Received: 23 July 2021 | Revised: 8 December 2021 | Accepted: 20 December 2021

DOI: 10.1111/hae.14487

Haemophilia WILEY

ORIGINAL ARTICLE

Bone mineral density in haemophilia – a multicentre study evaluating the impact of different replacement regimens

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Funding information
Skane University Hospital Research Fund, Sweden; Research and Development Council of Region Skåne (ALF), Sweden; H Järnhardt foundation, Sweden; Swedish Research Council, Sweden

Abstract

Aim: The aim of this study was to investigate if prophylactic treatment in severe haemophilia impact on bone mineral densisty (BMD) in adults with haemophilia A/B.

Methods: Subjects with haemophilia (n = 120) underwent bone-density measurement and clinical data was collected. BMD in subjects with severe haemophilia on high-dose prophylaxis (n = 41) was compared to BMD in subjects with mild haemophilia (n = 33) and to severe haemophilia treated with intermediate-dose prophylaxis (n = 32) or on-demand replacement therapy (n = 14).

Results: Subjects with severe haemophilia on high-dose prophylaxis showed BMD at total hip comparable to subjects with mild haemophilia (median BMD 955.8 and 977.4 mg/cm^2 (P = .17), respectively). No difference in BMD was found related to type of prophylactic regimen (median BMD 955.8 and 942.4 mg/cm^2, in high-dose and intermediate dose groups, respectively; P = .70). Subjects with severe disease treated on-demand had significantly lower BMD compared to subjects on a high-dose prophylactic regimen (median BMD 771.8 and 955.8 mg/cm^2 (P = .001), respectively). BMD decreased significantly with age, regardless of severity of haemophilia disease. In a multivariate analysis, adjusted for disease status and age, type of prophylactic regimen was not significantly associated with osteoporosis development.

Conclusion: We show that BMD differs in persons with severe haemophilia on propylaxis as compared to those treated on-demand, but that type of prophylactic regimen does not reflect on BMD. The difference between treatment groups was mainly explained by an age difference between groups. However, patients on prophylaxis displayed a high degree of normal BMD not far from mild haemophilia at comparative age.

KEYWORDS
bone mineral density, haemophilia A, haemophilia B, on-demand treatment, osteoporosis, replacement therapy

1 | INTRODUCTION

In haemophilia A and B, treatment with coagulation factor VIII (FVIII) or IX (FIX) replacement reduces bleeding frequency, and prevents deterioration of joint status and maintains quality of life.[1] Preemptive treatment, so called prophylaxis, was introduced, in Sweden and the Netherlands in the 1950s and 1960s, respectively. In Norway, on-demand treatment was standard of care until the beginning of the 1990s when prophylaxis was introduced. Today, in Sweden and Norway, high-dose prophylaxis is the standard regimen with doses of 25–40 IU/kg FVIII given at least three times weekly, starting before the age of 2 years (prior to first joint bleed). In the Netherlands, the regimen is based on intermediate dosing of 15–25 IU/kg three times weekly introduced after the first joint bleed.[2] FIX dosing is based on longer intervals due to the longer half-life of FIX compared to FVIII. Both dosing strategies improves joint health compared to on-demand treatment,[1,3–6] however, better joint outcomes is found in patients receiving high-dose versus intermediate-dose prophylaxis, whereas quality of life is indistinguishable after decades of follow-up.[2]

Thanks to prophylaxis, today's persons with haemophilia (PWH) lead a near to normal life allowing for normal physical activity level. Several studies have reported reduced bone mineral density (BMD) in PWH.[7–11] Low BMD was associated with severity of joint disease, low activity score, presence of HIV and/or hepatitis C (HCV) infection and low body-weight.[11] Others suggested that long-term prophylaxis in subjects with severe haemophilia helps to preserve normal bone mineralization.[12]

We hypothesized that longterm prophylaxis may allow PWH to lead a normal life in terms of physical activity already from early childhood and that this would result in a BMD close to normal.

