The characteristics of hemophilic patients with decreased bone density in Cipto Mangunkusumo Hospital Jakarta

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ABSTRACT

Background: Hemophilia can cause musculoskeletal complications and decreased bone density is one of those complications. The profile of hemophilic patients with decreased bone density in Indonesia is still unknown.

Objective: To estimate the proportion of decreased bone density hemophilia and to learn the characteristics of hemophilic patients with decreased bone density.

Methods: This is a cross-sectional study done in June - November 2012. Subjects were adult hemophilic patients from 19-50 years old in Hematology- Oncology outpatient clinic Cipto Mangunkusumo Hospital. Estimated variables were bone density mass, age, body mass index, physical activity, arthropathy, substitution therapy, HIV, and HCV infection.

Result: 63 subjects were included in the study with median age of 26 years old. The proportion of decreased bone density in hemophilia was 6.3%. Subjects with decreased bone density were younger (19 years old vs 26 years old), have lower BMI (18,6 + 2,8 kg/m2 vs 21,5 + 3,8 kg/m2), used more substitution therapy (4047 IU/month vs 2000 IU/month), and have better clinical arthropathy score. HCV infection happened on 25% subjects with decreased bone density while HIV was on 1.6% of subjects.

Conclusion: Decreased bone density was found in 6.3% of subjects with hemophilia. They were younger, have lower BMI, better joint score, lower infection caused by transfusion, and more bleeding compared with subjects with normal bone density.

Hemophilia is a disorder of blood coagulation caused by deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). It is linked by mutation in X chromosom and is found in 1 of 10,000 births. Hemophilia A dominates the prevalence with more than 80-85% cases. [1] According to the survey data by World Federation of Hemophilia (WFH) in 105 countries in 2009, there were 150,000 cases of hemophilia.[2] Complications from hemophilia were caused by the disease itself or because of its treatment. One of the most common complications in hemophilia was musculoskeletal problems, and osteoporosis was a prime example.[3]

Osteoporosis is a disease characterized by low bone mass and bone structure deterioration causing fragility and increased risk of fracture.[4] Those with osteoporosis are commonly at high risk for fracture of pelvis, spine, and lower arms.[5] Currently, there are 200 millions of people with osteoporosis.[6] This disease was diagnosed using bone densitometry and measured according to the criteria from WHO with T score for post-menopause women and Z-score for younger people.[4]

Decreased bone densitiy in hemophilia was first reported by Gallacher et al in 1994.[7] A few studies after reported the same results in adults and children and it was later supported with a meta-analysis study.[7-14] Because bone density is related with the risk of fracture, hemophilic patients with decreased bone density will have increased risk of fracture.

In hemophilia, fracture is a complex problem because of its morbidity and good hemostasis is needed for perioperative and rehabilitative period.[1] Its management also needs cooperation between hematologists, surgeons, and medical rehabilitationists, besides expensive billing caused by coagulation factor concentrates.[15-17] They are become the main reason of risk factor identification hemophilia to prevent osteoporosis and fracture.

A number of studies about decreased bone density and related factors were done in various countries and regions.[9,10,14,18,19,20] This studies of osteoporosis in adults with hemophilia reported consistent result about decreased bone density in hemophilic patients compared with their normal counterpart. Unfortunately, these studies used T-score to define osteoporosis in young subjects and their Z-score cut-off points were different from recommendations in guidelines.[14,18,19] They also had different characteristics compared with Indonesian patients, so those results could not be applied here. Because of those limitations, this study was done to understand the proportion of decreased bone density in hemophilia and the patients' characteristics in Indonesia.

METHODS

This is a cross-sectional study to estimate the proportion of decreased bone density and to learn the patients' characteristics. The study was done from June 2012 – November 2012 in Hematology-Oncology outpatient clinic, Cipto Mangunkusumo Hospital.

Inclusion criteria used was hemophilic patients between 19-50 years old, while exclusion criteria were subjects with prosthesis on the location examination of BMD, antiviral for HIV or HCV, previous or ongoing treatment of osteoporosis (bisphosphonate, SERM, calcitonin, strontium ranelat, hormone replacement therapy); routine steroid for 6 weeks or more, one or more comorbid such as rheumatoid arthritis, SLE, CKD, and patients refusing to be involved in the study.

