Saboony *et al.*
Egyptian Rheumatology and Rehabilitation (2023) 50:6
https://doi.org/10.1186/s43166-023-00172-2

Egyptian Rheumatology and Rehabilitation

RESEARCH Open Access

Assessment of vascular endothelial growth factor a serum level in pediatric hemophilic arthropathy

Omar Ahmed M. N. Saboony[1], Mona Abdullah El Sebaie[1], Dalia Mohamed Ezz El Din El Mikkawy[1], Iman Ahmed Mohamed Ragab[2] and Hossam Salaheldin Abdelmohsen Labib[1*]

Abstract

Background Children with hemophilia have serious, recurrent joint bleeding that causes disabilities. Regular factor VIII concentrate replacements have not yet completely stopped intra-articular subclinical hemorrhages and permanent joint damage. The prevention of joint damage requires the early detection and management of this hemorrhage. Neoangiogenesis is crucial in the development of synovitis after recurrent hemophilic joint bleeding. This study assessed the level of serum Vascular endothelial growth factor A (VEGF-A) as a vascular biomarker in children with hemophilia A to determine its possible role as a diagnostic biomarker for hemophilic arthropathy.

Result A case–control study with 30 male children who had hemophilia A and 30 healthy controls was conducted. Patients had significantly higher serum VEGF-A levels than the control group (specificity was 70.0% and sensitivity was 83.3%). Hemophilia severity and Hemophilia Joint Health Score had a significant positive correlation with VEGF-A.

Conclusion Children with hemophilia A had significantly higher levels of VEGF-A in their serum. Additionally, VEGF-A had a significant positive correlation with Hemophilia Joint Health Score as well as the severity of the disease. In children with hemophilia A, VEGF-A can be used as a marker for early hemophilic arthropathy detection.

Keywords Vascular endothelial growth factor a, Hemophilia A, Arthropathy, Biomarkers, Pediatric arthropathy

Background

Hemophilia A is an X-linked recessive blood clotting disorder caused by a deficiency or decreased activity of clotting factor VIII (hemophilia A) or IX (hemophilia B). This deficiency increases spontaneous joint bleeding, especially in larger hinged joints. As a result, synovial inflammation and cartilage damage occur, eventually leading to hemophilic arthropathy (HA) [1]. The quantity of the factor determines the severity of the disease, which is classified as mild (factor level 5–40 IU/dL, or 5–40% of normal), moderate (1–5 IU/dL, or 1–5% of normal), and severe (1% of normal) [2]. Recurrent joint bleeding in hemophilia A causes irreversible joint damage, known as HA, which causes significant morbidity in hemophilia A patients. Hemophilia causes radiographic changes such as subchondral cysts, osteoporosis, and accelerated degenerative changes. Edema of the bone marrow, joint effusion or hemorrhage, synovial hypertrophy, and concurrent ligament tears are all possible complications [3]. Clinical examination and imaging are used to detect the progression of arthropathy; however, joint outcome measurements are insufficient for identifying early and subclinical joint damage. Biochemical markers that represent joint turnover have the ability to provide this important information about the joint status [4]. Furthermore, angiogenic factors were discovered to

*Correspondence:
Hossam Salaheldin Abdelmohsen Labib
dr.sam789@yahoo.com; hossam_salah@med.asu.edu.eg
[1] Physical Medicine, Rheumatology and Rehabilitation Department, Ain Shams University, Cairo, Egypt
[2] Pediatrics Medicine Department, Ain Shams University, Cairo, Egypt

be elevated and involved in the pathogenesis of HA. Vascular endothelial growth factor A (VEGF-A) is an angiogenic factor that has anti-apoptotic and mitogenic effects on endothelial cells, increases vascular permeability, and enhances cell migration. It actively contributes to the regulation of normal and pathological angiogenic processes [5]. This study assessed the level of serum VEGF-A as a vascular biomarker in children with hemophilia A to determine its possible role as a diagnostic biomarker for hemophilic arthropathy (HA).

Subjects and methods

A case-control study included 30 hemophilic A children and 30 age and gender matched healthy participants as controls. We recruited the patients from the author's unit between August 2021 and May 2022. Inclusion criteria included boys (aged 4 to 18) diagnosed with Hemophilia A according to World Federation of Hemophilia guidelines for hemophilia management (2020) [2]. Patients who had undergone arthroscopic or chemical synovectomy within the previous 2 years and combined bleeding with other organs were all excluded. The local ethics committee for the Faculty of Medicine authorized the research after receiving informed consent in writing from the participants' legal guardians (FMAUS, MS454/2021). Registered 18 Augest 2021—prospectively registered.

