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RESEARCH REPORT

Antiepileptic Medications Increase Osteoporosis Risk in Male Fabry Patients: Bone Mineral Density in an Australian Cohort

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Abstract *Background*: Fabry disease (FD) is an inherited X-linked lysosomal storage disease with widespread clinical manifestations. Small prospective studies have shown increased osteopenia and osteoporosis in male FD patients. Limited information however exists about bone metabolism and osteoporosis risk factors within this group. We reviewed osteoporosis risk factors within our cohort.

Methods: A retrospective analysis of bone mineral density (BMD) results and fracture incidence in 44 patients (22 males and 22 females) was undertaken. Dual X-ray absorptiometry scans were performed at the lumbar spine, hip and femoral neck. The impact of risk factors including renal function, antiepileptic drug (AED), analgesia and vitamin D levels were assessed.

Results: Male FD patients had low *T* scores at all sites (spine -1.2 ± 1.06, hip -1.6 ± 0.9, femoral neck -2.23 ± 1.01). Female *T* scores showed more typical distribution (spine -0.07 ± 1.47, hip 0.02 ± 1.14, femoral neck -0.49 ± 1.31). A higher incidence of osteopenia and/or osteoporosis occurred in males versus females (spine 46.9% versus 31.8%, hip 75.5% versus 18.2% and femoral neck 86.4% versus 45.5%). Multiple regression analysis showed a 50.8% ($p < 0.001$) reduction in femoral neck BMD with AED usage, after adjustment for age, gender and renal function. Non-traumatic fractures occurred in 27.3% males over 205 patient-years versus 4.6% in females over 149 patient-years, $p = 0.095$.

Conclusions: Low bone density was highly prevalent in male patients with increased incidence of non-traumatic fractures. AED usage significantly reduces BMD. Treatment to prevent BMD deterioration will depend on determining the bone turnover status.

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Introduction

Fabry disease (FD) is an X-linked lysosomal storage disease resulting from deficiency of the lysosomal enzyme α-galactosidase A (OMIM 301500) (Desnick et al. 2003). Deficiency results in impaired glycosphingolipid metabolism with resultant intracellular accumulation of globotriaosylceramide (Gb3). This accumulation causes cellular dysfunction especially of vascular endothelium resulting in organ damage either directly or via inducing hypertrophy, fibrosis or inflammation (von Scheidt et al. 1991). Clinical manifestations are widespread, predominantly involving the heart, kidneys, cerebrovascular system, peripheral nerves and skin (Zarate and Hopkin 2008; Mehta et al. 2009). Prior to the availability of enzyme replacement therapy (ERT), male life expectancy was reduced to 40–50 years by cardiovascular and renal disease (Mehta et al. 2009). While the long-term impact of ERT on life expectancy is still being evaluated, therapeutic improvements expose FD patients to long-term disease sequelae including osteoporosis.

Osteoporosis is a common disease characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue. Postmenopausal women and elderly men are at highest risk, with disease spectrum ranging from asymptomatic bone loss to disabling hip or

vertebral fractures. Secondary causes of osteoporosis include Cushing's syndrome, hyperparathyroidism, diabetes, hyperthyroidism, cardiovascular disease, gastrointestinal tract disease and cancer (Hofbauer et al. 2010; Montalcini et al. 2013). Chronic disease may share a common but unidentified mechanism leading to osteoporosis either through inflammatory responses or malnutrition (Montalcini et al. 2013).

Increased incidences of osteopenia (up to 87%) and osteoporosis (up to 26%) have been reported in FD (Germain et al. 2005; Mersebach et al. 2007; Germain 2010a). Avascular necrosis of the hip has been attributed to FD (Ross and Kuwamura 1993; Germain 2010b). Normal bone development is dependent on heredity, exercise capacity, nutrition and hormone levels (Ferrari et al. 2012). Low BMD fractures in the general male population are associated with low body mass index (BMI) and reduced exercise (Ebeling 2008), increasing age, diabetes, hypogonadism, excessive alcohol intake, previous fractures and history of stroke or falls (Drake et al. 2012). Risk factors for osteopenia identifiable in FD include low BMI, reduced exercise, antiepileptic drug (AED) usage (Petty et al. 2007) and potentially poor gastrointestinal absorption of vitamin D and calcium. Additionally, FD patients are at risk of renal impairment, diastolic heart failure and peripheral neuropathy, all negatively correlated with bone density (Hofbauer et al. 2010).

