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Osteoporosis Remains Constant in Patients with Hemophilia—Long-Term Course in Consideration of Comorbidities

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Abstract

Introduction Patients with hemophilia (PWHs) suffer from an increased risk of osteoporosis. Multiple hemophilia and hemophilic arthropathy associated factors correlate with a low bone mineral density (BMD) in PWHs. The aim of this study was to assess the long-term development of BMD in PWH as well as to analyze potentially influencing factors.

Methods A total of 33 adult PWHs were evaluated in a retrospective study. General medical history, specific-hemophilia-associated comorbidities, joint status using the Gilbert score, calcium level, and vitamin D level as well as at least two results of bone density measurements with a minimum range of 10 years per patient were taken into account.

Results The BMD did not change significantly from one point of measurement to the other. A total of 7 (21.2%) cases of osteoporosis and 16 (48.5%) cases of osteopenia were identified. The two following significant correlations could be revealed: the higher the patients' body mass index, the higher their BMD ($r = 0.41$; $p = 0.022$). Moreover, a high Gilbert score came along with a low BMD ($r = -0.546$; $p = 0.003$).

Conclusion Even if PWHs frequently suffer from a reduced BMD, our data suggest that their BMD remains constant on a low level in the course of time. A risk factor of osteoporosis often found in PWHs is a vitamin D deficiency and joint destruction. Therefore, a standardized screening of PWHs on BMD reduction by collecting vitamin D blood level and assessing joint status seems appropriate.

Keywords
- hemophilia
- osteoporosis
- osteopenia
- follow-up

Zusammenfassung

Einleitung Hämophilie-Patienten leiden an einem erhöhten Osteoporose-Risiko. Verschiedene Hämophilie- und Arthropathie-bedingte Faktoren korrelieren mit der Minderung der Knochendichte (BMD: Bone Mineral Density). Das Ziel dieser Studie war es, den Langzeitverlauf der Knochendichte von Hämophilie-Patienten und mögliche Einflussfaktoren darauf zu untersuchen.

Methode In einer retrospektiven Studie wurden 33 erwachsene Hämophilie-Patienten untersucht. Allgemeine und Hämophilie-spezifische Erkrankungen, der Gelenkstatus

Schlüsselwörter
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- Langzeit follow-up

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gemessen mit dem Gilbert-Score, Kalzium- und Vitamin D-Werte und zwei Knochendichtemessungen mit einem Mindestabstand von zehn Jahren wurden erfasst.

Ergebnisse Die Knochendichte änderte sich zwischen dem ersten und zweiten Messpunkt nicht signifikant. Bei 7 (21,2%) Probanden wurde eine Osteoporose und bei 16 (48,5%) Probanden eine Osteopenie diagnostiziert. Es konnten zwei signifikante Zusammenhänge ermittelt werden: Je höher der Body Mass Index (BMI) war, desto höher war die Knochendichte ($r = 0.41$; $p = 0.022$) und je höher der Gilbert Score war, desto niedriger war die Knochendichte ($r = -0.546$; $p = 0.003$).

Schlussfolgerung Auch wenn Hämophilie-Patienten häufig an einer reduzierten Knochendichte leiden, lässt diese Studie darauf schließen, dass die Knochendichte über die Zeit auf einem erniedrigten Level konstant bleibt. Da ein Vitamin D-Mangel und Arthropathien als Risikofaktoren für das Auftreten einer Osteoporose häufig bei Hämophilie-Patienten gefunden werden, sollten regelmäßige Screenings des Vitamin D-Spiegels und des Gelenkstatus erfolgen, um bei den betroffenen Patienten anhand der Ergebnisse ggf. die Knochendichte mittels DXA zu bestimmen.

Introduction

According to the World Health Organization (WHO), osteoporosis ranges among the most important diseases worldwide.[1] Not only does it affect postmenopausal women or elderly people, but also patients with hemophilia (PWHs) are suffering from an increased risk of osteoporosis. In 2007, Wallny et al pointed out that the number of joints affected by hemophilic arthropathy as well as the severity of their degeneration, muscle atrophy, low body mass index (BMI), and hepatitis C virus (HCV) infections and resulting physical inactivity correlate with a low bone mineral density (BMD) in PWH.[2] Case-control studies were able to confirm the correlation between hemophilia and osteoporosis, but failed to reveal a significant influence of BMI, physical inactivity, and concomitant viral infections on BMD.[3,4]

Until now, research on the long-term course of osteoporosis in PWH has not been published. The purpose of the present study was to assess BMD of PWH over a period of at least 10 years as well as to analyze the influence of possible risk factors and comorbidities over the course of time.