The aim of this study was to investigate if prophylactic treatment in severe haemophilia started at an early age has an impact on BMD in adults with haemophilia A and B. We compared BMD in subjects with severe haemophilia on high-dose prophylaxis to BMD in subjects with mild haemophilia, and also to BMD in subjects with severe haemophilia treated on-demand. Furthermore, to examine whether differencies in dosing strategies may impact BMD differently, BMD in subjects on high-dose versus intermediate-dose prophylaxis were compared.

2 | MATERIALS AND METHODS

2.1 | Study cohort

In total, 120 subjects were included from the three participating centres. These patients represented a convenience sample: eligible patients (see below) with a planned hospital visit were selected from the hospital files and asked to participate. All subjects were at least 18 years old and subjects born before 1949 were excluded due to long initial time without prophylactic treatment. Exclusion criterias were ongoing or recent corticosteroids treatment, metastatic bone disease, metabolic bone disease, previous orthopedic and/or rheumatologic-related surgery with joint or fracture devises as metal interferes with DXA measurement and a history of inhibitors to FVIII/FIX.

Data on diagnosis, age, body mass index (BMI), tobacco use, HCV and HIV status and concomitant diseases of significance for bone health was collected from medical files. Background characteristics at the time of investigation are presented in Table 1. The majority of the subjects were diagnosed with haemophilia A (HA; n = 100. HB = 20) with equal distribution in the study groups .

In order to investigate the impact of different prophylactic regimens, started at an early age, on bone mineralization the cohort (n = 120) was divided into four study groups: Severe haemophilia on regular high-dose prophylaxis at least during the years 1989–1999 (n = 41) from Sweden (High-dose); B) Mild haemophilia from Sweden (n = 33) (Mild); C) Severe haemophilia born between 1939 and 1981 and treated on-demand (n = 14) from Norway (On-demand); D) Severe haemophilia on regular intermediate-dose prophylaxis (n = 32) from the Netherlands (Intermediate-dose). The cohort with severe hemophilia on regular prophylaxis previously presented in Blood, 2013[2] were all eligible to participate. Study participants treated on-demand represented a convenience sample. Mild subjects were enrolled in order to age match, and stopped when number was reasonable. Exact figure on drop outs was not recorded. Median age at start of prophylaxis was comparable in the High-dose and Intermediate-groups: 2.5 (1-9) and 5 (3-7) years, respectively. Background characteristics of the High-dose and Intermediate-dose groups are found in Supplementary Table 1.

Included subjects underwent BMD measurement using DXA scanning at one occasion between January 2007 and Nov 2012 in Sweden, July 2010 and April 2011 in Norway and December 2010 and January 2012 in the Netherlands.

Informed consent was obtained from all subects. The study was approved by the Ethical Committees at each respective study centres. (Sweden, Lund University, Research, Sweden: Ref no 339/2006; Norway: Ref no 6.2008.1497; Netherlands: Ref no UMCU 10–142). The study was performed in accordance with the principles of the Helsinki declaration.

2.2 | Bone mineral density

BMD of lumbar spine (vertebrae L1-L4) and hip (femoral neck, trochanter and total hip) was measured by dual X-ray absorptiometry (DXA) and was expressed as g/cm^2. The DXA measurements were performed using machines from two different manufacturers: in Sweden (Malmö and Gothenburg) and Norway (Oslo) the Lunar Prodigy (Lunar Corporation, Madison, Wisconsin, USA) and in the Netherlands (Utrecht) the Hologic Discovery DXA System (Hologic Inc., Marlborough, Massachusetts, USA).