Dual-energy X-ray absorptiometry (DEXA) is a validated, quick, safe and precise measurement of BMD (Johnell et al. 2005; Blake and Fogelman 2009). Low BMD, particularly at the hip, predicts osteoporotic fracture risk (Marshall et al. 1996; Stone et al. 2003; Johnell et al. 2005). *Z* scores, comparing BMD to age and gender-matched cohorts, are preferred in men age under 50 and premenopausal women (International Society of Clinical Densitometry (ISCD) 2013). The World Health Organization (WHO) and International Osteoporosis Foundation however defines osteoporosis as $\geq$2.5 standard deviations (SD) below average BMD value of young healthy women, or *T* score, (the NHANES (National Health and Nutrition Examination Survey) III values) at a single anatomical reference site (Kanis et al. 2011; Ferrari et al. 2012).

In this retrospective study, we assessed bone density and biochemistry of a heterogeneous cohort of FD patients.

Methods

Study Population

Patient records and the Fabry clinical research database from the Royal Melbourne Hospital from May 2000 to August 2013 were reviewed retrospectively. All patients that had undergone routine in-house bone density screening measurements were included. Follow-up bone density measurements taken, at least 4 years after initial assessment, were subsequently reviewed.

Informed consent was obtained for data analysis from all patients. Clinical information including BMI, renal function (radioisotope creatinine clearance and 24-h urine collection), smoking status, antiepileptic drug usage, fracture history and ERT usage were retrieved from the local data registry or patient contact.

Dual X-Ray Absorptiometry

The decision for bone density evaluation was based on clinical risk profile at the discretion of treating physician. All measurements were obtained on a single machine within the Royal Melbourne Hospital Bone Metabolism Unit. Standard measurements at the lumbar spine, hip and femoral neck were employed. Values were expressed as both *T* and *Z* scores using the WHO classification of BMD abnormalities [normal *T* score > -1 SD below the mean for young adults; osteopenia *T* score < -2.5 SD to < -1 SD; osteoporosis *T* score < -2.5; severe osteoporosis *T* score < -2.5 with spontaneous fracture (Kanis 1994)]. A *Z* score of ≤ -2.0 SD is defined as "below the expected range for age," and a *Z* score of > -2.0 SD is "within the expected range for age" (International Society of Clinical Densitometry (ISCD) 2013). *T* scores were used for further analysis, with osteoporosis grouped with or without fracture.

Biochemistry

Serum concentrations of calcium (normal 2.10–2.60 mmol/L), phosphate (normal 0.8–1.0 mmol/L), lactate dehydrogenase (normal 210–420 IU/L) and alkaline phosphatase (ALP) (normal 30–120 IU/L) were measured by standard biochemical methods. Serum levels of 25-hydroxy vitamin D (replete 55–108 nmol/L) were assayed using standard radioimmunoassay techniques.

Statistical Analysis

Descriptive statistics were presented as median with range or mean and standard deviation. Shapiro–Wilk test was used to assess all continuous variables for normality prior to data analysis. Pearson correlation was used to assess the correlations between continuous variables (e.g. vitamin D and BMI). The relationship between continuous variables and gender were assessed using either Student *T*-test or Wilcoxon Rank–Sum tests, and categorical variables were tested using Fisher's exact test. Multiple regression analysis was used to determine the impact of the use of AED on BMD measures while adjusted for age, gender, smoking