Methods

The study was performed in a descriptive, retrospective study design. The study cohort was composed of adult male patients treated in the Haemophilia Comprehensive Care Centre in Bonn that had already been part of Wallny et al's study cohort in the year 2006.[2] By detailed data collection and analysis, suitable patients were identified and recruited during their regular visit at the Haemophilia Comprehensive Care Centre in Bonn. Written informed consent was obtained from all participants. Reasons against recruitment were the change of treatment center in the meantime, death, or the refusal to participate.

The study protocol was approved by the Medical Ethics Committee of Rheinische Friedrich-Wilhelms-University Bonn.

Variables and Measurement

Data were collected using a standardized test battery. General information like age and BMI and medical data extracted from the patients' health records were taken into consideration. Among those were:

- Type and severity of hemophilia.
- Comorbidities.
- Long-term medication.
- Infections with HCV or human immunodeficiency virus (HIV).

At least two results of bone density measurements per patient were taken into account, with a minimum temporal distance of 10 years. In each case, BMD was measured on lumbar spine and femoral neck by means of dual-energy X-ray absorptiometry (DEXA). This method is recommended for BMD measurement by the WHO. Interpretation of the results following the WHO definition is shown in ►Table 1.

The joint status was evaluated in a standardized manner by means of the Gilbert score.[5]

To exclude secondary causes for osteoporosis, available laboratory values were collected and analyzed.

To minimize possible gaps in the data and to identify individual risk factors for osteoporosis, all participants were asked about their detailed case history. In addition, every patient had to rate the following aspects subjectively:

- Joint pain (Visual Analogue Scale; VAS).[6]
- Quality of life (Short Form-36 Health Survey; SF-36).[7]
- Functional health status (Haemophilia Activities List; HAL).[8]

Statistics

The absolute and relative frequencies, the arithmetical mean, and the standard deviation (SD) were calculated for all variables. As this study is a follow-up research, the *t*-test of linked samples (*t*-score of first and last tests) was used for

Table 1 WHO definition of the BMD based on DEXA results

t-Score	Interpretation
≥ -1 SD	Physiological
-1 to ≥ -2.5 SD	Osteopenia
< -2.5 SD	Osteoporosis
< -2.5 SD plus bone fracture	Manifest osteoporosis

Abbreviations: BMD, bone mineral density; SD, standard deviation; WHO, World Health Organization.
Note: t-Score is defined as the count of standard deviations (SDs) differing from the arithmetical mean of the BMD peak value of a healthy 30-year-old human.

significance testing. A value of $p < 0.05$ was considered statistically significant. The data were analyzed using SPSS Version 23.0 (IBM Corp., Armonk, New York, United States).

Results

A total of 33 male patients with hemophilia A or B participated in the study. The average follow-up period was 12.8 ± 1.7 years (range: 10.0–15.3). The average age was 53.76 ± 11.54 years (range: 31–74) at the time of follow-up, and the average BMI was 25.9 ± 3.9 kg/m^2 (range: 19.6–35.5). In total, 29 (87.9%) patients suffered from severe hemophilia (factor level of <1%), 3 patients (9.1%) from moderate hemophilia (factor level of 1–5%), and only 1 patient (3.0%) from a mild form of hemophilia (factor level of >5%). In the following, considering the small sample size, the collective was divided into two groups: patients with severe and patients with nonsevere hemophilia. Regarding the factor replacement strategy, 29 (87.9%) patients were under early primary prophylaxis and 4 (12.1%) patients were under on-demand treatment.