To allow for comparisons between the different machines a standard spine phantom (spine region vertebraes L1-L4) was measured 15 times on each machine and a mean BMD value was calculated: Malmö: 1177 g/cm^2; Gothenburg: 1172 g/cm^2; Oslo: 1174 g/cm^2; Utrecht: 1020 g/cm^2. Based on the phantom measurements, a standardized BMD (sBMD (expressed in mg/cm^2)) was calculated for lumbar spine and hip using previously published formulas.[13,14]

TABLE 1 Background characteristics of the study cohort

	High-dose	Mild	On-demand	Intermediate-dose
Number (n, tot n = 120)	41	33	14	32
Haemophilia A (n, % of tot)	34 (82.9)	28 (84.8)	12 (85.7)	26 (81.3)
Age (median, IQR)	32 (24-40)	40 (29-52)	46 (43-56)	29 (23-35)
BMI (median, IQR)	23.4 (20.9-26.4)	25.0 (23.7-27.0)	24.8 (23.6-27.1)	24.0 (21.5-25.6)
Current user and/or historic of tobacco (n, % of tot)	16 (39.0)	19 (57.6)	7 (50.0)	18 (56.3)
Hepatitis C pos at any time by PCR (n, % of total)	34 (82.9)	9 (27.3)	13 (92.9)	18 (56.3)
Concomitant disease of significance for bone mineralization (n, % of tot)	3 (7.3)	1 (3.3)	1 (7.1)	1 (3.1)

BMI: body mass index.

No standard phantom is available for total body measurements and no formula published for total body comparisons. To be able to include also total body measurements, BMD total body values from the DXA Utrecht were similarly adjusted to measurements obtained from the other instruments by multiplying with a factor obtained from the phantom comparisons described above (factor 1.15398) and were presented as *adjusted* BMD (aBMD) expressed in mg/cm^2. All comparisons and statistical analyses were performed based on sBMD and aBMD values.

In addition, to apply diagnostic critera (osteoporosis, osteopenia, normal), T-scores were calculated based on the adjusted sBMD value using the previously reported[15] formula: Patient mean (BMD) – Young adult mean/SD (adjusted T-score, aT-score). In accordance with World Health Organization definition, a T-score within 1 SD (+1 or −1) of the young adult mean is considered normal; low bone mass is a bone density between 1 and 2.5 SD below the young adult mean (−1 to −2.5 SD); osteoporosis is defined as a bone density -2.5 SD or more below the young adult mean (−2.5 SD or lower).[16]

2.3 | Data analysis

Descriptive information of background characteristics of the four study groups (High-dose, Mild, On-demand and Intermediate-dose) is presented as frequencies, percentages, median and interquartile range (IQR). To investigate the impact of potential confounders (age, BMI, tobacco and HCV), the distribution of these variables was compared and tested using the ANOVA test and presented as means and percentages. The distributions of age and HCV prevalence were significantly different between the study groups, hence these variables were included in the multivariable regression analysis.

The primary analysis aimed to investigate BMD in the High-dose study group compared to BMD in Mild, On-demand and Intermediate-dose study groups in that order. Results are presented as median sBMD (mg/cm^2). The difference in median sBMD was tested using the Mann Whitney test. Proportions of a pathologic aT-score (i.e. osteopenia and osteoporosis) were compared according to treatment regimen using the Fisher's exact test.

Coninuous parameters with a skewed distribution were compared using the Mann Whithey test, proportions were compared using the Fisher exact test.

A multivariable analysis was performed with the Mild study group as reference. The impact of age, HCV status and treatment regimen (defined as the four study groups and repeated with data from subjects on high- and intermediate dose prophylaxis merged into one group) on aBMD at femoral neck and total hip was tested. The results are presented as odds ratio and 95.0% confidence interval (CI 95%).

A P-value < .05 was considered statistically significant. Statistical analyses were performed in SPSS Statistics version 22 (IBM Corporation Armonk, New York, USA), Prism7 (GraphPad Software Inc., La Jolla, California, USA) and OpenEpi (www.openepi.com) version 3.01.

3 | RESULTS

3.1 | Study cohort

The mean age at the time of investigation was significantly different between groups (P < .001); the mean age was highest in the On-demand group (49.0 years) and lowest in the Intermediate-dose group (29.5 years). BMI was within normal range in all groups and there were no differences in tobacco habits (Table 2).