Every patient was subjected to the following:

I *Medical history and clinical examination* with particular attention paid to the number of bleeding episodes in 6 months, the severity of hemophilia, joint pain, and swelling duration.

II *Clinical evaluation of the joint with the Hemophilia Joint Health Score (HJHS):* The HJHS assesses both elbows, knees, and ankles by evaluating and scoring 11 items which include swelling, its duration, axial alignment, muscle atrophy, crepitus, loss of flexion, loss of extension, instability, joint pain, strength, and gait. The highest grade permitted was 148 (total elbow score from 0 to 20, total ankle and knee score from 0 to 26, gait score is separately assessed from 0 to 4), and high values proposed more severe joint damage [6].

Functional assessment using the Functional Independence Score in Hemophilia (FISH): eight activities, including eating, grooming, dressing, chair transfers, squatting, walking, and step-climbing, were evaluated as part of an objective assessment of the participant's ability to perform various tasks. Each activity was given a grade between 1 and 4 based on how much assistance was needed to complete it. The lowest score, 8, denotes the worst function, and the highest score, 32, denotes the best function [7].

VEGF-A serum level assessment (performed on both the patients and control groups):

The concentrations of VEGF-A in serum were determined using an Enzyme-Linked Immunosorbent Assay kit (Shanghai Korean Biotech Co., LTD.). In this test, a 96-well plate with an antibody that is specific for human VEGF-A

Statistical analysis

Version 20.0 of the statistical package for social sciences was used to analyze the recorded data (SPSS Inc., Chicago, IL, USA). The mean and standard deviation were used to express quantitative data (SD). Frequency and percentage were used to express qualitative data. The statistical significance of the difference between more than two means was evaluated using the independent-samples *t* test of significance. The statistical significance of the difference between more than two means was evaluated using the ANOVA test. The strength of the correlation between two sets of variables was evaluated using Pearson's correlation coefficient (*r*) test. ROC curve analysis was used to determine the overall predictiveness of parameters as well as the best cut-off value with the detection of sensitivity and specificity at this cut-off value. The confidence interval was set to 95%, and the acceptable margin of error was set to 5%. As a result, the *P* value was considered significant at the level of ≤ 0.05.

Results

Demographic data

Both the control group and the patients were all men. There were no significant age differences between groups (Tables 1 and 2).

Results of HJHS and FISH score

Total HJHS for the patients was 0 to 28, with a mean and standard deviation of (7.033 ± 7.005). Their total FISH score ranged from 8 to 32, with a mean and standard deviation of 30.767 and 4.423, respectively (Table 3).

Results of VEGF-A level assessment and its correlation with other parameters

The patients with hemophilia A had a significantly higher serum level of VEGF A (ng/L) than the control group (patients were 326 ± 198.192, vs the control group 110.267 ± 100.755, $P < 0.001$) (Table 4).

Serum VEGF-A was found to be higher in more severe types of hemophilia ($P < 0.001$) (Table 5).

VEGF-A had a significant positive correlation with total HJHS ($p = 0.008$) but a non-significant negative

Table 1 Comparison between patients and control groups as regards the age

Age (years)	Group						*t* test		
	Patients			Control			*T*	*P* value	sig
Range	6	–	17	5	–	16	1.769	0.082	NS
Mean ± SD	10.833	±	3.364	9.400	±	2.896			

P value < 0.05 significant and *P value < 0.001* highly significant

Table 2 Demographic date of the patients

		Patients	
		Number	Percent %
Family history	Yes	9	30%
	No	21	70%
Rregular or demand therapy	Regular	24	80%
	Demand	6	20%
Severity of hemophilia	Mild	4	13.3%
	Moderate	3	10%
	Severe	23	76.7%

Table 3 Result of HJHS and FISH scores and their correlation to VEGF in studied patients

	Descriptive data		Correlations†	
			VEGF-A (ng/L)	
	Range	Mean ± SD	*R*	*P* value
HJHS	0–28	17.03 ± 7.05	0.476	0.008*
FISH	8–32	30.7 ± 4.4	− 0.048	0.800

VEGF-A vascular endothelial growth factor A, *FISH* Functional Independence Score in Hemophilia, *HJHS* Hemophilia Joint Health Score

P value < 0.05: significant; *P value < 0.001* highly significant

† Pearson's correlation coefficient (*r*) test

level of 65 pg/mL had a sensitivity of 83.33% and a specificity of 70% (Fig. 1 and Table 7).