Thirty-one patients (93.9%) were tested HCV-positive, with 26 of them (78.8%) being considered cured by new therapy strategies with pegylated interferons and direct-acting antivirals (DAAs).[9] Thirteen participants (39.4%) were HIV-positive, all currently undergoing combined antiretroviral therapy (cART). However, only four of them (12.1%) were under the polymerase chain reaction detection limit at the time of follow-up. Twelve patients (36.4%) had no further comorbidities. The remaining 21 most frequently suffered from hypertension ($n = 16$), diabetes mellitus type 2 ($n = 4$), dyslipidemia ($n = 3$), and liver cirrhosis ($n = 3$). All comorbidities are listed in ►Table 2.

The analysis of the laboratory values showed an average calcium level of 2.30 ± 0.07 mmol/L (reference value: 2.15–2.5 mmol/L) and an average phosphate level of 0.94 ± 0.16 mmol/L (reference value: 0.81–1.45 mmol/L) at the time of follow-up. The average level of vitamin D was 19.91 ± 10.39 ng/mL (reference value: 30–100 ng/mL). In 26 cases (78.8%) we observed a vitamin D deficiency (<30 ng/mL).

At the beginning of the observation period, the average *t*-score of the lumbar spine was -0.75 ± 1.40, whereas during the follow-up, it accounted for -0.39 ± 1.68. The average

Table 2 Comorbidities (*n*)

Hypertension	16 (48.5%)
Diabetes mellitus type 2	4 (12.1%)
Liver cirrhosis	3 (9.1%)
Dyslipidemia	3 (9.1%)
Depression	2 (6.1%)
Bronchial asthma	2 (6.1%)
Coronary heart disease	1 (3.0%)
Metabolic syndrome	1 (3.0%)
Hypothyreosis	1 (3.0%)
Hyperthyreosis	1 (3.0%)
Stroke	1 (3.0%)

t-score of the femoral neck was recorded as -1.35 ± 1.21 during the first measurement, and -1.37 ± 1.26 for the second measurement. There was no significant change in BMD from one point of measurement to the other ($p = 0.117$ and $p = 0.893$). According to the WHO definition, there were 7 patients (21.2%) with osteoporosis and 18 patients (54.5%) with osteopenia at the beginning of the observation period. At the time of follow-up, there were 7 cases (21.2%) of osteoporosis, too, and 16 cases (48.5%) of osteopenia.

Furthermore, the joint status, as objectified by the Gilbert score, did not change in the course of time, with the total score being 22.07 ± 14.23 points at first, and 21.63 ± 14.75 points at follow-up ($p = 0.651$). Using the HAL, the study participants rated their level of physical activity with a mean score of 70.14 (± 25.77) out of 100, but no significant association with BMD was found.

Concomitant infections with HCV or HIV did not lead to a significant change in *t*-score. Also, the specific antiviral therapies did not have a significant influence on BMD in the course of time. The same applies to the severity of hemophilia (►Table 3).

Consumption of nicotine and alcohol, despite being well-known risk factors for osteoporosis, did not affect bone mass in a statistically significant way. This is also true for our patients' most frequent comorbidities such as hypertension, diabetes mellitus type 2, dyslipidemia, and liver cirrhosis. Even repetitive local or systemic cortisone therapy did not affect patients' BMD in the course of time.

All in all, a total of 16 (48.5%) patients received an antiosteoporotic therapy. But neither receiving basic nor specific osteoporotic therapy (three patients were treated with bisphosphonates and in one of those patients treatment was changed to Denosumab after a while) caused a significant change in their BMD.

However, the following significant correlations could be revealed: the higher the patients' BMI, the higher was the measured BMD ($r = 0.41$; $p = 0.022$). Moreover, a high Gilbert score came along with a low *t*-score ($r = -0.546$; $p = 0.003$). There was no correlation between the delta of the *t*-score and the delta of Gilbert score though.