The HCV prevalence was significantly higher in patients with severe haemophilia and most prevalent in the High-dose (83%) and On-demand (93%) groups, which included older patients (Table 2). Very few subjects had a concomitant disorder; (HIV (n = 5), chronic obstructive pulmonary disease (n = 1) and vertebral compression fractures (n = 1)) evenly distributed between groups (High-dose n = 3, Mild n = 1, On-demand n = 1 and Intermediate-dose n = 1, Table 1), and therefore we did not exclude these subjects from the data analyses. The median FVIII-level in Mild haemophilia subjects at the time of the visit investigation was .18 IU/mL (IQR .08-.41, n = 31). Age at onset of prophylaxis was 2.5 (1-9) and 5 (3-7) years in the High-dose and Intermediate-dose group, respectively. At the time of study inclusion all High-dose subjects were on regular prophylaxis (n = 41, 100%)

TABLE 2 Frequency of clinically relevant factors for osteoporosis development in the study groups

		High-dose (n = 41)	Mild (n = 33)	On-demand (n = 14)	Intermediate-dose (n = 32)	Total (n = 120)	*P value*
Age at DEXA scanning	Mean	33.6	41.1	49.0	29.5	36.4	.000
	Std. Deviation	11.2	14.8	7.9	6.7	12.6	
	Std. Error	1.7	2.6	2.1	1.2	1.2	
	95% CI for Mean	30.1-37.1	35.9-46.4	44.4-53.6	27.1-31-9	34.1-38.7	
	Range	18-56	18-66	38-60	19-41	18-66	
BMI at time of inclusion (mean kg/m2)	Mean	23.8	25.4	25.3	24.0	24.5	.122
	Std. Deviation	3.4	3.9	2.6	3.2	3.5	
	Std. Error	.5	.7	.7	.6	.3	
	95% CI for Mean	22.7-24.8	24.1-26.8	23.8-26.8	22.8-25.1	23.8-25.1	
	Range	18.4-29.8	18.5-36.1	21.2-30.3	16.8-31.8	16.8-36.1	
Tobacco use (current and/or historic; yes %)	Percentage	39	56	50	58	50	.364
Hepatitis C positive (current and/or historic; yes %)	Percentage	83	56	93	27	62	.000

CI, confidence interval; BMI, body mass index.

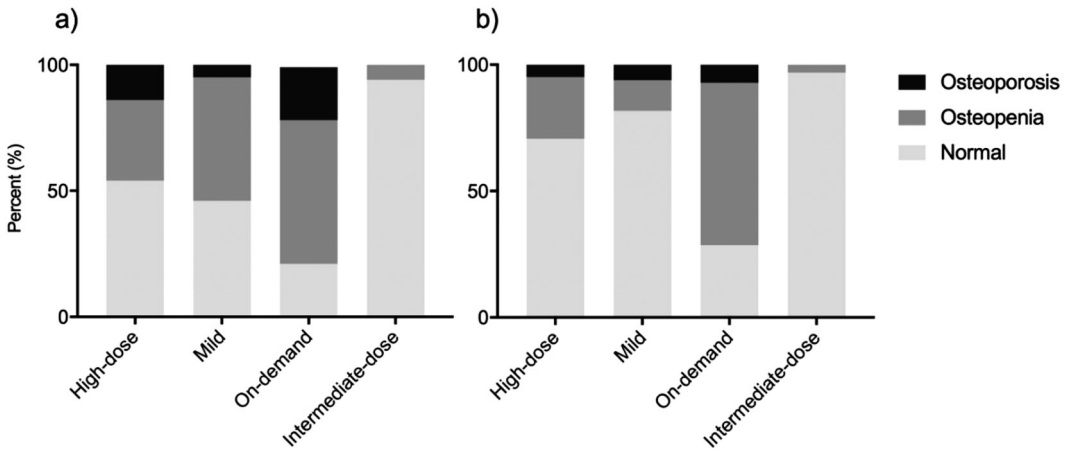

FIGURE 1 Bone mass density measured as adjusted T-score at Femoral Neck (A) and Total Hip (B), respectively

and the majority of the Intermediate-dose subjects (n = 31, 96.9%). Recombinant clotting factors were used in the majority of the subjects in both groups: High-dose subjects n = 39 (95.1%) and Intermediate group n = 26 (83.9%). Characteristics for the study groups on regular prophylaxis are presented in Supplementary Table 1.