The variables included in the estimation were age, BMI, hormone replacement therapy, physical activity, clinical arthropaty degree, radiological arthropaty degree, HIV, HCV, bone density measurement, and history of fracture. BMD examination was done with GE Lunar Scan and the results were reported using Z-score. Decreased bone density was defined as *Z-score* -2 or less. HJHS score was estimated using guidelines according to International Prophylaxis Study Group. Knee radiologic photos were interpreted by a radiologist using Arnold-Hilgartner score. Score of 3 or more was categorized as significant arthropaty.

The data of subject characteristics is presented in tables. Numeric data with normal distribution is presented in mean + standard deviation (SD) while abnormal distribution is presented in median. Categorical data is presented in amount (n) and percentage. Statistic processing was done using SPSS.

RESULTS

Between June – November 2012, a tracing to 152 hemophilic patients living in Jabodetabek listed in Integrated Hemophilia Team was done. Out of 84 patients that were managed to be contacted, 63 of them fulfilled inclusion criteria to be involved in the study. Their characteristics are seen on the table 1.

All subjects in this study were male with median age of 26 years old (19-46 years old) and most of them graduated from high school and university. 53 subjects had hemophilia A while the rest of them had hemophilia B and most of them had severe hemophilia. About 74.6% of subjects had normal BMI and 25.4% had low BMI. 54% subjects had Hepatitis C while HIV was found in 1 subject.

History of fracture was found in 14,3% of subjects. All of them had normal bone density and most of them (90%) were caused by trauma. Median BMD of those subjects was 1,159 g/cm^2 while the median BMD of subjects without any fracture history was 1,023 g/cm^2.

Table 1 The characteristics of the subjects in study

Variable	Total (n = 63)
Age (years), median (min-max)	26 (19-46)
Age at diagnosis (month), median (min-max)	9 (1-324)
Duration since diagnosis (month), median (min-max)	268 (60-492)
Education, n (%)	
- Basic (elementary - junior high school)	1 (1,6)
- Middle (senior high school)	49 (77,8)
- Advanced (college or university)	13 (20,6)
Body mass index (kg/m^2), mean + SD	21,4 + 3,8
Type of hemophilia, n (%)	
- Hemophilia A	53 (84,1)
- Hemophilia B	10 (15,9)
Degree of hemophilia severity, n (%)	
- Mild hemophilia	5 (7,9)
- Moderate hemophilia	18 (28,6)
- Severe hemophilia	40 (63,5)

Variable	
Substitution therapy in the last 1 month	
- Factor VIII (IU), median (min-max)	2000 (0-7350)
- Factor IX (IU), mean + SD	2366,2 + 1443,4
Substitution therapy per kg body weight in the last 1 month	35,5 (0-126,9)
- Factor VIII (IU/kg), median (min-max)	39,5 + 27,5
- Factor IX (IU/kg), mean + SD	
Substitution therapy in the last 3 months	
- Factor VIII (IU), median (min-max)	6000 (0 - 21550)
- Factor IX (IU), mean + SD	5469,7 + 3117,3
Substitution therapy per kg body weight in the last 3 months	101,1 (0-359,4)
- Factor VIII (IU/kg), median (min-max)	89,8 + 57,6
- Factor IX (IU/kg), mean + SD	
BMD (g/cm^2), median (min-max)	1,036 (0,808-1,337)
HCV infection, n (%)	
- Positive	34 (54)
- Negative	29 (46)
HIV infection, n (%)	
- Positive	1 (1,6)
- Negative	62 (98,4)

Table 2 Fracture on hemophilic subjects

Variable	Total (n=63)
History of fracture, n (%)	
- Positive	9 (14,3)
Location of fracture, n*	
- Clavicle	4
- Femur	3
- Tibia	1
- Patella	1
Fibula	1
Cause of fracture, n*	
- Traffic accident	6
- Domestic accident	1
- Nature disaster (earthquake)	1
- Minimal trauma	2
- Negative	54 (85,7)

Proportion of decreased bone mass density was 6.3%. But the results were different when using Z-score and T-score. Bone density characteristics of the subjects can be seen below.