Table 3 Comparison between t-scores before and after follow-up with regard to different influencing factors

Influencing factor		Count	t-Score lumbar spine			t-Score femoral neck		*p*-Value
		Abs. (rel.)	Old (mean ± SD)	New (mean ± SD)	*p*-Value	Old (mean ± SD)	New (mean ± SD)	
None		33 (100%)	−0.75 ± 1.40	−0.39 ± 1.68	0.177	−1.35 ± 1.21	−1.37 ± 1.26	0.893
HCV	Positive over all	31 (93.9%)	−0.90 ± 1.31	−0.51 ± 1.63	0.177	−1.48 ± 1.15	−1.47 ± 1.24	0.962
	Positive over all	5 (15.1%)	−1.85 ± 1.08	0.33 ± 2.33	0.063	−1.96 ± 0.92	−1.53 ± 1.14	0.534
	Cured	26 (78.8%)	−0.75 ± 1.29	−0.65 ± 1.51	0.615	−1.40 ± 1.18	−1.46 ± 1.27	0.655
HIV	Positive over all	13 (39.4%)	−1.08 ± 1.00	−0.83 ± 1.11	0.423	−1.46 ± 1.31	−1.25 ± 1.51	0.455
	Over PCR detection limit	9 (27.3%)	−1.37 ± 0.97	−1.33 ± 1.01	0.917	−1.56 ± 1.11	−1.66 ± 1.14	0.701
	Under PCR detection limit	4 (12.1%)	−0.57 ± 0.94	0.05 ± 0.70	0.320	−1.26 ± 1.82	−0.43 ± 1.99	0.208
Hemophilia	Severe	29 (87.9%)	−0.78 ± 1.41	−0.31 ± 1.72	0.790	−1.45 ± 1.24	−1.43 ± 1.28	0.869
	Nonsevere	4 (12.1%)	−0.59 ± 1.56	−0.88 ± 1.56	0.356	−0.64 ± 0.76	−0.95 ± 1.16	0.380
Comorbidity	Hypertension	16 (48.5%)	−0.45 ± 1.04	0.17 ± 1.70	0.155	−1.62 ± 1.20	−1.61 ± 1.45	0.960
	Diabetes mellitus type 2	4 (12.1%)	0.21 ± 0.29	−0.27 ± 0.42	0.367	−0.81 ± 1.43	−0.20 ± 1.68	0.053
	Liver cirrhosis	3 (9.1%)	−2.41 ± 1.44	−1.05 ± 1.63	0.063	−2.25 ± 0.83	−2.00 ± 0.87	0.498
Osteoporosis medication	All	16 (48.5%)	−0.99 ± 1.24	−0.67 ± 1.44	0.240	−1.81 ± 1.19	−1.69 ± 1.49	0.581
	Antiresorptive	3 (9.1%)	−2.55 ± 0.86	−1.70 ± 0.95	0.110	−3.07 ± 0.16	−3.55 ± 0.78	–
Glucocorticoids		11 (33.3%)	−0.90 ± 1.80	−0.67 ± 1.75	0.412	−1.34 ± 1.27	−1.45 ± 1.34	0.517
Alcohol		28 (84.8%)	−0.65 ± 1.48	−0.46 ± 1.71	0.458	−1.11 ± 1.18	−1.14 ± 1.31	0.842
Nicotine		16 (48.5%)	−0.86 ± 1.30	−0.49 ± 1.75	0.332	−1.31 ± 1.14	−1.56 ± 0.94	0.231
Vitamin D deficiency		26 (78.8%)	−0.71 ± 1.45	−0.33 ± 1.67	0.169	−1.07 ± 1.16	−1.13 ± 1.16	0.603
Normal vitamin D		13 (39.4%)	−0.91 ± 1.35	−0.60 ± 1.85	0.499	−2.32 ± 0.89	−2.17 ± 1.34	0.740

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; SD, standard deviation.

Regarding patients' subjective morbidity rating (see above), no relevant relation to bone mass could be found.

Discussion

Low BMD is a known issue in patients with hemophilia; Gallacher et al already recognized this correlation in the 1990s.[10] Several further studies provide similar results.[2,11–13] So far, there is a lack of literature on the long-term development of BMD in PWH and its potentially influencing factors over time.

Our study shows that, on the one hand, BMD is reduced in PWH, but on the other hand, remains constant for the observed time span of at least 10 years. The cause of the reduced BMD in PWH is still unknown.

