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Bone Density in Haemophilia: A Single Institutional Cross-sectional Study

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Abstract

Introduction—Haemophilia has been associated with low bone mineral density (BMD). However, prior clinical studies of this population have neither clearly elucidated risk factors for development of low BMD nor identified who may warrant screening for osteoporosis.

Aim—To evaluate the relationship between BMD and hemophilic arthropathy and other demographic and clinical variables.

Methods—We undertook a cross-section study of BMD in adult men with haemophilia. Measures of predictor variables were collected by radiographic studies, physical examination, patient questionnaires, and review of medical records.

Results—Among 88 enrolled subjects, the median age was 41 years (IQR: 20); median femoral neck BMD (n=87) was 0.90 g/cm² (IQR 0.24); and median radiographic joint score was 7.5 (IQR 18). Among subjects <50 years (n=62), after controlling for BMI, alcohol, HIV, and White race, BMD decreased as radiographic joint score increased (est.β=−0.006 mg/cm²; 95% CI −0.009, −0.003; partial R²=0.23). Among subjects ≥50 years (n=26), 38% had osteoporosis (T score −2.5) and there was no association between BMD and arthropathy.

Conclusion—Risk factors for low BMD in men with haemophilia < 50 years include hemophilic arthropathy, low or normal BMI, and HIV. Men with haemophilia over age 50 years should have routine screening for detection of osteoporosis.

Keywords

bone density; haemophilia; Pettersson score; arthropathy

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Introduction

As the life expectancy of those with haemophilia increases [1]: the risk of developing age-related disorders such as osteoporosis also increases. Risk factors for the development of osteoporosis include small body size, comorbid conditions, diet, sedentary lifestyle, tobacco use and high alcohol consumption [2]. Haemophilia has also been associated with reduced bone mineral density (BMD) [3]. Hemophilic arthropathy, caused by recurrent hemarthrosis, has been associated with low BMD on univariate analyses [4-6], but results of multivariable analyses are conflicting [7, 8]. The association between low BMD and arthropathy may be the result of reduced weight-bearing activity leading to accelerated loss of bone mass [9, 10]. Alternatively, hemarthrosis may lead to osteoclast activation and bone resorption [11]. Other causes of low BMD may include comorbid conditions such as HIV and hepatitis C [12-14], and the direct effect of low clotting factor levels [15].

When considering the population of men at large, most, but not all guidelines, recommend screening men over the age of 70 years regardless of risk factors and those 50-64 years if clinical risk factors are present [16-19]. Haemophilia has been listed as a relevant comorbid condition by one [20] out of four [16, 21, 22] guiding organizations; however, reports of BMD in patients with haemophilia have not provided information to allow clinicians to determine who should be screened for osteoporosis.

To determine if hemophilic arthropathy is independently associated with BMD and to better define the hemophilic population that may benefit from screening with dual energy x-ray absorptiometry (DEXA), we undertook a cross-sectional study of BMD in adults with haemophilia.

Methods

Participants

After approval by the Emory University Institutional Review Board, recruitment letters were sent to adult men over the age of 25 years with haemophilia A or B of any severity evaluated at the Emory/Childrens Healthcare of Atlanta Haemophilia Treatment Center during the past two years (n=163). These patients were again invited to participate during regularly scheduled clinic visits. Patients were excluded if they had a known history of osteoporosis or other metabolic bone disease at enrollment.

Variables

Patient demographics and personal characteristics collected included age, race, ethnicity, body mass index from measured height and weight (BMI, kg/m²), alcohol consumption (drinks/day), smoking (yes/no), and daily calcium consumption (mg/day) using a self-administered Short Calcium Questionnaire [23].

Clinical, radiographic, and self-reported measures of hemophilic arthropathy were recorded. The clinical joint score was determined by one of three physical therapists according to the recommendations of the Orthopedic Advisory Committee of the World Federation of Haemophilia (WFH) [24] and is the sum of the scores for six joints [ankles (0-12), knees (0-12), and elbows (0-10); sum 0-68]. Using the Pettersson scoring system, plain radiographs of bilateral ankles, knees, and elbows were scored by a single radiologist [25]. The radiographic joint score is the sum of the six individual joint scores (each 0-13; sum 0-78). Higher clinical and radiographic scores indicate more joint disease. Lastly, patients were asked about the number and location of target joints (target joint definition: 4 bleeds during the previous 6 months or 20 bleeds over a lifetime).