Discussion

Hemophilia A is a common hereditary blood disorder. Children born with hemophilia have frequent bleeding episodes, particularly in the muscles and joints. Repeated hemarthroses cause hemophilic arthropathy, which is characterized by the damage of joint cartilage, pain, and a reduced range of motion, as well as severe limitations in physical activity [8], neo-angiogenesis contributes to the progression of hemophilic joint diseases [9].

Biomarkers are helpful for measuring joint turnover as they reveal the pathogenic mechanisms resulting from joint bleeds. In the early stages, these markers could monitor the underline joint pathology more precisely and closely than diagnostic ultrasound and Magnetic resonance imaging [10]. The aim of this study is to assess the level of serum VEGF-A as a vascular biomarker in children with hemophilia A to determine its possible role as a diagnostic biomarker for hemophilic arthropathy (HA).

Angiogenesis is the initial cause of joint pathology that opens the synovium up to more ingredients and inflammatory agents. Therefore, it is important in the development and progression of joint pathology following recurrent joint bleeding [11]. Increasing the level of VEGF-A encourages cell migration and division of vascular endothelial cells, and serves as a key regulator of angiogenesis [12].

In our study, the serum level of VEGF-A in hemophilic A children was statistically significantly higher than in controls. This study reinforces a previous study by Andrawes et al. [13], who noticed a rise in serum VEGF levels in their hemophilic A patients compared to

Table 4 Comparison between patients and control group as regards VEGF-A

VEGF-A (ng/L)	Group						*t* test		
	Patients			Control			*t*	*P* value	Sig
Range	50	–	690	60	–	350	5.315	< 0.001*	HS
Mean ± SD	326	±	198.19	110.267	±	100.755			

P value < 0.05 significant and *P value < 0.001* highly significant, *VEGF-A* vascular endothelial growth factor A

correlation with FISH score ($p = 0.800$) (Table 3). A non-significant negative correlation between VEGF-A and the type of treatment regimen ($p = 0.921$) (Table 6).

ROC curve analysis

In order to distinguish between patients with hemophilia A and healthy boys using serum VEGF-A, a cut-off point

Table 5 Serum VEGF-A was found to be higher in more severe types of hemophilia

		VEGF-A (ng/L)				ANOVA test		
		N	Mean	±	SD	*F*	*P* value	Sig
Severity of hemophilia	Mild	4	57.500	±	9.574	16.459	< 0.001*	HS
	Moderate	3	73.333	±	11.547			
	Severe	23	405.652	±	152.668			
	Total	30	338.571	±	186.877			

P value ≤ *0.05* Significant and *P value* ≤ *0.001* highly significant, *VEGF-A* vascular endothelial growth factor A

Table 6 Comparison between treatment regimens as regards VEGF-A

		VEGF-A (ng/L)				*t* test		
		N	Mean	±	SD	*t*	*P* value	Sig
On regular or on demand	Regular	24	324.167	±	173.178	−0.100	0.921	NS
	Demand	6	333.333	±	299.644			

P value < *0.05* significant and *P value* < *0.001* highly significant, *VEGF-A* vascular endothelial growth factor A

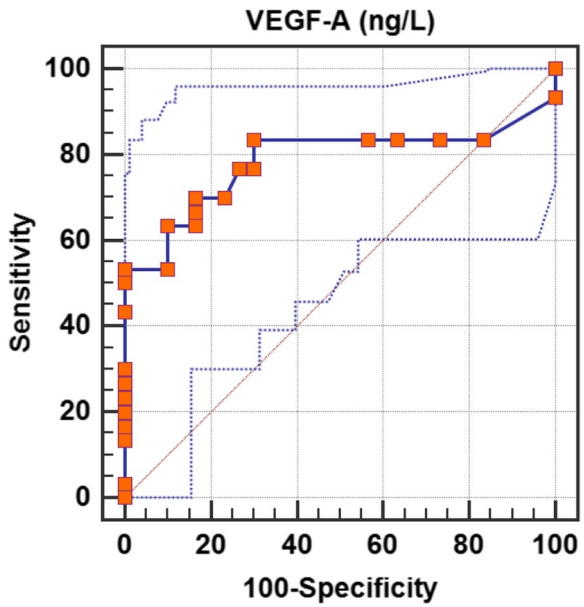

Fig. 1 Receiver operating characteristic curve ROC for VEGF-A as a predictor for HA in hemophilic patients