Table 1 Patient characteristics – baseline

	Male ($N = 22$)	Female ($N = 22$)
Age (years)	40.4 ± 9.1	45.6 ± 13.2
Renal replacement therapy (*n*)	7	0
Smoking (*n*)	7	6
AED (*n*)	13	2
Fracture prevalence	3	1
BMI (kg/m^2)	22.8 ± 3	28.5 ± 8.4, $p = 0.044$
^{51}Cr-EDTA GFR (ml/min/1.73 m^2)	87.3 ± 32.8 (13/22 Pt)	73.9 ± 13.2 (8/22 Pt)
CrCl (ml/min) – 24 h	131.6 ± 41.2 (15/22 Pt)	126.7 ± 34.6 (19/22 Pt)

AED anti-epileptic drug, *BMI* body mass index, *GFR* glomerular filtration rate, *CrCl* creatinine clearance

and renal replacement therapy (RRT). The analyses were performed using GraphPad Prism v6.0c for Mac OSX (1994–2013 GraphPad Software Inc.) and XLSTAT Version 2013.5.04 (1995–2013 Addinsoft). Results were considered significant when the p value was <0.05.

Results

Study Population

Of 78 adult patients receiving their primary Fabry care at our centre, 44 had at least one BMD measurement between May 2000 and August 2013. This consisted of 22 males (aged 40.4 ± 9.1 years) and 22 females (aged 45.6 ± 13.2 years). The median follow-up time was 11 years (range 1.8 to 13.6 years) for males and 7.6 years (range 1.2–12.7 years) females. At the time of 1st DEXA scan, 18 male and 8 female patients were receiving ERT. Patient characteristics are shown in Table 1.

Seven male patients reached chronic kidney disease stage 5 (CKD5) requiring haemodialysis, with five subsequently receiving a renal transplant, prior to the first BMD. This group was defined as receiving RRT. Thirteen male and two female patients required neuropathic pain relief with an AED, at the time of first BMD test. Carbamazepine (CBZ) was the initial AED selected, commencing at 200 mg daily, and titrated to effect with maximal dose of 800 mg. A single patient used phenytoin for neuropathic pain relief. Where analgesia with CBZ was ineffective, patients were changed to pregabalin at dose range 75–300 mg daily. Smoking incidence was similar in males and females. A significant difference in BMI existed between male and female groups (22.8 ± 3 versus 28.5 ± 8.4, $p = 0.044$). No correlation was evident between BMI and BMD. One male and one female patient with severe vitamin D deficiency were excluded from further analysis.

Dual X-Ray Absorptiometry

BMD was significantly lower in males than females at the spine, hip and femoral neck ($p = 0.011$, $p < 0.001$ and $p < 0.001$), respectively (see Table 2). Scatter plots of individual T scores, for males and females, at each site show large gender differences (see Fig. 1). The distribution of patients to normal, osteopenic and osteoporotic (with or without fracture) classification was according to the WHO T score guidelines (see Fig. 1). The incidence of osteopenia and/or osteoporosis was significantly different between males and females at the hip and femoral neck but not at the lumbar spine (male hip 75.5% versus female hip 18.2%, $p < 0.001$ and male femoral neck 86.4% versus female femoral neck 45.5%, $p = 0.004$). Z scores, at the femoral neck, were also significantly different, with 7/17 males less than 50 years old compared to 1/13 premenopausal women having osteoporosis, $p = 0.004$.

AED had a significant impact on BMD of male patients at all sites: spine ($p = 0.007$), hip ($p < 0.001$) and femoral neck ($p = 0.003$) (see Table 2). RRT in males was associated with lower bone density at the femoral neck ($p = 0.02$) and approached significance at the hip ($p = 0.056$) but not at lumbar spine ($p = 0.54$) (see Table 2). Multivariate analysis showed AED usage was the predominant factor associated with reduced BMD, with a 50.8% reduction in BMD at the femoral neck when adjusted for gender, age and RRT (see Table 3). The BMD results at the femoral neck had 68.1% correlation with spine and 92.6% with hip. Smoking had minimal effect on the bone mineral status. While only four male patients were not on ERT, the BMD scores at the femoral neck were comparable to those on ERT.