Table 3 Bone density on hemophilia

Variabel	Total subyek (n=63)
BMD (g/cm^2), median (min-max)	1,036 (0,808-1,337)
Decreased bone density according to the ISCD*	
Z-score < -2, n(%)	4 (6,3%)
Z-score > -2, n(%)	59 (93,7%)
osteopenia and osteoporosis according to the WHO**	
Normal (T-score>-1), n (%)	40 (70,2%)
Osteopenia/osteoporosis (*T-score* <-1), n (%)	17 (29.8%)

*The criteria of decreased bone density according to the ISCD is used for males younger than 50 years old and pre-menopause females using cut-off *Z-score* < -2

** osteopenia and osteoporosis according to the WHO is used for post-menopause females and males older than 50 years old

All subjects with decreased bone density had hemophilia A, lower BMI, lower incidence of HCV or HIV infection, and younger compared with subjects with normal bone density. There was a significant difference of substitution therapy between subjects with normal and decreased bone density. Subjects with decreased bone density used substitution therapy twice as much as subjects with normal bone density in the last 1 month (median 4047 IU/month vs 2000 IU/month). The same tendency also happened in substitutional therapy

use in the last 3 months (10872,5 IU vs 6632,6 IU).

Both groups had similar level of physical activities. In decreased BMD group, their arthropaty scores were better but the incidence rates of knee arthropaty were similar in both groups. The subjects' characteristics can be seen below.

Table 4 The characteristics of subjects with decreased bone density

Variable	Subjects with decreased bone density (n=4)	Subjects with normal bone density (n=59)
Age (years), median (min-max)	19 (19-21)	26 (19-46)
Age at diagnosis (months), median (min-max)	8 (1-36)	9 (1-324)
Duration of disease since diagnosis (month), median (min - max)	223 (192-244)	279 (60-492)
Hemophilia severity, n(%)		
- Mild hemophilia	0 (0)	5 (8,5)
- Moderate hemophilia	2 (50)	16 (27,1)
- Severe hemophilia	2 (50)	38 (64,4)
BMI (kg/m²), mean + SD	18,6 + 2,8	21,5 + 3,8
Substitution therapy in the last 1 month (IU), median (min-max)	4047 (0-6020)	2000 (0-7350)
Substitution therapy per kg body weight in the last 1 month (IU/kg), median (min-max)	83,4 (0-114,2)	35,5 (0-126,9)
Substitution therapy in the last 3 month (IU),mean + SD	10872,5 + 7796,9	6632,6 + 4923,3
Substitution therapy per kg body weight in the last 3 months (IU/kg), mean + SD	213,9 + 155,9	113,3 + 83,9
BMD (g/cm²), median (min-max)	0,900 (0,823-0,949)	1,062 (0,808-1,337)
Physical activity score (HAL score), mean + SD	69,6 + 12,8	71 + 13,4
Clinical arthropaty score (HJHS score), mean + SD	18,7 + 4,4	23,2 + 11,8
Radiologic arthropaty, n (%)		
Significant arthropaty	3 (75)	46 (80,7)
No significant arthropaty	1 (25)	11 (19,3)
HCV infection, n(%)		
Positive	1 (25)	33 (55,9)
Negative	3 (75)	26 (44,1)
HIV infection, n(%)		
Positive	0 (0)	1 (1,6)
Negative	4 (100)	58 (98,4)

DISCUSSION

There are 1,571 hemophilic children and adults in Indonesia. 152 hemophilic adults living in Jabodetabek were listed and 79 of them went to Hematology Oncology Outpatient Clinic of Cipto Mangunkusumo Hospital at least once in the last 6 months. This was the first study of bone density in hemophilic patients in Indonesia.

