 0.81	0.11 ± 1.36
Left hip BMD (g/cm²)	0.89 ± 0.15	0.79 ± 0.16[a]	0.92 ± 0.16	0.80 ± 0.13[b]	0.92 ± 0.15
Left hip BMD (g/cm²)[e]	0.89 ± 0.13	0.82 ± 0.14[a]	0.91 ± 0.11	0.80 ± 0.12[d]	0.91 ± 0.12
Left hip BMC (g)	4.42 ± 0.87	3.86 ± 0.70	4.47 ± 0.99	4.08 ± 0.72	4.53 ± 0.90
Left hip T score (SD)	−0.75 ± 1.15	−1.19 ± 1.25[a]	−0.17 ± 1.20	−1.62 ± 0.72[d]	−0.47 ± 1.14
Left hip z score (SD)	−0.37 ± 1.02	−0.20 ± 1.23	−0.12 ± 1.11	−1.04 ± 0.82[d]	−0.15 ± 1.00
L2-L4 BMD (g/cm²)	1.10 ± 0.21	0.99 ± 0.21[a]	1.15 ± 0.18	0.99 ± 0.18[b]	1.14 ± 0.21
L2-L4 BMD (g/cm²)[e]	1.10 ± 0.18	1.02 ± 0.20[a]	1.13 ± 0.17	0.99 ± 0.16[d]	1.14 ± 0.18
L2-L4 BMC (g)	49.6 ± 10.6	43.1 ± 8.48[a]	51.2 ± 9.88	45.0 ± 10.5	51.2 ± 10.4
L2-L4 T score (SD)	−0.31 ± 1.60	−1.15 ± 1.55[c]	0.31 ± 1.42	−1.45 ± 1.14[d]	0.08 ± 1.57
L2-L4 z score (SD)	−0.05 ± 1.46	0.08 ± 1.37	0.06 ± 1.39	−0.95 ± 1.08[d]	0.26 ± 1.45

The significances of differences were evaluated by ANOVA, followed by post hoc testing using Bonferroni.
Data are presented in means ± SD, according to menopausal status and renal function, given by low or normal glomerular filtration rate (GFR).
[a]$P < 0.05$, premenopausal women vs. postmenopausal women.
[b]$P < 0.05$, patients with low GFR vs. patients with normal GFR.
[c]$P < 0.01$, premenopausal women vs. postmenopausal women.
[d]$P \leq 0.01$, patients with low GFR vs. patients with normal GFR.
[e]Adjusted for differences in body weight.

the lumbar spine and hip, respectively. Osteopenia and osteoporosis of the lumbar spine were demonstrated in 27% ($n = 14$) and 6% ($n = 3$), respectively. Regarding the femoral neck, 46% ($n = 24$) and 4% ($n = 2$) revealed osteopenia and osteoporosis, respectively. Only 37% ($n = 19$) of the Fabry patients exhibited normal total and regional bone mineral status. Patients with osteopenia at the femoral neck were characterized by significantly lower mean weight and BMI compared with the normal BMD group. Also, patients with low or normal BMI presented significantly lower BMD of both lumbar spine and femoral neck, compared with overweight and obese counterparts.

Predictors of regional BMD

In univariate analyses, the lumbar spine BMD was positively associated with body weight ($R^2 = 0.24$, $P < 0.001$) and BMI ($R^2 = 0.18$, $P < 0.01$), but negatively associated with impaired renal function ($R^2 = 0.10$, $P = 0.02$) and presence of menopause ($R^2 = 0.15$, $P = 0.03$; women only). There was a significant correlation between lumbar spine BMD and genotype ($R^2 = 0.24$, $P < 0.001$). In the multivariate analysis, the main determinants were body weight, impaired renal function, and genotype, together explaining 48% of the variance in lumbar spine BMD ($P < 0.001$). In the female population: body weight, impaired renal function, and menopausal status accounted for 52% of the variance in lumbar spine BMD ($P < 0.001$). The residual variance was 0.15 g/cm^2 (both 15% of mean lumbar spine BMD). Addition of BMI, age, sex, and estrogen therapy did not explain further variance. In univariate analyses of the femoral neck BMD, a positive association was seen with body weight ($R^2 = 0.30$, $P < 0.001$), BMI ($R^2 = 0.20$, $P < 0.001$), and height ($R^2 = 0.09$, $P = 0.03$). Femoral neck BMD was negatively associated with presence of menopause ($R^2 = 0.15$, $P = 0.03$, women only), impaired renal function ($R^2 = 0.10$, $P = 0.02$), and age ($R^2 = 0.08$, $P = 0.04$). In the multivariate analysis, body weight, impaired renal function, and menopausal status overall predicted 51% of the variance in femoral neck BMD ($P < 0.001$, women only). The residual variance was 0.13 g/cm^2 (14% of mean lumbar spine BMD). Addition of BMI, age, family relation, sex, and estrogen therapy did not explain further variance. For most univariate and multivariate analyses, exclusion of patients with known risk factors ($n = 8$) could explain somewhat further variance but did not change overall conclusions.