Additional clinical variables were collected using questionnaires and medical record review. Self-reported information included: prior bone fractures (location and associated trauma: spontaneous, low trauma or high trauma) [26], family history of hip fracture and osteoporosis, and history of glucocorticoid (> 3 months) or testosterone use. Information gathered from medical records included: type of haemophilia, severity of haemophilia [categorized by baseline plasma level of FVIII or FIX into severe (< 1%), moderate (1%-5%), and mild (>5%)], current or past history of FVIII/FIX inhibitory antibody (inhibitor), current use of prophylactic factor infusions (< 1 factor product infusion per week to prevent bleeding events), history of joint surgery, > 10% weight loss during the past 12 months, and comorbid conditions such as rheumatoid arthritis, nephrolithiasis, thyroid disease, chronic obstructive pulmonary disease, gastrointestinal diseases (celiac disease, Crohn's disease and ulcerative colitis), and HIV and hepatitis C diagnosis and treatment history. Subjects were considered to have chronic liver disease if they had viremia and/or evidence of fibrosis on past liver biopsy.

Physical activity and functional capacity were measured using the Framingham Physical Activity Index (PAI) [27], a performance test [Timed Up-and-Go (TUG) test] [28], and a self-assessment instrument [Haemophilia Activities List (HAL)] [29]. The PAI captures self-reported typical daily amount and intensity of leisure and work time physical activity. The validated TUG test measures the time it takes for a person to rise from a sitting position, walk 3 meters, and return and be seated. A time of > 14 seconds has been associated with a high fall risk [28, 30]. The HAL covers 7 domains: lying/sitting/kneeling/standing, functions of legs, functions of arms, use of transportation, self-care, household tasks, and leisure activities and sport. The summary score was used in this analysis.

Laboratory tests included Serum 25-hydroxy vitamin D (quantitative chemiluminescent assay) and total and free testosterone concentrations (liquid chromatography tandem mass spectrometry) [31].

BMD (g/cm^2) was measured by DEXA of the right and left femoral neck, total hip and spine using a Lunar Prodigy instrument (GE Medical Systems, Madison, WI). Among patients > 50 years, BMD was classified according to the World Health Organization (WHO) classification system. The number of standard deviations (T) below young normal controls categorized BMD as normal ($T \geq -1$), osteopenic (T between -2.5 to -1), or osteoporotic ($T < -2.5$) [32]. Among patients < 50 years, Z scores compared subject BMD to similarly aged persons [normal ($Z \geq -1$), low normal (Z between -2 and -1), low ($Z < -2$)] [17].

Fracture risk, 10 year probability of hip and major osteoporotic fracture, was calculated using the FRAX® WHO Fracture Risk Assessment Tool in those subjects > 50 years and older who did not have osteoporosis and in all subjects age 40-49 years [33].

Statistical Analysis

Descriptive statistics were calculated for all variables. For each age group (< 50 years and > 50 years), the relationship with each covariate and BMD (lower value of the right and left femoral neck) was evaluated using simple linear regression. Covariates, such as factor VIII, were log transformed as needed to linearize the relationship. Multiple linear regression was performed with femoral neck BMD as the outcome and arthropathy, represented by radiographic joint score, as the primary predictor. Although plain radiographs are limited in their assessment of early joint disease, this measurement was used since 1) adult participants were anticipated to have advanced arthropathy, 2) a single radiologist evaluated all films, and 3) radiographic scores are not dependent on subject recall. Final models were selected using stepwise forward selection; variables were kept in the model if they were significant

($p < 0.05$) or confounded the relationship between femoral neck BMD and radiographic joint score. Regression diagnostics were performed.