The median age of subject in the study was 26 years old with range of age between 19-46 years old. This median age complies with the age of peak bone mass and in accordance with the age of subjects in previous studies.[10,14,21,26,37,38] The eldest was 46 years old, unlike a few studies before with subjects older than 50 years old.[18,20,21,22,37-39] The age limitation in this study made uniform bone density measurement possible according to the standard of ISCD to prevent bias caused by age.

Most subjects in this study had normal or high BMI with average of 21.4 kg/m² and similar with studies done by Naderi and Mansouritorghabeh.[14,38]

All subjects had on demand substitution therapy, meaning that factors were given only if bleeding had already happened. Median use of factor VIII in this study subjects was 2000 IU in the last 1 month or roughly around 24000 IU per year. This was larger than average factor VIII use in Indonesia, which was about 17211 IU in 2006.[40] Median use of factor VIII per

kilogram body weight in this study was 35,5 IU/kg or roughly around 426 IU/kg in one year. This was lower than on demand therapy in Taiwan as reported by Liou et al (median use of factor VIII 1342,1 IU/kg/year) but higher than data in report by Naderi et al from Iran (average use of 28,8 IU/kg/year - 31,1 IU/kg/year).[38,41] Up to this day, Iran still use on demand therapy for hemophilia.[42] The dosage in this therapy was 10 times lower compared with the dosage in prophylaxis therapy in study by Khawaji et al (median use of 4106 IU/kg/year).[19]

In this study, the proportion of HCV infection was 54%, which was quite big compared with the study done by Khawaji in which he reported a proportion of 26,9%.[19] Other studies done by Wallny et al, Katsarou et al, and Gerstner et al showed bigger proportion of HCV infection than this study.[9,18,20] The proportion estimated in this study was similar with a study done in Europe.[43]

There was only a subject with HIV infection (proportion of HIV infection 1,6%). This result was different from other studies reported by Khawaji et al, Linari et al, Wallny et al, Katsarou et al, and Gerstner et al in which the proportion of HIV infection was between 11,5%-40,3%.[9,18,20,21,37]

In this study, the proportion of decreased bone density in this study was 6.3% and that result was lower from other similar studies done outside of Indonesia and can be seen on

table 5. This difference was possibly caused by difference estimation using Z-score in this study while other studies used T-score. Choosing Z-score in this study was based on several reasons. Z-score was the standard score for males younger than 50 years old according to the ISCD. Z-score also allows objective measurement and it was estimated by comparing bone density of subjects to those in the population, while T-score was estimated by comparing to density of peak bone mass population. The weakness of using T-score was younger subjects would have lower bone density and prevalence of decreased bone density would became higher.[72] When adhering to the criteria by WHO, the proportion of osteopenia and osteoporosis was 29,8% and it was similar with previous studies.

Table 5 Decreased bone density in hemophilia

Study and location	Age of subjects	Decreased bone density definition	Decreased bone density proportion	Refference
Wallny et al, Germany (2007)	Average age of 41,4 + 13,1 years old	T-score	43,5% osteopenia, 25,8% osteoporosis σ	9
Nair et al, India (2007)	Average age of 29,53 + 9,27 years old	T-score	50% osteoporosis σ	10
Gerstner et al, USA (2009)	Median age of 41,5 years old (18-66)	T-score	43% osteopenia, 27% osteoporosis σ	18
Mansouritorghabeh et al, Iran (2009)	Average age of 30,57 + 12,18 years old	T-score	35,7% osteoporosis σ	50
Katsarou et al, Greek (2010)	Median age of 36 (18-60)	T-score	52% osteopenia, 55,6% osteoporosis σ	20
Khawaji et al, Sweden (2010)	Average age of 30,5 years old	T-score	40% osteopenia σ	21
Linari et al, Italy (2012)	Median age of 41,5-45,8 years old**	Z-score	Decreased bone density by 23%***	37
Naderi et al, Iran (2012)	Average age of 27,73 + 9,5 years old	T-score	50% osteoporosis, 7,5% osteopenia σ	38
Anagnostis et al, Greek (2012)	Average age of 45,87 + 15,15 years old	Z-score	Decreased bone density by 26,9%	46
This study	Median age of 26 years old (19-46)	Z-score	Proportion of decreased bone density of 6,3%	-