controls. They came to the conclusion that VEGF was a key mediator of either the inflammatory process or neoangiogenesis in HA. In the synovium, stimulated macrophages and neutrophils produce more VEGF, resulting in neoangiogenesis. Neoangiogenesis allows inflammatory cells to be transported to the inflammatory area. Also, it provides oxygen and nutrients to the inflammatory cells, causing more chemokines and metalloproteinases to be produced, resulting in more inflammation. They recommended the use of VEGF for the early prediction of joint affection in boys with severe hemophilia A [13].

Our results coincide with those of Xu et al. [14], who revealed that hemophilic patients had significantly higher VEGF levels than healthy participants. Patients with joint bleeding had significantly higher levels of VEGF than patients without joint bleeding. Joint bleeding was related to both CRP and VEGF levels in patients with severe hemophilia, which could be used as diagnostic markers to predict joint bleeding [14]. In contrast to Zetterberg et al. [15], who found no significant difference in VEGF levels in plasma and platelets between hemophilic

Table 7 ROC curve between patients and control group

ROC curve between case and control						
	Cutoff	Sens	Spec	PPV	NPV	Accuracy
VEGF-A (ng/L)	> 65	83.33	70.0	73.5	80.8	78.4%

VEGF-A vascular endothelial growth factor A, *ROC* receiver operating characteristic

patients and controls, hemophilic synovial tissue had a significant increase in VEGF-positive cells compared to controls. This disparity, we believe, stems from the fact that we measure VEGF serum levels rather than plasma and platelet levels. Furthermore, the age range of our patients' means ± SD was (10.83 ± 3.364), whereas it was 32 ± 17 years in their study.

Musculoskeletal evaluation is an important part of integrated care for people who have hemophilia. The HJHS is a feasible and dependable method for detecting early joint changes in hemophiliac children and adolescents [16]. In our study, the total HJHS range was 0 to 28, and the mean was (17.03 ± 7.005). Total HJHS and serum VEGF-A had a significant positive correlation, indicating that serum VEGF-A may play a role in HA as a biomarker for severity and was able to monitor joint affection. There was also a highly significant relationship between VEGF-A levels and the severity of hemophilia**.** There was an increase in HJHS among hemophiliac children with hemophiliac arthropathy in our study. Prasetyo et al. [17] discovered that hemophilic patients with HA had an increase in total HJHS, which supports our finding. Similarly, Andrawes et al. [13]. Increase in HJHS among hemophiliac children in our study due to repeated joint bleeding, which results in hemophiliac arthropathy in target joints. This finding is supported by the result of Prasetyo et al. [17] who found that increase in the total HJHS of their hemophilic patients (ranged from 0 to 35) which indicated joint affection. Likewise, Andrawes et al. [13] used HJHS to assess the musculoskeletal condition in their study, with a mean ± score of 4.5 ± 3.0 and a range of 0 to 11. There was a significant positive correlation between total HJHS and serum VEGF-A, demonstrating the significance of neoangiogenesis as an independent mechanism involved in HA.

Our study did not reveal any significant correlation between VEGF and the method of factor treatment. Andrawes et al. [13] found a significant correlation between serum VEGF level and treatment type. This disparity may be due to the difference in sample size, as we had 30 patients while they had 50. Additionally, all of their patients were severe hemophilic patients, whereas our patients were mild, moderate, and severe. Furthermore, the majority of our patients (80%) were on regular therapy, whereas only 62% of their patients were on regular therapy.

The FISH score was established as a performance-based evaluation method to assess functional ability objectively. It can also be used to assess functional independence change after therapeutic intervention [7]. In our research, we found that the total FISH score was (30.7 ± 4.4). In addition, we discovered a non-significant negative correlation with VEGF-A. Because no other studies had been conducted to evaluate the serum level of VEGF and its correlation with FISH score, we had to compare our results with those obtained using FISH by comparing the mean of the score. Our findings were in opposition to those of Kachooei et al. [18], who discovered that the total FISH score was (25.8 ± 3.6). Additionally, Tlacuilo et al. [19] disagreed with the findings of our study in terms of FISH score. Their study involved 60 pediatric patients with FISH scores ranging from (15 to 28) and a mean of (25.8 ± 3.6), all of whom were receiving on-demand treatment for hemophilia. Our rationale is that while 80% of the patients in our study were receiving regular hemophilia treatment, these studies were conducted on a majority of patients receiving on-demand treatment. In addition, their patients were larger than ours.