3.2 | BMD measurements

BMD was measured at lumbar spine, femoral neck and total hip and is presented as mean adjusted BMD (aBMD) (Supplementary Table 2) and adjusted T-score (aT-score) (Figure 1). aBMD in the High-dose group was compared to aBMD in Mild, On-demand and Intermediate-dose subjects, respectively. aBMD at lumbar spine was comparable in all study groups (Supplementary Table 2). aBMD at both femoral neck and total hip was comparable in High-dose versus Mild and Intermediate-dose subjects, respectively (Figure 2). However, a significantly higher median aBMD was measured in High-dose subjects as compared to On-demand subjects at both the femoral neck ($P = .0041$) and total hip ($P = .001$) loci (Figure 2). This difference was further obvious with a significantly higher proportion of subjects having a pathologic aT-score in the On-demand group compared to the High-dose group ($P = .04$ at femoral neck and $P = .008$ at total hip) (Figure 1). Furthermore, the prevalence of a pathologic aT-score was significantly lower in Intermediate-dose subjects when compared to High-dose subjects ($P = .0001$ at femoral neck and $P = .003$ at total hip) (Figure 1).

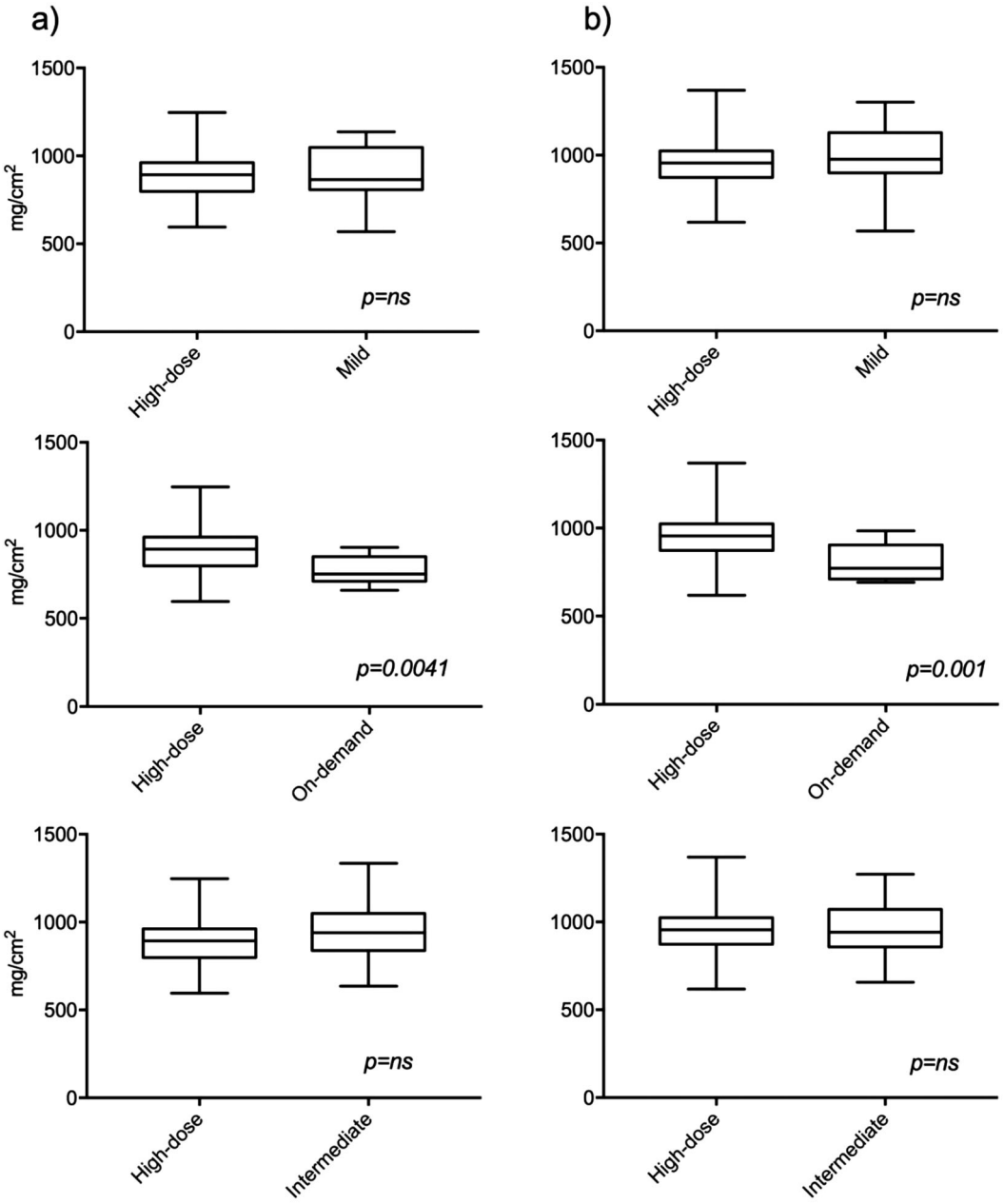

FIGURE 2 Comparison of adjusted median bone mass density (mg/cm^2) in High-dose subjects versus Mild, On-demand and Intermediate-dose subjects at Femoral Neck (A) and Total Hip (B), respectively

To test the hypothesis that appropriate prophylaxis potentially can impact bone mineralization, we hereafter analysed the effect of age, HCV status and treatment regimen (defined as study group) on osteoporosis development (defined as normal versus abnormal T-score) in a multivariate analysis with the Mild study group as reference group. Data was analysed by both separating the prophylaxis regimens (High-dose versus Intermediate-dose) and by merging High- and Intermediate-dose aBMD data into one study group (Table 3a and 