Table 2 BMD T scores total and male subgroup analysis

Patients	*N*	Spine	Hip	Femoral neck
Female	22	−0.07 ± 1.47	0.02 ± 1.14	−0.49 ± 1.31
Male	22	−1.2 ± 1.06[a]	−1.6 ± 0.9[a]	−2.23 ± 1.01[a]
Male subgroups				
AED use	13	−1.46 ± 0.92	−1.84 ± 0.86	−2.47 ± 1.03
Non-AED use	8	−0.39 ± 0.81[b]	−0.88 ± 0.34[b]	−1.54 ± 0.62[b]
RRT	7	−1.30 ± 1.24	−2.02 ± 0.68	−2.86 ± 0.72
Non-RRT	14	−1.00 ± 0.90	−1.27 ± 0.84[c]	−1.90 ± 0.73[c]
Smokers	7	−0.80 ± 0.49	−1.55 ± 1.05	−2.07 ± 1.15
Non-smokers	14	−1.25 ± 1.17	−1.51 ± 0.78	−2.20 ± 0.96

RRT renal replacement therapy, *AED* antiepileptic drug use for neuropathic pain
[a] Male versus female – spine $p = 0.011$, hip $p < 0.001$ and femoral neck $p < 0.001$
[b] AED versus non-AED – spine $p = 0.007$, hip $p < 0.001$ and femoral neck $p = 0.003$
[c] RRT versus non-RRT – hip $p < 0.056$ and femoral neck $p = 0.02$