Laboratory analyses

Mean PTH was 5.1 (2.0–16.5) pmol/L. Twenty percent ($n = 10$) had hyperparathyroidism with PTH above the upper reference level at 6.9 pmol/L. Patients with impaired renal function had significantly higher PTH concentration than those with preserved renal function, 6.5 (2.0–22.6) pmol/L vs. 4.8 (1.5–9.1) pmol/L ($P < 0.05$) as illustrated in Figure 1 by normal means ± SD. PTH was associated with urinary excretion of protein ($P < 0.05$), but not with bone mineral measurements. The mean concentration of OC was 11.7 ± 5.2 μg/L. OC was increased in three patients. OC was significantly associated with urinary excretion of protein and albumin, but not with renal function. As depicted in Figure 2, OC was significantly higher in patients with lumbar spine osteopenia or osteoporosis, defined by T scores, (13.0 ± 5.4 μg/L) compared with those with normal bone mineralism of the lumbar spine (10.4 ± 3.1 μg/L) ($P = 0.04$). This could not be confirmed when the analysis was based on BMD z scores. Mean IGF-I SDS was 0.09 ± 1.15 SD. IGF-I was positively associated with body weight, BMI, OC, total and femoral neck BMD, and all measures of BMC ($P < 0.01$).
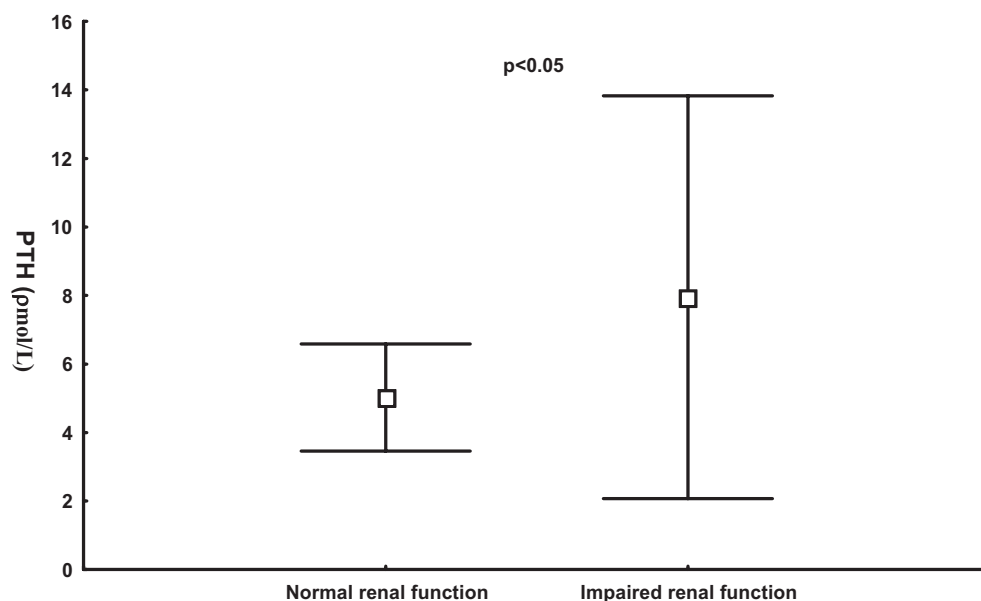