A radiographic joint score was not available for 20 subjects because one or more of the 6 component joints was not scored. Similarly, clinical joints scores were missing for 18 subjects. This was primarily due to joint replacement or other major surgical intervention on the joint, precluding accurate scoring. Four other variables had 1 to 3 missing values (vitamin D, $n=2$; calcium intake, $n=3$; testosterone, $n=3$; BMD, $n=1$). Missing values were multiply imputed so that the whole sample could be analyzed using methods described by McKnight et al [34]. Since joint replacement or other surgical intervention is associated with poor joint health, we performed a sensitivity analysis to evaluate whether conclusions were biased by using imputed radiographic joint scores, by giving all missing joints the highest score possible and repeating the multiple regression analysis.

To evaluate a simple predictive model of low BMD among haemophilia patients younger than 50 years, we examined the receiver operative characteristic (ROC) curve of the following model. The outcome, low BMD, was defined by there being at least one of three bones (right and left femoral neck and the spine) with a Z score < -2 . There were 4 subjects missing one of the three scores and these subjects were assigned the worst BMD categorization from their observed values, understanding that there might be some classification error. A sensitivity analysis assigned subjects with missing information the next lower BMD category. Three dichotomous predictors were included: reporting > 1 joint with either 20 lifetime bleeds or 4 recent bleeds, HIV status, $\text{BMI} < 25 \text{ kg/m}^2$. One subject chose not to undergo a DEXA and was not included in this analysis.

The target sample size was 120, based on $\alpha=0.05$ and having 85% power to detect 5% variation in BMD explained by arthropathy (as measured by radiographic joint score), while other covariates explained 30% of BMD variation in a multivariate linear model. All analyses were performed with SAS v9.3 software (SAS Institute Inc, Cary, NC, USA.) and α was set at 0.05.

Results

Between April 2010 until September 2011, 88 subjects were enrolled (Figure 1). The median age was 41 years and two thirds were White race (Table 1). Heavy alcohol intake (> 2 drinks/day) was uncommon (10%, $n=9$). One third had serum 25-hydroxy vitamin D levels $< 20 \text{ ng/ml}$. TUG times were ≥ 14 seconds in 8% of subjects. The majority (81%) had haemophilia A, 43% had severe disease, and few had current factor VIII/IX inhibitor ($n=5$, 6%) or were currently on prophylaxis medication ($n=20$, 23%). HIV and liver disease were common ($n_{\text{HIV}}=26$, 30%; $n_{\text{liver}}=49$, 56%). Hepatitis C was the cause of liver disease in all but one subject who had hepatitis B and suspected hepatitis D. Among the 26 HIV infected subjects, 16 were currently or previously on protease inhibitors and 10 had not ever received a protease inhibitor. The median CD4 count of those who were HIV positive was 556 (Q1, Q3: 228, 770). A history of low impact fractures was present in 24% ($n=21$) of subjects. Low total testosterone levels for those younger than 70 years of age ($< 250 \text{ ng/dl}$) were common, although only 11% ($n=9$) had low free testosterone levels ($< 70 \text{ ng/dl}$). One quarter of subjects reported at least 4 bleeds in > 1 joint in the past 6 months and 59% reported > 20 bleeds in > 1 joint over a lifetime. For subjects with all 6 joints evaluable, the median radiographic joint score was 7.5 ($n=68$, Q1, Q3: 0-18) and the median clinical joint score was 12 ($n=70$, Q1, Q3: 7, 22). The median BMD of the femoral neck was 0.90 g/cm^2 ($n=87$, Q1, Q3: 0.78, 1.02). Among those < 50 years, 21% had low femoral neck BMD; in this age group, lower BMD scores became more frequent with increasing haemophilia severity

(Figure 2a). Among subjects ≥ 50 years, 38% had osteoporosis with this distribution changing little by haemophilia severity (Figure 2b).

Given age-specific interpretations of DEXA, we examined risk factors for low BMD separately in the two age groups (Table 2). In bivariate models among those < 50 years, there were statistically significant ($p < 0.05$) increases in BMD with increases in BMI, physical capability/activity as measured by PAI and HAL, and baseline factor VIII (log transformed); BMD decreased if the patient was currently receiving prophylactic factor infusions, HIV infected, had liver disease, > 3 month exposure to glucocorticoids, or worsening joint disease as measured by three methods. Radiographic joint score explained 24% of the variability in BMD (est. $\beta = -0.007$; 95%CI $-0.010, -0.003$), clinical joint score explained 10% (est. $\beta = -0.006$; 95%CI $-0.010, -0.001$), and total number of target joints, 19% (est. $\beta = -0.033$; 95%CI $-0.050, -0.015$). Among those ≥ 50 years and older, none of the demographic or health variables were found to be statistically associated with femoral neck BMD.