3b). Tobacco use and BMI were left out of the analysis as these variables were not significantly correlated with BMD in the univariate analysis (Table 2). In the multivariate analysis of aBMD at femoral neck age, but neither HCV infection, nor treatment regimen, were significantly associated with osteoporosis development. However, for aBMD at total hip, age and also treatment regimen (on demand versus any prophylaxis, i.e. high-and intermediate dose combined) showed a significant effect on osteoporosis development (Table 3b).

4 | DISCUSSION

This multicentre cross-sectional study shows that subjects with severe haemophilia A and B on regular lifelong prophylaxis have bone mineral density, measured as aBMD, comparable to subjects with mild haemophilia. The aBMD decreased significantly with age, regardless

TABLE 3A Impact on BMD at femoral neck and total hip from age, HCV infection and haemophilia treatment in univariable and multivariate analyses

Femoral neck		Univariable (OR)	CI (95%)		*P value*	Multivariable (OR)	CI (95%)		*P value*
Age		1.114	1.068	1.162	.000	1.090	1.038	1.144	.001
Current or historic HCV infection (pos vs neg)		3.598	1.654	7.826	.001	2.953	.853	10.226	.087
Treatment strategy using Mild haemophilia as reference group	High-dose	.636	.253	1.603	.338	.550	.123	2.460	.434
	Intermediate-dose	.442	.164	1.195	.108	.671	.159	2.827	.587
	On-demand	4.421	.850	22.985	.077	1.118	.162	7.701	.910
Total hip		**Univariable (OR)**	**CI (95%)**		***P value***	**Multivariable (OR)**	**CI (95%)**		***P value***
Age		1.055	1.021	1.090	.001	1.074	1.025	1.126	.003
Current or historic HCV infection (pos vs neg)		2.803	1.182	6.649	.019	1.081	.350	3.335	.892
Treatment strategy using Mild haemophilia as reference group	High-dose	1.862	.613	5.658	.273	3.769	.797	17.828	.094
	Intermediate-dose	2.357	.749	7.419	.143	7.059	1.442	34.559	.016
	On-demand	11.250	2.617	48.366	.001	8.968	1.682	47.815	.010

Mild haemophilia is reference.