Fig. 1. Parathyroid hormone (PTH) levels (pmol/L) in 48 patients with Fabry disease and normal ($n = 36$) versus impaired ($n = 12$) renal function, determined by low glomerular filtration rate measured by EDTA clearance. Data are presented in normal means ± SD, but statistical analysis was based on log transformed data.
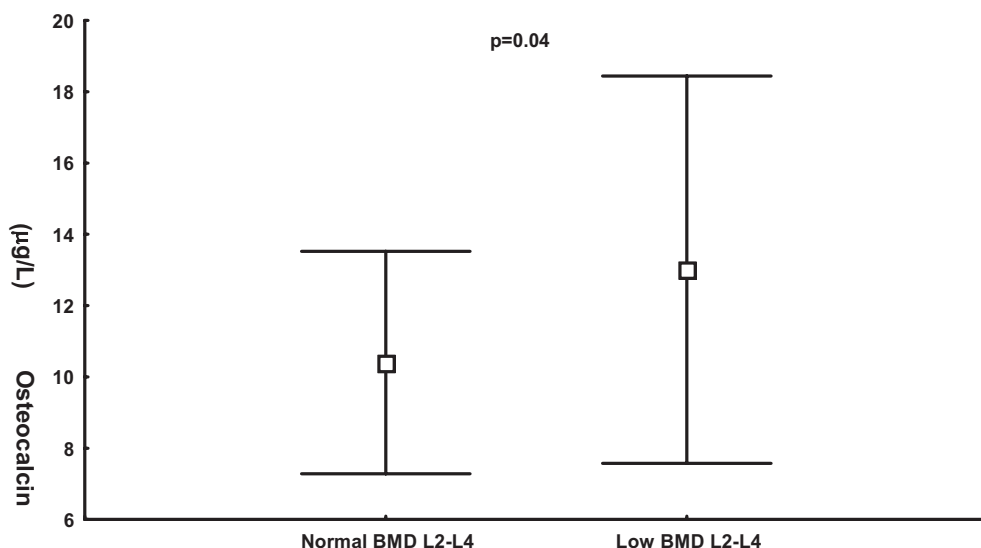
Fig. 2. Osteocalcin concentration in 31 Fabry patients with normal BMD of lumbar spine (L2–L4) compared with 16 Fabry patients with osteopenia or osteoporosis of lumbar spine (BMD less than −1 SD below the young adult mean value). Data are presented in means ± SD.

DISCUSSION

This study demonstrates that osteopenia is a common feature of FD. In this cohort of 53 adult Fabry patients, almost half of the patients had femoral neck osteopenia, whereas osteopenia of the lumbar spine was observed in 27%. Mainly women of menopausal age and patients with ESRD were diagnosed with manifest osteoporosis. The results reported here correspond well with the recent data published by Germain et al.[11,14] reporting osteopenia or osteoporosis in the majority of the examined population (*n* = 23).

The multiple regression analysis showed that in female patients with untreated FD: body weight, renal function, and menopausal status overall predicted more than 50% of the variation in lumbar spine BMD, and likewise for femoral neck BMD. The present finding that low body weight is a risk factor for low BMD is in agreement with studies in healthy individuals.[15–18] This is partly explained by a greater body size and bone size in heavier patients. Also, mechanical stress on bone is greater in obese than in lean individuals. Patients with FD have previously been characterized by weight loss[9] and low BMI.[10] In accordance with this, 15% of our population had a BMI below 20 kg/m^2. Gastrointestinal manifestations of FD including postprandial indigestion, nausea, cramps, reflux, and diarrhea are likely to contribute to the lower BMI.[9] Although malnutrition may lower BMI and thereby BMD, also malabsorption of vitamin D may further add to the secondary osteoporosis.

As expected, total and regional BMD were significantly higher in the premenopausal women compared with the postmenopausal women. The tendency of a beneficial impact of estrogen therapy on BMD among postmenopausal women did not reach statistical significance.

With the progression of FD, the prevalence and severity of renal impairment are augmented as a result of increasing deposits of Gb$_3$ in this organ. BMD of the lumbar spine and femoral neck were significantly lower in patients with impaired renal function compared with those with preserved renal function. This finding was evident, even after adjustment for differences in body weight. Not only may the presence of renal impairment induce osteopenia and osteoporosis, but dialysis treatment may also further deteriorate the bone mineralisation.[19] Only two patients in this cohort received hemodialysis because of ESRD. Both revealed manifest osteoporosis; however, the small number did not justify further analysis regarding the possible influence of dialysis in this population.