In multivariate modeling to control for covariates in subjects < 50 years, radiographic joint score independently explained 23% of the variability in BMD, with BMD decreasing 0.006 mg/cm² per unit increase in the joint score [95% CI $(-0.009, -0.003)$] (Table 3). Also associated with decreasing BMD were decreasing BMI ($R^2 = 0.12$), decreasing alcoholic drinks/day ($R^2 = 0.09$), and HIV infection ($R^2 = 0.08$). Race was kept in the model as it confounded the association between the radiographic joint score and BMD. Altogether, these 5 variables explained 42% of BMD variability. Once these variables were in the model, no others were independently associated with BMD. The sensitivity analysis where missing joint scores were assigned the highest possible score produced similar estimates (not shown). When the radiographic joint score was replaced by the clinical joint score in the final model, clinical joint score was also negatively associated with BMD ($p = 0.041$), though less of the variation in BMD was explained by joint disease using the clinical measurement (average adjusted $R^2 = 0.30$, partial $R^2 = 0.08$). The FRAX score was calculated for 40-49 year olds ($n = 17$) and those ≥ 50 years without osteoporosis ($n = 10$). Four subjects (3/17 40-49 years and 1/10 ≥ 50 years) had a 10 year probability of hip fracture $> 3\%$. None had a 10 year risk of major osteoporotic fracture $> 20\%$.

ROC

A model containing 3 easily ascertained dichotomous predictors [the presence of > 1 target joint (≥ 4 recent bleeds or ≥ 20 lifetime bleeds), BMI < 25 kg/m², and HIV] was used to determine ROC curves for the prediction of low BMD in subjects < 50 years. Combinations of two predictors were evaluated: HIV and BMI < 25 kg/m², > 1 clinical target joint and BMI < 25 kg/m², and the presence of > 1 clinical target joint and HIV; and found to provide an area under the curve (AUC) of 0.7428, 0.7845, and 0.7236 respectively (Figure 3). Use of any one individual predictor provided an AUC of 0.7035. The addition of HIV to the BMI and target joint model did not increase the AUC (AUC_{full.model} = 0.7898 vs. AUC_{BMI,targetjoint} = 0.7845). To assess the impact of misclassifying BMD due to relying on partial information ($n = 4$), a sensitivity analysis assigned subjects with missing information (DEXA performed on one-side, right or left, only) the next lower BMD category. This reclassification did not yield different results (not shown).

Discussion

There are two major findings of this study. First, in men ≥ 50 years with haemophilia, osteoporosis and osteopenia are common. Second, decreasing BMD in men < 50 years with haemophilia is independently associated with increasing hemophilic arthropathy.

The National Osteoporosis Foundation (NOF) recommends BMD screening of all men greater than 70 years and men 50-69 years when there is concern based on their risk factor profile [35]. Although NOF lists haemophilia as a risk factor, its recommendations do not indicate that haemophilia alone constitutes a risk profile warranting BMD screening. Other groups' have not addressed haemophilia as an osteoporosis risk factor [16-18]. Prior studies of BMD in haemophilia populations have not specifically evaluated a cohort of men over 50 years nor applied the WHO criteria of T score -2.5 for the diagnosis of osteoporosis. In a study by Anagnostis et al, 12/38 (32%) of patients had a T score < -1.0 compared with 21/26 (81%) in our cohort; however Anagnostis et al did not differentiate between osteoporosis and osteopenia [7]. Despite these differences, both studies demonstrate prevalence estimates of abnormal BMD that are substantially greater than general population estimates of 3% in men 50-59 years and 60-69 years, 4% in men 70-79 years and 10% in those ≥ 80 years [36]. Our findings suggest that haemophilia alone is of sufficient risk to warrant DEXA screening for the detection of osteoporosis in men ≥ 50 years of age.