TABLE 3B Impact on BMD at femoral neck and total hip from age, HCV infection and haemophilia treatment in univariable and multivariate analyses showing High- and Intermediate-dose aBMD data merged into one study group

Femoral neck		Univariable (OR)	CI (95%)		*P value*	Multivariable (OR)	CI (95%)		*P value*
Age		1.114	1.068	1.162	.000	1.089	1.038	1.144	.001
Current or historic HCV infection (pos vs neg)		3.598	1.654	7.826	.001	2.822	.836	9.522	.095
Treatment strategy using Mild haemophilia as reference group	Prophylaxis	.544	.237	1.250	.151	.198	.063	.618	.005
	On-demand	4.421	.850	22.985	.077	1.282	.199	8.270	.794
Total hip		**Univariable (OR)**	**CI (95%)**		***P value***	**Multivariable (OR)**	**CI (95%)**		***P value***
Age		1.055	1.021	1.090	.001	1.070	1.022	1.121	.004
Current or historic HCV infection (pos vs neg)		2.803	1.182	6.649	.019	.951	.314	2.882	.929
Treatment strategy using Mild haemophilia as reference group	Prophylaxis	2.070	.752	5.701	.159	5.007	1.147	21.850	.032
	On-demand	11.250	2.617	48.366	.001	9.607	1.805	51.141	.008

of severity of haemophilia disease. Moreover, the multivariate analysis showed a suggested positive effect of replacement therapy on bone mineralization in total hip.

4.1 | Pathophysiology and clinical interpretation

It has been suggested that BMD is lower in PWH compared to healthy individuals.[8–11] The pathogenesis is not clarified, but several risk factors for osteoporosis development are more common in PWH, such as HIV and/or HCV infection[17–19] and immobilisation due to severe joint disease.[20–24]

The potential direct role of FVIII on bone mineralization have been investigated in mice finding the severe haemophilia A mice to have a decreased BMD compared to wild type. Moreover, it has been suggested that since thrombin stimulates differentiation and activity of osteoblasts, low FVIII plasma-level could impair bone remodelling and mineralization.[25] This has not been systematically investigated in humans. However, patients with severe haemophilia on lifelong prophylaxis have been shown to develop normal bone mineralization and BMD comparable to mild disease.[12] Here, we wanted to evaluate the potential impact of FVIII/FIX replacement therapy on bone mineralization by comparing subjects with severe haemophilia on different dosing regimens and comparing severe and mild haemophilia.

Indeed, subjects on prophylaxis had a BMD comparable to subjects with mild disease. We found a significant impact of age on BMD in the multivariate analysis, while the impact of treatment regimen on BMD was inconsistent depending on measurement location; a significant correlation was shown in total hip measurements, but not at femoral neck. Mean BMD at total hip was also highest among subjects with mild haemophilia followed by subjects on intermediate-dose prophylaxis. Subjects treated on demand had lowest mean BMD, but they were also the oldest. How this difference, related to measurement location, should be interpreted is not clear. Previous studies have shown that there is commonly a difference between femoral neck and total hip[26] . Total hip measurement is more commonly used in clinical practice since changes might be obvious in an early phase of osteoporosis development, because of a higher trabecular bone content. In contrast, femoral neck measurements were used early on and regularly in clinical trials; femoral neck BMD being particularly low in the elderly when the cortical thinning as part of bone loss becomes more prominent.[27,28] Therefore, discrepancies can be found and what parameter best mirrors osteoporosis development in haemophilia is not known.