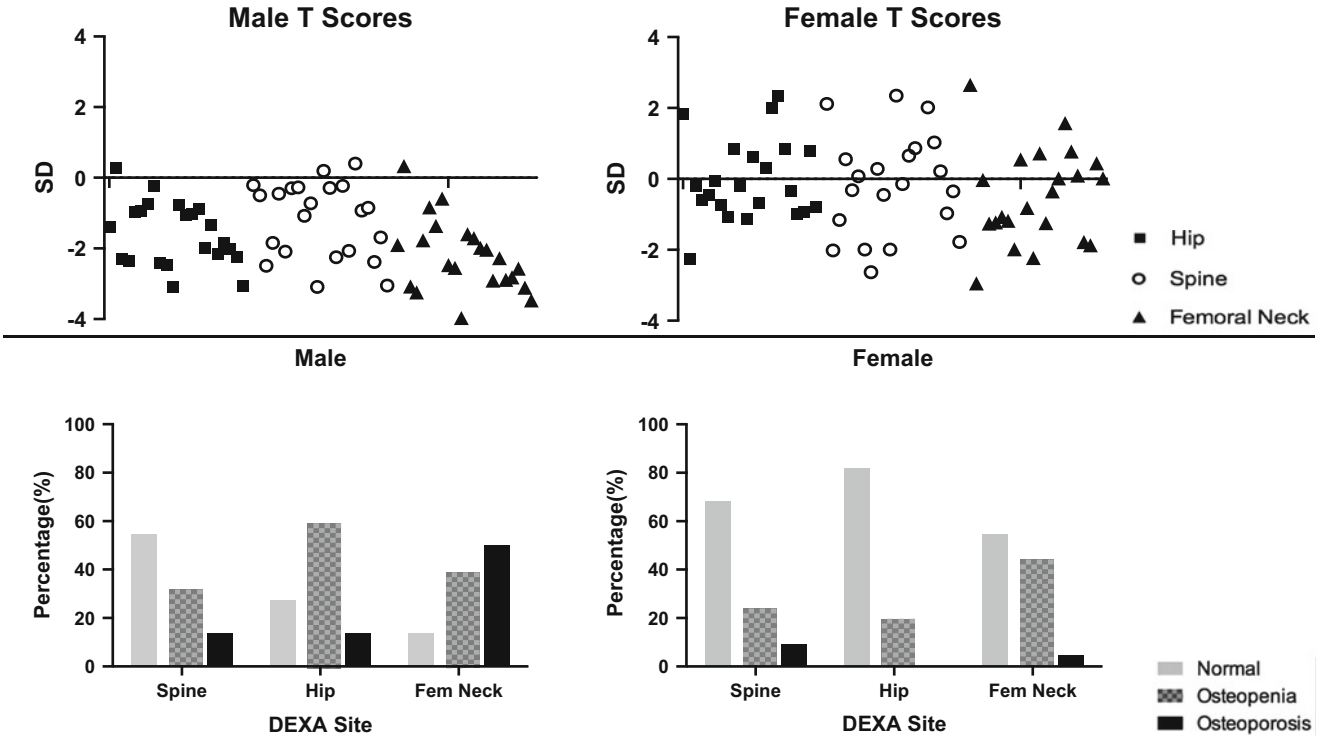

Fig. 1 Scatter plot of BMD *T* Scores and WHO BMD *T* score classification. First bone mineral density (BMD), measured by Dual X-ray absorptiometry, for each patient. Normal BMD > −1 SD below mean young adult, Osteopenia BMD <−1 to >−2.5 SD, Osteoporosis BMD <−2.5 SD (± fracture)

Biochemistry

Serum calcium (males 2.36 ± 0.10 versus females 2.38 ± 0.07 mmol/L, $p = 0.38$) and phosphate (males 1.01 ± 0.23 versus females 1.14 ± 0.12 mmol/L, $p = 0.03$) were both within normal ranges but lower in males than females at the time of first BMD. In contrast, serum alkaline phosphatase (males 92.95 ± 23.88 versus females 75.90 ± 28.73 IU/L, $p = 0.042$) and LDH (males 466.9 ± 156.9 versus females 444.3 ± 111.3 IU/L, $p = 0.61$) were higher in males than females. LDH was above the normal range but not significantly different

Table 3 Femoral neck multivariate analysis

Risk factor	Coefficient	95%CI	*p* value
AED	−1.508	−2.28 to −0.73	<0.001
Male	−0.82	−1.59 to −0.06	0.035
RRT	−0.55	−1.47 to 0.37	0.234
Age	−0.03	−0.06 to −0.001	0.041

RRT renal replacement therapy, *AED* antiepileptic drug use for neuropathic pain
Chronic AED usage reduces femoral neck bone mineral density by 50.8% after adjusting for age, gender and renal function

between males and females. Vitamin D levels were not available for all patients at baseline. A comparison of absolute nadir of vitamin D obtained for all patients during the study review showed the male having lower levels (males 40.4 ± 17.1 versus females 55.6 ± 28.6 nmol/L, $p = 0.051$). Furthermore, 15/19 males versus 11/21 females had vitamin D ≤55 nmol/L at some time point during the review period.

Patient Outcomes

Non-traumatic fractures were recorded as first incident fracture only. At baseline, three males had experienced non-traumatic fractures and only a single female. By the end of the follow-up period, a total of six males (27.3%) and a single female (4.6%) had experienced non-traumatic fractures. The total follow-up time was 205 patient-years for males versus 149 patient-years for females. Median age at time of fracture for men was 44.5 years (range 35–58 years) with four fractures occurring before 40 years of age. Of the seven patients with non-traumatic fractures, all were on AED and three were on RRT at the time of fracture. Neither gender difference nor presence of CKD5 altered the incidence of non-traumatic fractures ($p = 0.095$ and $p = 0.17$, respectively, Fisher's exact).

Follow-up BMD measurements were available in 12 patients (eight males and four females), all on ERT. The scans were performed at a median of 4.3 years (range 4–10 years) after initial scan. Repeat BMD showed no statistical change at the spine, hip or femoral neck; however, results were variable.