In persons < 50 years, joint disease was significantly associated with decreased BMD, accounting for 23% of the variation seen in BMD. For each one point increase in the radiographic joint score, there was a decrease in BMD of 0.006 g/cm^2 . Additionally, for each 1 kg/cm^2 increase in BMI, there was an increase in the BMD of 0.009 g/cm^2 . The association of BMD with arthropathy has been seen in other studies [4-6, 8], but not all [7]. One of the three studies that demonstrated a univariate association between joint disease and BMD was performed in the United States. This study enrolled 30 subjects 18 to 66 years with moderate (13%) or severe (87%) haemophilia and used range of motion as a measure of joint disease. Our study more robustly supports the associations by only including subjects over the age of 25 years (therefore more likely to be at peak bone mass), including a range of severities, and evaluating multiple measures of joint disease. Anagnostis et al performed multivariable analysis to evaluate the independent effect of joint disease on BMD in Greek haemophilia patients of any severity (62% mild, 20% moderate and 18% severe) and did not find an association between hemophilic arthropathy and low BMD [7]. However their multivariable analysis included two measure of joint disease (number of affected joints and severity of arthropathy as measured by the Petersson score) which may have resulted in collinearity and loss of effect.

Increased BMI and HIV have also been previously reported to be associated with low BMD in studies involving populations without haemophilia [12, 37]. In those with HIV infection, low BMD is thought to be the result of the viral infection and the protease inhibitors commonly used for treatment. Our study was not powered to differentiate the effect of HIV infection and protease inhibitors on BMD. Studies among the general population have shown a benefit to BMD of moderate alcohol use (up to two drinks per day in men)[38, 39]. In contrast to moderate alcohol use, heavy alcohol use (> 2 drinks per day) is associated with reduced BMD (reference). Since heavy alcohol use was rare in this cohort ($< 10\%$), the positive association between BMD and alcohol seen in this study likely reflects the beneficial effects of moderate alcohol consumption [2].

This study has several limitations. The sample size was too small either to assess the impact of infrequent clinical characteristics, such as inhibitors, or to validate a predictive model to identify patients 40 - 49 years who would benefit from DEXA screening. Similarly, given its cross-sectional design, this study was not able to capture the impact of BMD on the particularly relevant outcome of fracture incidence. Lastly, although a racially diverse sample, it represents one institution which may limit its generalizability.

This study also has several strengths. First, it was not limited to those with severe disease, thus we were able to demonstrate that those with mild and moderate disease, in addition to

those with severe disease, are at risk when they are 50 years. Second, joint disease was evaluated through radiographs, clinical examination, and a self-report of joint bleeding, with consistent results. Third, our analysis was able to assess and adjust for additional relevant clinical variables. Finally, our study population was racially diverse, with one-third of participants being of Black race.

Conclusion

As men with haemophilia are living longer lives, it is important to understand how haemophilia affects age-related disorders such as osteoporosis. This study adds to the literature and for the first time demonstrates that men with haemophilia of any severity above the age of 50 years should be screened using DEXA for the presence of osteoporosis. In men with haemophilia 40-49 years age, further study is needed to validate clinical characteristics that may guide the use of screening DEXA. Relevant variables to consider in a larger study are the presence of more than one target joint, BMI < 25 kg/m² and/or HIV infection. Until such studies are done, men with haemophilia aged 40-49 years should be clinically assessed and screening DEXA considered if combinations of these variables are present. Additionally, given the high prevalence of low BMD, all men with haemophilia regardless of age should be counseled regarding health habits that promote skeletal health including adequate calcium and vitamin D intake, moderate weight-bearing physical activity, and avoidance of tobacco and high alcohol consumption.

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C.K., A.A., D.A. and L.E. designed the study. A.A., W.C., M.R., S.S., L.S., and C.K. completed the data collection. C.K. and L.E. performed the analysis and wrote the manuscript. A.A., D.A., W.R., M.R., S.S., L.S. and L.E. critically reviewed and edited the manuscript.

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Figure 1.
Flow diagram of subject recruitment and enrollment

Figure 2. The distribution of BMD status among patients <50 years (a) and ≥ 50 years (b) by disease severity. BMD categorization is based on Z scores (a) or T scores (b) of the spine and left and right femoral neck.