The spectrum of bone disease associated with ESRD is complex. Deficiency of the active metabolite of vitamin D (1,25(OH)$_2$D) causes hypocalcaemia and defective mineralization of osteoid with increase in the osteoid to mineral ratio[20] generating the low BMD.[21] Secondary hyperparathyroidism is an important factor in this osteopenia causing osteoclastic bone resorption. Rix[22] has confirmed that the skeletal changes after ESRD are signified by reduced BMD and elevated PTH and by the biochemical markers of both bone formation and resorption. In the present study, hyperparathyroidism was diagnosed in 20% of the studied Fabry patients. The level of PTH correlated well with both urinary excretion of protein and presence of impaired renal function, determined by low GFR. However, no association between PTH and bone mineral status was found. These findings suggest that the PTH level is amplified in response to renal affection in FD and precedes the loss of bone mineral. On the contrary, the OC concentration was significantly higher among patients with osteopenia of the lumbar spine, compared with those with normal lumbar spine BMD. Thus, OC may exhibit a compensatory role after osteopenia. The IGF-I SDS was positively associated with body weight, BMI, OC, total and femoral neck BMD, and all measures of BMC. Both IGF-I and growth hormone are known to

stimulate bone turnover inducing long-term amplification of bone mass.[23]

In general, mutations may influence the activity and/or the stability of the α-gal A. More than 180 different mutations have been identified—almost one unique mutation in each family. The clinical picture displays a large variety both within and between families, although two phenotypically very different groups of patients have been identified: classical and atypical. Atypical cases usually have residual α-gal A activity.[2] In our study, genotype may predict 24% of the lumbar spine BMD, whereas hip BMD was unaffected by genotype.

It is well recognized that the potent impact of physical exercise with resistance exercise and mechanical loading favors increased bone mass.[16,24] Schiffmann[25] has described that patients with FD are prone to avoiding exercise because of hypohidrosis and heat intolerance. Other possible explanations involve relative hypoxia[26] and reduced cardiac exercise capacity.[27] Physical inactivity may have attenuated bone mineral loss and osteopenia in our study subjects; however the possible impact of a sedentary lifestyle on bone mineral status is beyond the scope of this study.

Studies of patients with type-1 diabetes mellitus have demonstrated an association between BMD and microvascular complications.[28,29] Likewise, the vascular sequels of FD may add to the osteopenia in this population.

Besides the mentioned risk factors, skeletal accumulation of Gb_3 may account for part of the bone manifestations. Bone involvement with osteopenia and pathologic fractures are some of the most disabling aspects of Gaucher disease.[30–32] In Gaucher disease, cell infiltration can induce physical compression of the intramedullary blood vessels and bone marrow tissue. The skeletal response to ERT has been promising with an increase in mean BMD after 6 months of ERT, but this did not reach statistical significance until 4.5 years after commencement of ERT.[32] Changes in BMD are slow, as they are probably dependent on normalization of bone marrow. Measurement of BMD by dual energy x-ray absorptiometry was indicative of the resolution of generalized osteopenia during ERT of patients with Gaucher disease.[30]

The lifetime fracture risk of perimenopausal women with a BMD of 1 SD below average is 30% and, for a population with a BMD of 2 SD below average, about 60%. The combination of reduced BMD and an increased propensity toward falls because of neuropathy[33] and visual impairment[34–36] may predispose Fabry patients to an increased fracture rate.

In summary, this study demonstrated that FD was frequently complicated by osteopenia of the lumbar spine and femoral neck. BMD could be determined by body weight, renal function, and genotype and in women also by body weight, renal function, and menopausal status. The present analyses of predictors are of high clinical value in the discovery of pathogenic mechanisms for development of osteopenia and osteoporosis and to identify those patients who are specifically at risk of skeletal complications. The level of PTH mainly reflected renal function, whereas OC was significantly higher among patients with osteopenia, suggesting a compensatory role. After the recent successful introduction of ERT, patients may live to experience the painful and disabling consequences of osteoporosis. Whether patients with FD will demonstrate the same improvements in BMD in response to ERT, likewise their Gaucher counterparts, remains to be established. Besides ERT, this population may be candidates for investigative trials of adjunctive agents such as bisphosphonates. Following this report we recommend the screening and monitoring of BMD in patients with FD, especially in those patients presenting with proteinuria or renal impairment or reduced BMI.

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