σCriteria of osteopenia and osteoporosis using WHO *T-score*
*The study divided subjects into 2 groups with different mean age
**The study divided subjects into 3 groups with different median age
***Decreased bone density using Z-score < -2

Low proportion of decreased bone density in this study gave new insight in studying bone density of hemophilic patients. This was the second study involving adult hemophilics using standard measurement of bone density. A study done by Linari et al also used Z-score, but subjects with osteopenia had Z-score between -1 and -2 while osteoporosis had Z-score less than -2.[37] Its grouping method was also not in accordance to the guidelines from ISCD, in addition to involving subjects older than 50 years old.[38]

The difference of results between this study and of Linari et al could be caused by a number of factors. Linari et al involved older subjects with the eldest being 73 years old, causing higher proportion of decreased bone density. Another reason could be the location of study, since Europe as Linari's study place had different race and sunlight exposure while Johnell et al reported that every 10° away from equator increased the risk of osteoporosis as much as 0,6%.[45]

Another study done by Anagnostis et al in Greece in 2012 used bone density measurement in accordance to the standard and reported decreased bone density in 26.9% of their subjects.[46] But its limitation was involving subjects older than 50 years old with the eldest being 76 years old.[46] The characteristics of subjects with decreased bone density in this study also different than its predecessor because they were younger with lower BMI compared with studies by Gerstner et al and Naderi et al.[18,38] They also had lower incidence of HCV and HIV infection compared with Gerstner's report.[18] Substitution therapy was higher compared with osteopenic subjects in Naderi's report (83,4 IU/kg in 1 month vs 31,1 IU/kg in 1 year).[38] These differences in characteristics contributed to the different proportions of decreased bone density. Although there were differences found in the studies,

it can be concluded that decreasing bone density happens in hemophilia.

In this study, subjects with decreased bone density were younger with more frequent bleeding buth similar physical activity scores and better joint scores than normal subjects. These might be because younger age meant good joints. Good joints allow more physical activities which contributed to more bleeding.

There were 10 histories of fractures in 14.3% of subjects involved in the study, and it was similar with Anagnotis (16%) but lower than Grestner (20%), Gallacher (36,8%), and Khawaji (23,3%).[7,18,21,46] It was bigger than Nair (12%) though.[10] The difference could not be explained fully since not all studies described their location, the causes of fractures, and physical activity measurement. The fracture location was similar with Gallacher, Khawaji, and Anagnostis, in which most of them happened not on the bone with risk of pathologic fracture.[18,21,46] Most of the fractures in this study (90%) were traumatic injuries, which explained the reason they happened in subjects with normal bone density. Level of physical activities in subjects with or without fractures was similar (average HAL scores 71,9 + 12,6 vs 65,4 + 16,4), meaning fractures happened were caused by the intensity of trauma. The causes of fractures in this study were different from Anagnostis report because they report 53% of fractures caused by mild trauma.[46] The difference of proportion of subjects with fragility fracture on this study with studies by Anagnostis et al and Gerstner et al probably because studies by Anagnostis et al. and Gerstner et al included older subjects.[18,46]

Gerstner et al reported 50% of fractures in subjects with decreased bone density while Anagnostis reported 18%.[18,46] Based on these and other studies, it seems there is no exact

explanation of decreased bone density in hemophilia as a cause of fracture.

As for significant age gap in this study, a report from Gerstner had different result because his study subjects who had normal bone density were 20 years younger than those with low bone density.[18] Wallny reported that age had negative correlation with BMD, meaning older age had lower *T-score*.[9] Both of the studies' results were different from this study result. This could be explained by some reasons. Subjects with decreased bone density in this study had lower BMI, which was a risk factor of osteoporosis both in hemophilic and non hemophilic groups. Low BMI is known to correlate with low peak bone mass and contributed to the loss of bone mass.[4] Wallny reported BMI to had negative correlation with bone density.[9] Gerstner reported that their subjects with osteoporosis had significant low BMI.[18] The relationship between low BMI with hemophilic population was confirmed in a metaanalysis. [11]