Figure 3.

ROC curves for predicting low BMD ($Z < -2$) among patients < 50 years with the full model containing 'BMI <25 ', "reporting more than 1 joint with either at least 20 lifetime bleeds or at least 4 recent bleeds", and HIV+ status. AUC for the individual predictors were 0.7035 for BMI, 0.6595 for bleed, and 0.6338 for HIV status

Table 1

Demographic and Health-Related Characteristics of Haemophilia Patients (n=88)

Variable	n (%) or Median (Q1, Q3)
Demographics	
Age, years	41 (32, 52)
Race	
White	58 (66%)
Black	27 (31%)
Other	3 (3%)
Hispanic ethnicity	5 (6%)
BMI, kg/m ²	26 (23, 29)
Diet and personal habits	
Alcohol >2 drinks/ day	9 (10%)
Current smoker	18 (20%)
Vitamin D, ng/ml (n=86)	26 (18, 34)
Vitamin D < 20 ng/ml (n=86)	29 (33%)
Total Calcium, mg/day (n=85)	1266 (886, 1721)
Physical Capability/ Activity	
TUG, seconds	9.3 (8.0, 10.7)
HAL Sum	77 (51, 94)
Framingham PA index	31 (28, 36)
Haemophilia Measures	
Haemophilia A	71 (81%)
Disease Severity	
mild	26 (30%)
moderate	24 (27%)
severe	38 (43%)
Inhibitor, current	5 (6%)
Inhibitor, past	5 (6%)
Prophylaxis, current	20 (23%)
Prophylaxis, past	13 (15%)
Other health history	
HIV positive	26 (30%)
CD4 count	556 (228,77)
Liver disease	49 (56%)
HCV viral load positive	39 (44%)
HCV antibody positive	65 (74%)
Spontaneous fracture	5 (6%)
Low trauma fracture	21 (24%)
Family history of osteoporosis	10 (11%)
Weight loss (10% in past yr)	16 (18%)
>3 month glucocorticoids	11 (13%)

Variable	n (%) or Median (Q1, Q3)
Nephrolithiasis	14 (16%)
Testosterone, Total (ng/dl)	
70 years (n=3)	97 (84, 244)
<70 years (n=83)	313 (197,411)
Testosterone, Free (pg/ml)	
70 years (n=3)	42 (38, 94)
<70 years (n=83)	127 (90, 162)
Joint Disease	
Target joints	
>1 (4 bleeds in past 6mo)	22 (25%)
>1 (20 bleeds in lifetime)	52 (59%)
Total # of target joints ¹	2 (0, 4)
Radiographic joint score (n=68)	7.5 (0, 18)
Clinical joint score (n=70)	12 (7, 22)
Primary outcome (n=87)	
Bone mass density ² , g/cm ²	0.90 (0.78, 1.02)

¹Total number of target joints with either 4 bleeds in the past 6 months or 20 bleeds in lifetime

²Worst of right and left femoral neck measurements

Table 2Bivariate Association of Femoral Neck BMD with Demographic and Health Variables, by Age Group¹