ROC curve analysis in our study revealed a cut-off point value of more than 65 ng/L with a sensitivity of 83.3% and specificity of 70%. This strongly suggests that serum VEGF-A has the ability to distinguish between the patients and controls. The sensitivities and specificities of VEGF-A in detecting hemophilic arthropathy were 78% and 88%, respectively in the study by Andrawes et al. [13], and similarly, Xu et al. [14] found that the ROC curve produced a sensitivity of 82.8% and a specificity of 68.3%, which was also close to our results.

The following are some of the study's limitations: First, we did not compare and correlate the serum VEGF A level with the radiological modality that is typically used to detect HA. Second, the small number of study participants.

Conclusion

Children with hemophilia A had significantly higher levels of VEGF-A in their serum. Additionally, VEGF-A had a significant positive correlation with HJHS as well as the severity of the disease. In children with hemophilia A, VEGF-A can be used as a marker for early HA detection.

Abbreviations

FMASU	Faculty of Medicine, Ain Shams University
FISH	Functional Independence Score in Hemophilia
HA	Hemophilic arthropathy
HJHS	Hemophilia Joint Health Score
ROC	Receiver operating characteristic
VEGF-A	Vascular endothelial growth factor A

Acknowledgements

Not applicable.

Authors' contributions

OA was responsible for the following tasks: data collection, writing the first draught, reviewing it, contributing to the work's design, clinical work, and data interpretation. MA completed the following tasks: placed the study design, followed the patients, and revised the draught paper. DM did the following: provided an idea, formal evaluation, data collection, editing and reviewing the draught, clinical work, data interpretation, and revising. IA participated in conceptualization and formal analysis, and revised the draft paper. HL did the

following: data collection, writing the first draught, editing, and reviewing it; contributing to the work's design; and participating in conceptualization, formal analysis, data interpretation, and revision. All authors read and approved the final manuscript.

Funding
No funding was received to this article.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by Ain Shams University, Faculty of Medicine Research Ethics Committee (REC) FWA 000017585. (FMAUS, MS454/2021. A written informed consent was obtained from the participants' legal guardians sharing in the study.

Consent for publication
Written consent was taken from the participants' legal guardians and available upon request.

Competing interests
The authors declare that they have no competing interests.

Received: 30 December 2022 Accepted: 20 January 2023
Published online: 30 January 2023