Discussion

This study revealed a very high prevalence of osteopenia and osteoporosis in the Fabry male population, in concordance with previous studies. We observed a higher prevalence of osteopenia and osteoporosis in males at the femoral neck (86% and 50%, respectively) than previously reported (Mersebach et al. 2007; Germain et al. 2005; Germain 2010a, b). In the seminal paper by Germain et al. (2005), examining BMD in 23 male Fabry patients, all site incidences of osteopenia and osteoporosis of 87% and 39%, respectively, were detected. However at the femoral neck alone, this was reduced to osteopenia 43.5% and osteoporosis 8.7%, respectively. Mersebach et al. (2007) compared 21 men and 32 women with FD and noted a significant difference in BMD between male patients and premenopausal women but no difference in males and postmenopausal women. In our study, however, the male FD cohort had much lower BMD scores than females at all sites, independent of menopausal status. Lower BMD, in males in our cohort, was also associated with increased fracture incidence independent of age and renal function.

A multivariate analysis showed a 50.8% ($p < 0.001$) reduction in femoral neck BMD with long-term usage of AED, after adjustment for age, gender and renal function. While low BMD appears attributable to FD, either directly or indirectly, AED use and to a lesser extent RRT have a significant impact. The requirement for AED and RRT are both consequences of disease severity. AEDs are usually initiated in childhood through to adolescence in males for analgesia secondary to Fabry-related neuropathic pain. This time period coincides with peak bone formation. Neuropathic pain severity may ease after young adulthood with reduction in AED usage. Additionally, ERT in Australia is not commenced until late adolescence, and this has been shown to reduce AED requirement. Whether the cause of lower BMD in male FD patients is due to impaired osteoclast and/or osteoblast function, poor nutrition status including vitamin D status, sex hormone level alteration or reduced exercise tolerance will need further elucidation.

Many FD patients require low dose AED, predominantly carbamazepine (CBZ), for neuropathic pain relief. AED use has been suggested to reduce absorption and utilization of vitamin D, alter parathyroid hormone (PTH) and calcitonin levels and reduce bioavailable serum oestrogens (Pack et al. 2011; Verrotti et al. 2010). Studies looking at the impact of CBZ on BMD and bone turnover markers are conflicting with some showing increased turnover (Verrotti et al. 2010), while others show no changes in BMD (Pack et al. 2011).

CBZ as a cytochrome p450 enzyme inducer has been suggested to accelerate vitamin D metabolism and thus reduce calcium absorption from the gut. More recent reviews however show inconsistent changes to vitamin D, calcium levels and PTH (Nakken and Taubøll 2010) in patients taking AEDs. Importantly, most reviews detailing AED use involve medication levels greater than those required for neuropathic pain relief. Cumulative drug load of AED has been reported as the dominant factor in fracture occurrence in epilepsy community (Petty et al. 2007). Additionally, neuropathic pain limits exercise tolerance and sunlight exposure, which may contribute to lower bone density and vitamin D deficiency in our cohort.

In the general male population, the predominant risks for osteoporosis are hereditary, sex steroid levels and chronic disease states (Kanis et al. 2011). Multiple secondary risk factors exist in men including excessive alcohol use, low calcium or vitamin D intake, smoking, low BMI, reduced exercise, AED use, liver or kidney disease (Ebeling 2008; Drake et al. 2012). The relationship between fracture risk and vitamin D level, as currently measured, remains inconclusive (Lips et al. 2010). Indeed, current routine monitoring of vitamin D for fracture prevention is unreliable, and the utility of routine vitamin D assay is disputed (Isenor and Ensom 2010). In our study, we found no association with vitamin D and BMD scores, although vitamin D levels in males were consistently lower than in females.

Limited information exists on hormonal changes in FD patients, but normal testosterone (Hauser et al. 2005; Mersebach et al. 2007), oestradiol and sex hormone-binding globulin (SHBG) (Hauser et al. 2005) levels have been reported. Bioavailable oestrogens, e.g. oestradiol, involved in bone metabolism, are formed by the aromatization of testosterone in peripheral fat. Oestrogen levels are also dependent on SHBG levels. Male FD patients frequently have low BMI, possibly related to poor gastrointestinal absorption or increased metabolic demand, which may impact on peripheral oestrogen formation. Secondly, most AEDs induce liver enzymes that consequently cause increases in SHBG and hence reduce available oestradiol. Interestingly in the small study by Hauser et al. (2005), follicle-stimulating hormone and prolactin levels were elevated, while testosterone and luteinizing hormone were normal, which may suggest subclinical deficiency of sex hormones in FD patients.