In general, a vitamin D deficiency is a frequently mentioned influencing factor on BMD. With vitamin D being essential for the bone metabolism, a lack of it results in an increased risk for osteoporosis.[14] Within our study cohort, 78.8% of the patients suffered from a vitamin D deficiency (<30 ng/mL). Kempton et al reported reduced vitamin D levels in one-third up to one-half of the PWHs.[15] By contrast, according to Rabenberg et al, only 38.4% adults in the standard German population (38.3% of all men) suffer from a vitamin D deficiency.[16] Thus, a screening for vitamin D deficiency and contingent substitution of vitamin D seem to be reasonable.

As stated above, almost half of our participants (48.5%) received an osteoporosis basic therapy with calcium and vitamin D, three participants were treated with bisphosphonates in addition to that, and in one of those patients, treatment was changed to Denosumab (Prolia), which had been given for a period of 16 months prior to his last DEXA scan. However, our data show that this kind of therapy did not result in a relevant improvement of their BMD. In fact, neither an increase nor a decrease of BMD over time could be found. According to Orwoll et al, osteoporosis basic therapy and bisphosphonates can generally improve BMD in male patients.[17] Anagnostis et al examined the effect of bisphosphonates in PWH, detecting a reduction of bone resorption along with a BMD enhancement on lumbar spine.[18]

One-third of our patients were repetitively treated with oral or local glucocorticoids on demand during the observation period. But although glucocorticoids are a known risk factor for osteoporosis due to inhibition of the body's vitamin D production and osteoblasts' activity,[19] no significant decline in *t*-score could be identified compared with the participants not receiving glucocorticoids. Liu et al[29] provide a possible explanation for this, stating that the inhibition of osteoblasts' activity requires high doses of glucocorticoids.

The influence of concomitant infections (HCV and HIV) on the bone mass has been a widely discussed topic. Wallny et al pointed out that PWH with HCV infection had significantly lower BMD levels than hemophiliacs without such an infection.[2] This corresponds with observations made on nonhemophilic, nontreated HCV-positive patients.[20] Our results suggest that neither HCV infections nor treatments with interferons or DAA affect BMD in hemophiliacs in a significant way over time. Bedimo et al described a decrease in bone resorption markers due to treatment with pegylated interferon and ribavirin.[21] They did not explore the development of BMD though. To the best of our knowledge, there is no research on DAA's influence on BMD until now.

Along with Wallny et al who could not identify a significant influence of a concomitant infection with HIV on BMD in PWH, our data did not reveal such an influence in the course of time.[2] Still there are observations that nonhemophilic HIV-positive patients have generally lower BMD levels.[22] Furthermore, Bolland et al stated that a cART therapy indeed causes an initial decrease in bone mass, but 1 to 2 years after cART induction, BMD levels stagnate without further decrease.[23]

Wallny et al suggested that physical inactivity, resulting from joint destruction and concomitant chronic pain, could be the main reason for osteopenia and osteoporosis.[2] Bielemann et al could prove the significant influence of physical activity on the bone mass during adolescent years, especially in young male.[24] In a meta-analysis, Paschou et al showed that low BMD levels already occurred in hemophilic children.[4] But they were not able to detect an influence of physical activity on bone mass. Thus, they assumed the reason of low BMD in PWH to be found in early childhood. However, in future studies on osteoporosis in PWH, the activity level of the patients should still be taken into account.

As our data show that BMD is constant in adult PWH over the course of time, even though on a low level, we suggest that physical inactivity has indeed some influence on BMD but cannot be the only reason. If it were the cause of low BMD, one would expect a progression of BMD loss.

We rather believe that the hemophilia disease itself could be the main cause for the low BMD in PWH. This assumption is supported by the results of Khawaji et al.[25] They pointed out that factor prophylaxis at an early age results in more physiological BMD values. Additionally, in 2013, Recht et al could provoke a loss of BMD by knockout of factor VIII gene in mice.[26]

The correlation of a high Gilbert score and low BMD values, as already pointed out by Wallny et al in 2007, could be verified in our follow-up.[2] Thus, it may be a useful option in clinical practice to pre-estimate a patient's benefit of more invasive osteoporosis diagnostics by means of the Gilbert score. Still, it is not possible to draw a conclusion from a quantitative shift of the Gilbert score to a quantitative shift of BMD.