References

1. van Vulpen LFD, Holstein K, Martinoli C (2018) Joint disease in haemophilia: pathophysiology, pain and imaging. Haemophilia Suppl 6:44–9
2. Srivastava A, Santagostino E, Dougall A et al (2020) WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia 26(Suppl 6):1–158. https://doi.org/10.1111/hae.14046
3. Maclachlan J, Gough-Palmer A, Hargunani R, Farrant J, Holloway B (2009) Haemophilia imaging: a review. Skeletal Radiol 38(10):949–57. https://doi.org/10.1007/s00256-008-0586-5. (Epub 2008 Sep 20. PMID: 18807029)
4. Van Bergen EDP, van Vulpen LFD, Schutgens REG, Mastbergen SC, Lafeber FPJG (2021) Biochemical marker research in hemophilic arthropathy: a systematic review. Blood Rev 47:100781
5. Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, Moldovan IM, Roman AL, Mihu CM (2018) Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. Rom J Morphol Embryol 59(2):455–467 (PMID: 30173249)
6. Feldman BM, Funk SM, Bergstrom BM, Zourikian N, Hilliard P, van der Net J, Engelbert R, Petrini P, van den Berg HM, Manco-Johnson MJ, Rivard GE, Abad A, Blanchette VS (2011) Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. Arthritis Care Res (Hoboken) 63(2):223–230
7. Poonnoose PM, Thomas R, Keshava SN, Cherian RS, Padankatti S, Pazani D, Kavitha ML, Devadarasini M, Bhattacharji S, Viswabandya A, John JA, Macaden AS, Mathews V, Srivastava A (2007) Psychometric analysis of the Functional Independence Score in Haemophilia (FISH). Haemophilia 13(5):620–626
8. Rendo P, Shafer F, Korth-Bradley JM et al (2013) Factors that influence the bleeding phenotype in severe hemophilic patients. Blood Coagul Fibrinol 24(7):683–690
9. Acharya SS, Kaplan RN, Macdonald D, Fabiyi OT, DiMichele D, Lyden D (2010) Neoangiogenesis contribute to the development of hemophilic synovitis. Blood 117(8):2484–93. https://doi.org/10.1182/blood-2010-05-284653. (Epub 2010 Dec 16. PMID: 21163925; PMCID: PMC3317791)
10. Sasaki C, Hiraishi T, Oku T et al (2019) Metabolomic approach to the exploration of biomarkers associated with disease activity in rheumatoid arthritis. PLoS ONE 14:e0219400
11. Forsyth AL, Rivard GÉ, Valentino LA, Zourikian N, Hoffman M, Monahan PE, Van Meegeren ME, Forriol F (2012) Consequences of intra-articular bleeding in haemophilia: science to clinical practice and beyond. Haemophilia Suppl 4:112–9. https://doi.org/10.1111/j.1365-2516.2012.02835.x. (PMID: 22726093)
12. Hamilton JL, Nagao M, Levine BR, Chen D, Olsen BR, Im HJ (2016) Targeting VEGF and its receptors for the treatment of osteoarthritis and associated pain. J Bone Miner Res 31(5):911–24. https://doi.org/10.1002/jbmr.2828. (Epub 2016 Apr 8. PMID: 27163679; PMCID: PMC4863467)
13. Andrawes NG, Saker HM, Salah El-Din NY, Abd Elhakim Hussain M (2020) Tissue-inhibitors of metalloproteinase-1 and vascular-endothelial growth-factor in severe haemophilia A children on low dose prophylactic recombinant factor VIII: Relation to subclinical arthropathy. Haemophilia 26(4):607–614. https://doi.org/10.1111/hae.14041. (Epub 2020 May 23. PMID: 32445517)
14. Xu H, Zhong R, Wang K, Li X, Zhao Y, Jiang J, Si S, Sun L (2020) Diagnostic values of inflammatory and angiogenic factors for acute joint bleeding in patients with severe hemophilia A. Clin Appl Thromb Hemost Jan-Dec 26:1076029619892683. https://doi.org/10.1177/1076029619892683. PMID:31996013;PMCID:PMC7098200
15. Zetterberg E, Palmblad J, Wallensten R, Morfini M, Melchiorre D, Holmström M (2014) Angiogenesis is increased in advanced haemophilic joint disease and characterised by normal pericyte coverage. Eur J Haematol 92(3):256–62. https://doi.org/10.1111/ejh.12227. (Epub 2013 Nov 25. PMID: 24168433)
16. Kuijlaars AR, der Net JV, Feldman BM, Aspdahl M, Bladen M, Boer WD, Matlary ED, Funk SM, Hilliard P, John JA, Kempton CL, Kleijn PD, Petrini P, Poonnoose P, Thomas S, Timmer MA, Trakymiene SS, Vlimmeren LV, Fischer K (2020) Evaluating international Haemophilia Joint Health Score (HJHS) results combined with expert opinion: Options for a shorter HJHS. Haemophilia 26(6):1072–1080. https://doi.org/10.1111/hae.14180
17. Prasetyo M, Moniqa R, Prihartono A, Setiawan SI (2021) Correlation between Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) score and Hemophilia Joint Health Score (HJHS) in patients with hemophilic arthropathy. PLoS One 16(4):e0248952. https://doi.org/10.1371/journal.pone.0248952. (PMID: 33826621; PMCID: PMC8026024)
18. Kachooei AR, Heidari A, Divband G, Zandinezhad ME, Mousavian A, Farhangi H, Aminzadeh B, Zarifian A, Bagheri F, Badiei Z (2020) Rhenium-188 radiosynovectomy for chronic haemophilic synovitis: evaluation of its safety and efficacy in haemophilic patients. Haemophilia 26(1):142–150. https://doi.org/10.1111/hae.13880. (Epub 2019 Dec 9. PMID: 31814241)
19. Tlacuilo-Parra A, Morales-Zambrano R, Tostado-Rabago N, Esparza-Flores MA, Lopez-Guido B, Orozco-Alcala J (2008) Inactivity is a risk factor for low bone mineral density among haemophilic children. Br J Haematol 140(5):562–7. https://doi.org/10.1111/j.1365-2141.2007.06972.x. (PMID: 18275434)

Publisher's Note