Variable	50 years				< 50 years			
	Estimate	95% Confidence Limits	P Value	R ²	Estimate	95% Confidence Limits	P Value	R ²
Demographics								
Age	-0.0005	(-0.006, 0.005)	0.86	<0.01	-0.005	(-0.011, 0.002)	0.14	0.04
White race (ref: all other)	0.069	(-0.034, 0.172)	0.18	0.07	0.016	(-0.083, 0.116)	0.74	0.00
BMI	0.007	(-0.001, 0.014)	0.08	0.12	0.013	(0.005, 0.020)	0.002	0.16
Diet and personal habits								
Alcohol drinks/ day	0.011	(-0.035, 0.058)	0.62	0.01	0.047	(-0.014, 0.108)	0.13	0.04
Current smoker (ref: not smoker)	-0.036	(-0.171, 0.100)	0.59	0.01	0.077	(-0.036, 0.191)	0.18	0.03
Vitamin D level	-0.002	(-0.006, 0.002)	0.38	0.03	0.000	(-0.003, 0.003)	0.92	<0.01
Total Calcium (per g)	0.035	(-0.057, 0.126)	0.44	0.03	-0.030	(-0.100, 0.043)	0.41	<0.01
Physical Capability/Activity								
TUG	0.003	(-0.010, 0.017)	0.63	0.01	-0.012	(-0.037, 0.013)	0.34	0.02
HAL Sum	-0.001	(-0.003, 0.001)	0.43	0.03	0.003	(0.001, 0.005)	0.001	0.17
PAI (per 10pts)	0.003	(-0.009, 0.015)	0.62	0.01	0.070	(0.004, 0.130)	0.04	0.07
Haemophilia Measures								
Haemophilia A (ref: B)	-0.045	(-0.169, 0.078)	0.45	0.02	0.041	(-0.081, 0.163)	0.50	0.01
Baseline FVIII (log)	-0.002	(-0.033, 0.030)	0.92	<0.01	0.053	(0.025, 0.081)	<0.001	0.19
Prophylaxis, current (ref: none)	0.006	(-0.131, 0.142)	0.93	<0.01	-0.110	(-0.214, -0.003)	0.04	0.07
Prophylaxis, past (ref: none)	0.050	(-0.134, 0.233)	0.58	0.01	-0.043	(-0.166, 0.079)	0.48	<0.01
Other health history								
HIV+ (ref: HIV-)	-0.076	(-0.188, 0.037)	0.18	0.08	-0.142	(-0.236, -0.048)	0.004	0.13
Liver Disease (ref: none)	0.036	(-0.067, 0.138)	0.48	0.02	-0.151	(-0.237, -0.065)	<0.001	0.17
Testosterone, Total	-0.012	(-0.093, 0.068)	0.76	<0.01	-0.061	(-0.157, 0.034)	0.21	0.03
Testosterone, Free	-0.021	(-0.101, 0.059)	0.60	0.01	0.025	(-0.080, 0.129)	0.64	<0.01
Spontaneous fracture (ref: none)	--	--	--	--	-0.067	(-0.257, 0.123)	0.48	<0.01
Fam hx of osteoporosis (ref: none)	--	--	--	--	-0.090	(-0.236, 0.056)	0.22	0.02
>3 month glucocorticoids	--	--	--	--	-0.180	(-0.304, -0.055)	0.006	0.12
Nephrolithiasis	--	--	--	--	0.040	(-0.163, 0.082)	0.51	<0.01
Weight loss	--	--	--	--	0.067	(-0.050, 0.184)	0.26	0.02
Joint Disease								
Total# of target joints	0.005	(-0.014, 0.024)	0.57	0.01	-0.033	(-0.050, -0.015)	<0.001	0.19
Radiographic joint score	0.0003	(-0.004, 0.004)	0.87	<0.01	-0.007	(-0.010, -0.003)	<0.001	0.24
Clinical joint score	0.0006	(-0.006, 0.004)	0.79	<0.01	-0.006	(-0.010, -0.001)	0.02	0.10

¹ Results from simple linear regression. In the older group, some models could not be run because of too few subjects with the predictor characteristic. For the 50 years models, imputation methods were used with Vitamin D, radiographic joint score, and clinical joint score due to missing data. All models in the <50 year group used imputation methods. Estimates are based on 100 imputations.

Table 3Association of BMD and Radiographic Joint Score in Under 50 Age Group.¹

Parameter	Estimate	95% Confidence Limits	P Value	Partial R-square ²
Intercept	0.711	(0.500, 0.922)		
Radiographic joint score	−0.006	(−0.009, −0.003)	<0.001	0.23
BMI	0.009	(0.002, 0.015)	0.01	0.12
Alcohol drinks/ day	0.056	(0.008, 0.104)	0.02	0.09
HIV+ (ref: HIV−)	−0.088	(−0.168, −0.006)	0.04	0.08
White race (ref: all other)³	0.074	(−0.009, 0.156)	0.08	0.06

¹ Multiple linear regression; Estimates are based on 100 imputations.² Average adjusted R²=0.42.³ NS, kept as a confounder of the relationship between radiographic joint score and BMD.