Ghosh et al reported an increased risk of fractures in patients with severe hemophilia.[27] Anagnostis et al calculated a greater risk for major osteoporotic and hip fractures, with lower 25(OH)D levels and physical activity scores in patients with low BMD compared with those with normal BMD.[28] In our opinion, the increased risk of osteoporotic fractures in patients with low BMD not suffering from a bleeding disorder should be reason enough to screen PWHs for the existence of reduced BMD and to induce an appropriate therapy.

Limitation

The main limitations of our study are the small sample size and the lack of a control group with nonhemophilic patients.

To verify our results, extensive case-controlled studies would be required. Additionally, due to the long period of observation and the technical upgrading in the meantime, not all DEXA scans were performed by the same device, meaning that the results are not 100% comparable. Furthermore, the *t*-score used to analyze BMD is not validated in patients under 50 years of age. Finally, the vitamin D levels were determined at any season, not considering that vitamin D levels naturally increase during summer months.

Conclusion

Patients with hemophilia frequently suffer from a reduced BMD. Our data suggest that BMD remains constant on a low level over the course of time though. Main determinants for the BMD in our cohort were BMI and the degree of hemophilic arthropathy. Concomitant viral infections, related therapies, other comorbidities, and lifestyle habits do not seem to have a significant influence on BMD in hemophiliacs. A general risk factor for osteoporosis often found in PWH is a vitamin D deficiency. Therefore, a standardized screening of patients with hemophilia on BMD reduction by collecting Gilbert score and vitamin D blood level seems appropriate. More invasive osteoporosis diagnostics and related therapy may follow the initial screening if necessary.

What Is Known about This Topic?

- Despite their sex and age, PWHs suffer from an increased risk of osteoporosis; several risk factors have been identified.[2,10–13,24,25]

What Does This Paper Add?

- To the knowledge of the authors, no data about the long-term course of BMD in PWH do exist yet, although it seems reasonable to monitor this issue as well as correlating factors to treat them correctly.
- The article suggests a simple screening for osteoporosis based on vitamin D levels and the Gilbert score.
- Our study also emphasizes that further research on the reason for osteopenia in PWH, which might be the lack of coagulation factor itself and its specific treatment, is necessary.

Conflict of Interest

The authors state that they have no interests which might be perceived as posing a conflict of bias.

Author Contributions

Ann.C.S., P.M., and And.C.S. performed chart review, data collection, and wrote the paper. S.K. and G.G. performed chart review and collection of clinical data. P.H.P., T.A.W., and J.O. analyzed results and re-edited the manuscript.