Another reason was subjects with decreased bone density used substitutional therapy twice as much as in normal subjects. Indonesia had on-demand therapy in hemophilia, so therapy could be assumed to represent bleeding incidents. This meant subjects with decreased bone density had more bleeding. This study also showed that duration of disease since diagnosis in subjects with low bone density was short, so it seemed that bleeding played more important roles in decreasing bone density in hemophilia. Result of this study also in accordance to the study by Naderi and colleague in Iran which showed that bleeding episodes are significantly more frequent in subjects with osteopenia or osteoporosis.[38] Results from this study and study by Naderi et al.[38] and also Liel et al.[35] suggests that there might be an association between bleeding and reduced bone density. However we still can not rule out that more bleeding in subjects with reduced bone density in this study is merely a consequence of the severity of hemophilia because all subjects with reduced bone density in this study were subjects with severe hemophilia. The association of bleeding and bone metabolism in hemophilia patients still needs futher studies to confirm the causal association.

In this study, there was no difference of physical activity level between both groups, similar to a study by Khawaji in 2009, but different from Gerstner who reported better physical activity in normal BMD and Anagnostis who reported positive correlation between physical activity score and bone density. [18,19,46] In Gerstner and Anagnostis studies, there was no explanation about bleeding frequency or substitutional therapy. Khawaji in 2010 reported significant correlation between duration and the intensity of physical acitivities with bone density, but this could only be applied to heavy activities and not related to total activities.[21] This study used HAL score to measure total activities by subjects and caused different results.

Knee arthropaty was also important because it was the most common place for hemarthrosis and had great impact in mobility. The incidence of knee arthropaties was similar in both groups, and this result was different from the result in Anagnostis study.

In this study, HIV infection was lower and found in a subject with decreased bone density. This was different than the result in studies by Gerstner, Katsarou, and Anagnostis, and it could be caused by the possibility of early diagnosis in those countries since transfusions were done early. This study only had a subject with HIV (1,6%), compared with Gerstner (37%), Anagnostis (38.9%), and Katsarou (6,7%).[18,20,46] A possible explanation for low HIV infection in hemophilia could be because of unmeasured role of cytokine proresorption TNF-α as the base of decreased bone density.

The subjects in this study had lower HCV infection than studies by Wallny, Gerstner, and Anagnostis.[9,18,46] Nair and Khawaji did not find the relationship between HCV and low bone density.[10,19] This difference could be caused by different level of liver fibrosis and viral load, which have not been studied.[28,47]

There were things that have not been studied yet, such as proinflammation cytokine, bone resorption and formation marker, relationship between independent variable and bone density, direct role of factor VIII deficiency to bone density, and patophysiology of decreased bone density in hemophilia. Considering the role of factor VIII in inhibition of RANKL and its synergic action with OPG, osteoclast activity is needed to be understood in people with factor VIII deficiency. The relationship between factor VIII and osteoclastogenesis also needs to be understood because the main treatment of osteoporosis is bisphosponate, which inhibits the role of osteoclast.

Other factors in bone metabolism and patophysiology of decreased bone density are also need to be considered. Gerstner and Anagnostis found an association between bone density with vitamin D in hemophilia.[18] Other studies by Gowda, Anagnostis, and Linari found vitamin D deficiency in majority of hemophilic subjects, both in adults and children. [37,46,48]

The study limitation was its cross-sectional design, because it could not define the causal relationship between variables. Its descriptive trait also denied any quantification of association between variables. Another limitation in this study was no examination of inhibitor, vitamin D, and bone metabolism done because of the limited fund. Nonetheless, this study points out that reduced bone density actually happened in hemophilia patients although the prevalence probably not as high as previous reports.

CONCLUSION

The proportion of decreased bone density in adult hemophilic subjects was 6.3%, with all of them had hemophilia A. Subjects with decreased bone density were younger, had lower BMI, had more substitution therapy, better arthropaty score, and lower incidence of blood transmitted infection compared with subjects with normal bone density.

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