Determinants of bone strength are the degree of mineralization, cumulative micro-damage and collagen cross-link formation (Nishizawa et al. 2013). Bone metabolic markers, both resorptive and formative, are the best non-invasive way to measure bone turnover and infer bone strength and may be a useful guide for measuring response to clinical therapies (Nishizawa et al. 2013). We found no utility in measuring ALP, calcium, phosphate or LDH as biomarkers for bone health in this cohort of FD patients. Bone resorption however can be accurately determined by measurement of type 1 collagen cross-linked C-telopeptide and tartrate-resistant acid phosphatase, while bone formation can be determined by measurement of bone-specific alkaline phosphatase and procollagen type 1 N-terminal pro-peptide (Nishizawa et al. 2013). Increased bone resorption is routinely managed with use of antiresorptive agents like bisphosphonates, while reduced bone formation with is treated with agents like recombinant PTH. Male FD patients are a high-risk group that would benefit from measuring bone turnover markers with view to designing an appropriate treatment.

There are limitations inherent in a retrospective observational study. Firstly, the population was small and heterogeneous in age and renal function. Secondly, AED use was dependent on neuropathic pain control and was thus variable. Thirdly, vitamin D levels and PTH were not available for most patients at first BMD measurement. Fourthly, sex hormone levels including testosterone, bioavailable oestrogens and SHBG were not measured. However, previous studies have questioned the role of testosterone replacement in men with osteoporosis (Kanis et al. 2011). Fifthly, an appropriate control group with a comparable chronic disease burden is difficult to determine. Comparison to other chronic diseases may reveal the impact on BMD of factors like exercise capacity, diet and depression. Finally, an assessment of ataxia and cerebrovascular events were not included in this review but both of which may be increased in advanced Fabry disease. These in turn can increase fall frequency and fracture incidence.

In conclusion, BMD identified male FD patients at significantly higher risk of osteoporosis than both female FD patients and unaffected males. AEDs significantly reduce BMD, but whether bone metabolism can be improved by reducing AED exposure, improving gastrointestinal absorption of vitamin D or calcium, or even by earlier ERT initiation is yet to be determined. ERT alone appears inadequate to improve bone mineral density based on preliminary findings in this review. In Australia, there are few funded treatment options available for osteoporosis in men, but all affected patients were treated with vitamin D supplementation. Trials using bone turnover markers to determine whether increased bone resorption or reduced bone formation predominate in Fabry patients, in combination with sex hormone status, are in progress and may direct appropriate treatment for this high-risk group.

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Take-Home Message

Osteoporosis is highly prevalent in male Fabry patients, and antiepileptic medications, used for neuropathic analgesia, increase the risk of osteoporotic fractures.

Compliance with Ethics Guidelines

Details of Contributions of Individual Authors

Andrew Talbot was primarily responsible for planning the study and conducting the analysis of all bone mineral data. He also performed the primary data interpretation, including statistical analysis and original manuscript preparation.

Joanna R Ghali contributed to data collection and interpretation including manuscript editing.

Kathy Nicholls consented all patients and was the primary clinician responsible for bone mineral examination and pathology requests and follow-up. She also contributed to data interpretation and original manuscript preparation.

Conflict of Interest

Andrew Talbot has received research support, speaker honoraria and travel assistance from Shire Corporation and Sanofi Corporation, speaker honoraria and travel assistance from Dainippon Sumitomo Pharma Co. and research support from Amicus Therapeutics and Protalix Biotherapeutics.

Joanna R Ghali has received research support, speaker honoraria and travel assistance from Shire Corporation and Sanofi Corporation and research support from Amicus Therapeutics and Protalix Biotherapeutics.

Kathy Nicholls has received research support, speaker honoraria and travel assistance from Shire Corporation and Sanofi Corporation and research support from Amicus Therapeutics and Protalix Biotherapeutics.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for data analysis of results included in the study.

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