References

1 WHO. WHO scientific group on the assessment of osteoporosis at primary health care level. 2007. Accessed January 2, 2023 at: https://frax.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf
2 Wallny TA, Scholz DT, Oldenburg J, et al. Osteoporosis in haemophilia - an underestimated comorbidity? Haemophilia 2007;13 (01):79–84
3 Iorio A, Fabbriciani G, Marcucci M, Brozzetti M, Filipponi P. Bone mineral density in haemophilia patients. A meta-analysis. Thromb Haemost 2010;103(03):596–603
4 Paschou SA, Anagnostis P, Karras S, et al. Bone mineral density in men and children with haemophilia A and B: a systematic review and meta-analysis. Osteoporos Int 2014;25(10):2399–2407
5 Gilbert MS. Prophylaxis: musculoskeletal evaluation. Semin Hematol 1993;30(3, Suppl 2):3–6
6 Huskisson EC. Measurement of pain. Lancet 1974;2(7889): 1127–1131
7 Morfeld M, Bullinger M, Nantke J, Brähler E. The version 2.0 of the SF-36 Health Survey: results of a population-representative study [in German]. Soz Praventivmed 2005;50(05):292–300
8 van Genderen FR, van Meeteren NL, van der Bom JG, et al. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. Haemophilia 2004;10 (05):565–571
9 Kronenberger B, Zeuzem S. New developments in HCV therapy. J Viral Hepat 2012;19(Suppl 1):48–51
10 Gallacher SJ, Deighan C, Wallace AM, et al. Association of severe haemophilia A with osteoporosis: a densitometric and biochemical study. Q J Med 1994;87(03):181–186
11 Nair AP, Jijina F, Ghosh K, Madkaikar M, Shrikhande M, Nema M. Osteoporosis in young haemophiliacs from western India. Am J Hematol 2007;82(06):453–457
12 Mansouritorghabeh H, Rezaieyazdi Z, Badiei Z. Are individuals with severe haemophilia A prone to reduced bone density? Rheumatol Int 2008;28(11):1079–1083
13 Mansouritorghabeh H, Rezaieyazdi Z, Saadati N, Saghafi M, Mirfeizi Z, Rezai J. Reduced bone density in individuals with severe hemophilia B. Int J Rheum Dis 2009;12(02):125–129
14 Nakamichi Y, Udagawa N, Suda T, Takahashi N. Mechanisms involved in bone resorption regulated by vitamin D. J Steroid Biochem Mol Biol 2018;177:70–76
15 Kempton CL, Antoniucci DM, Rodriguez-Merchan EC. Bone health in persons with haemophilia. Haemophilia 2015;21(05):568–577
16 Rabenberg M, Scheidt-Nave C, Busch MA, Rieckmann N, Hintzpeter B, Mensink GB. Vitamin D status among adults in Germany–results from the German Health Interview and Examination Survey for Adults (DEGS1). BMC Public Health 2015;15:641
17 Orwoll ES, Binkley NC, Lewiecki EM, Gruntmanis U, Fries MA, Dasic G. Efficacy and safety of monthly ibandronate in men with low bone density. Bone 2010;46(04):970–976
18 Anagnostis P, Vyzantiadis TA, Charizopoulou M, et al. The effect of monthly ibandronate on bone mineral density and bone turnover markers in patients with haemophilia A and B and increased risk for fracture. Thromb Haemost 2013;110(02):257–263
19 Wood CL, Soucek O, Wong SC, et al. Animal models to explore the effects of glucocorticoids on skeletal growth and structure. J Endocrinol 2018;236(01):R69–R91
20 Orsini LG, Pinheiro MM, Castro CH, Silva AE, Szejnfeld VL. Bone mineral density measurements, bone markers and serum vitamin D concentrations in men with chronic non-cirrhotic untreated hepatitis C. PLoS One 2013;8(11):e81652
21 Bedimo R, Kang M, Tebas P, et al. Effects of pegylated interferon/ribavirin on bone turnover markers in HIV/hepatitis C virus-coinfected patients. AIDS Res Hum Retroviruses 2016;32(04): 325–328
22 Biver E, Calmy A, Delhumeau C, Durosier C, Zawadynski S, Rizzoli R. Microstructural alterations of trabecular and cortical bone in

long-term HIV-infected elderly men on successful antiretroviral therapy. AIDS 2014;28(16):2417–2427
23 Bolland MJ, Grey A, Reid IR. Skeletal health in adults with HIV infection. Lancet Diabetes Endocrinol 2015;3(01):63–74
24 Bielemann RM, Domingues MR, Horta BL, et al. Physical activity throughout adolescence and bone mineral density in early adulthood: the 1993 Pelotas (Brazil) Birth Cohort Study. Osteoporos Int 2014;25(08):2007–2015
25 Khawaji M, Akesson K, Berntorp E. Long-term prophylaxis in severe haemophilia seems to preserve bone mineral density. Haemophilia 2009;15(01):261–266
26 Recht M, Liel MS, Turner RT, Klein RF, Taylor JA. The bone disease associated with factor VIII deficiency in mice is secondary to increased bone resorption. Haemophilia 2013;19(06):908–912
27 Ghosh K, Madkaikar M, Jijina F, Shetty S. Fractures of long bones in severe haemophilia. Haemophilia 2007;13(03):337–339
28 Anagnostis P, Vakalopoulou S, Vyzantiadis TA, et al. The clinical utility of bone turnover markers in the evaluation of bone disease in patients with haemophilia A and B. Haemophilia 2014;20(02):268–275
29 Liu W, Zhao Z, Na Y, Meng C, Wang J, Bai R. Dexamethasone-induced production of reactive oxygen species promotes apoptosis via endoplasmic reticulum stress and autophagy in MC3T3-E1 cells. Int J Mol Med 2018;41(04):2028–2036