Even though, the multivariate analysis suggests age to be the most important explanatory variable for variation in BMD in this study cohort, some findings need to be discussed. There is no major age difference beetween the two prophylactic groups, hence the variation may be explained by other factors not studied here. It has been shown that Dutch PWH tend to be more physically active compared to for example Swedish patients. Increased intensity and duration of training in adult PWH has been shown to increased BMD in the lumbar spine, whereas no improvement of general BMD was shown.[29]

Bone accrual, resulting in the peak bone mass, mainly occurs during childhood and adolescence.[22] Therefore ifferences in physical activity during adulthood does not seem to be a predictor of BMD.[26] Since both the High-dose and Intermediate-dose regimens result in fewer hemarthroses and fewer joint problems, a higher physical activity in the Dutch cohort during growth might be a stronger predictor of bone health later in life than just more intense treatment with FVIII/FIX. This explanation also fits with a lower mean BMD in the On-demand group. Our study does not support findings from animal studies indicating that FVIII/FIX deficiency, resulting in impaired thrombin generation, primarily explains low BMD in PWH since the High-dose group has higher FVIII plasma levels compared to the Intermediate-dose group. However, as even low FVIII levels elicit substantial amounts of thrombin there might be a threshold effect for thrombin which usually is overcome during both High-dose and Intermediate-dose prophylaxis. Hypothetically lower BMD in the High-dose group compared to the Intermediate-dose group could be explained by differences in HCV prevalence and physical activity and intensity of prophylaxis plays a minor role.

4.2 | Strenghts and limitations

Our study has some limitations; age of the subjects was not evenly distributed among the treatment groups, with no subjects in the Intermediate-dose group being above the age of 41 years (mean 29.5 years) and no subjects treated On-demand younger than 38 years (mean 49 years). While acknowledging this limitation, we still consider that the study provides valuable insight into bone health in PWH. The study is based on real-world treatment regimens, this is a strength since economic and other considerations influence ability to treat; hence, we provide data covering different aspects of treatment. Furthermore, we show that those with mild haemophilia has higher BMD than those with severe haemophilia treated prophylactically at comparable ages, and as many of the group subjects have normal aT-scores, it is plausible to argue that prophylactic treatment is beneficial for BMD outcome. We were not able to recruit patients treated on demand at similar ages and therefore age matched comparisons could not be achieved and the strong impact of age on BMD and restricted number of patients hamper the possibility to disclose more subtle reasons for potential BMD differences. The limitation of using different machines for DEXA measurement of patients was handled by using the same standard phantom in all sites, in accordance with standard recommendations.[30] It cannot be ruled out that the use of standardized and adjusted BMD, and note crude BMD, values introduces a potential bias due to machine differences. However, the multi-centre design allowed us to include a much larger cohort of study subjects than what would have been possible in a single-centre study, and we believe the information we contribute with is valuable.

5 | CONCLUSION

This study investigates the hypothesis that intensity of replacement therapy could influence BMD in persons with haemophilia. We show that BMD statistically differs in persons with severe haemophilia with lifelong High-dose propylaxis as compared to those with severe haemophilia treated On-demand treatment, but the difference was mainly explained by age. However, patients on lifelong prophylaxis of any regimen displayed a high degree of normal aTscore and a BMD not far from mild haemophilia at comparative ages. This is reassuring since previous studies have suggested that persons with haemophilia in general have reduced BMD.

ACKNOWLEDGEMENT

The authors thank all participating study subjects for valuable contribution to this study. Moreover, the authors would like to acknowledge Prof Erik Berntorp, Lund University, who initiated this study and were responsible for the early phase of the study. This work was supported by grants from the Swedish Research Council, H Järnhardt foundation, Skåne University Hospital Research Fund and the Research and Development Council of Region Skåne (ALF), Sweden.

CONFLICTS OF INTERESTS

KF, KEA and JK have no conflicts of interests to declare. PAH has received lecture honoraria from Takeda, SOBI, Bayer, Pfizer, Roche, Octapharma, NovoNordisk, CSL and BMS.

AUTHOR CONTRIBUTIONS

KÅ and KF designed the research and KÅ, KF and PH acquired the data. JK performed the data analysis. JK and KF performed the uni- and multivariate analyses. All authors contributed to interpretation of data analyses. JK wrote the manuscript. All authors revised the manuscript and contributed to its final version. All authors approved of the submitted version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Klintman J, Akesson KE, Holme PA, Fischer K. Bone mineral density in Haemophilia – a multicentre study evaluating the impact of different replacement regimens. *Haemophilia*. 2022;28:239–246. https://doi.org/10.1111/hae.14487