Long-term impact of joint bleeds in von Willebrand disease: a nested case-control study

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ABSTRACT

Patients with severe von Willebrand disease (VWD) may develop arthropathy after joint bleeds. Information on its prevalence and severity is limited. We aimed to assess the occurrence and severity of arthropathy in VWD and its impact on daily life. VWD patients with and without verified joint bleeds were matched for age, sex and Factor VIII level or von Willebrand Factor activity in a nested case-control study within the Willebrand in the Netherlands study. Assessments included the Hemophilia Joint Health Score (0-124), Pettersson score (0-13 per joint X-ray), Hemophilia Activity List score (0-100), joint pain (Visual Analog Scale 0-10), and the Impact on Participation and Autonomy questionnaire (0-20). Arthropathy was defined as a Hemophilia Joint Health Score of 10 or higher, or a Pettersson score over 3 of at least one joint. We included 48 patients with verified joint bleeds (cases) and 48 controls: 60% males, mean age 46 years (range 18-80), median von Willebrand Factor activity 5 *versus* 8 IU/dL and Factor VIII 24 *versus* 36 IU/dL. Arthropathy occurred in 40% of the cases *versus* 10% of the controls ($P<0.01$). The cases reported more functional limitations compared to the controls (median Hemophilia Activity List score: 88 *vs.* 100, $P<0.01$). Arthropathy was related to joint pain and less social participation (Visual Analog Scale>3: 13 of 19 *vs.* 3 of 28, $P<0.01$, and median score on the participation questionnaire 6.1 *vs.* 0.9, $P<0.01$). In conclusion, arthropathy occurs in 40% of VWD patients after joint bleeds and is associated with pain, radiological abnormalities, functional limitations, and less social participation (*Dutch trial register: NTR4548*).

Introduction

Von Willebrand disease (VWD) is a congenital bleeding disorder with a population prevalence of 0.6-1.3%.[1] VWD is caused by a deficiency (type 1), dysfunction (type 2) or absence (type 3) of von Willebrand factor (VWF) and is mainly associated with mucocutaneous bleeding and menorrhagia. Joint bleeds also occur in

VWD, predominantly in severely affected patients with concomitant low Factor VIII levels (FVIII).[2] Low FVIII occurs because its chaperone protein VWF, which protects FVIII from degradation, is (partly) missing. In hemophilia patients with FVIII or FIX deficiency, recurrent joint bleeds are the main cause of pain and functional limitations, which is known as hemophilic arthropathy.[3] Joint bleeding occurs in half of the patients with type 3 VWD and in 5-10% of moderate and severe type 1 and type 2 VWD patients.[4] However, hardly any information is available on the existence and severity of blood-induced arthropathy in VWD.[5]

There are no data on joint health and the influence of arthropathy on daily life activities in VWD.[5] In the Willebrand in the Netherlands (WiN) study, almost a quarter of the patients reported joint bleeds. These joint bleeds appeared to have a negative impact on health-related quality of life and joint integrity, according to self-reported and retrospective medical file data.[4] To describe and measure health and disability, the World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF) standard has been endorsed. This standard focuses on impact rather than cause of disability, including functioning and participation, as well as environmental and personal factors.[6] It is, therefore, useful to study the consequences of joint bleeds in VWD within this broad ICF perspective.

It is important to assess joint outcome after joint bleeds in order to find and implement optimal treatment strategies that prevent or diminish arthropathy.[7] The primary objective of this nested case-control study is to assess both occurrence and severity of arthropathy in patients with VWD after joint bleeds (ICF domain on body structure and function), compared to VWD patients without clinically overt joint bleeding, and to compare self-perceived functional abilities and social participation (ICF domains on activity and participation) between these two groups. The secondary objective is to explore a possible association between arthropathy and environmental and personal factors (ICF contextual factors).

Methods

Ethical approval was obtained from the medical ethical committee of the University Medical Center Utrecht, the Netherlands (*Dutch trial register: NTR4548*).

Study population

A nested case-control study was performed within the national cohort WiN study between August 2013 and July 2015. Cases were selected from this WiN study cohort, based on verified joint bleeds (VWD-JB patients).[2,4] Adult patients with VWD according to the definitions of the WiN study (historically lowest VWF activ-

Table 1. Baseline characteristics of 48 von Willebrand disease patients treated for joint bleeds and 48 controls.

		VWD-JB patients n=48	VWD controls n=48
Sex Females (n, %) 19 (40%) 19 (40%)	Males (n, %) 29 (60%) 29 (60%)		
Age (y)	Males (median, range)	45 (18-78)	48 (20-80)
	Females (median, range)	48 (18-74)	47 (18-73)
Type VWD*	1 (n, %)	8 (17%)	20 (42%)
	2 (n, %)	21 (44%)	25 (52%)
	2A (n)	15	17
	2B (n)	5	5
	2M (n)	0	2
	2N (n)	1	1
	3 (n, %)	19 (39%)	3 (6%)
Levels (IU/dL; med, IQR)†	VWF:Ag	13 (1-36)	22 (12-28)
	VWF:Act	5 (0-14)	8 (3-30)
	FVIII:C	24 (3-46)	36 (24-54)
Cumulative n. of joint bleeds‡	No. JB (n, %)		34 (71%)
	Once	8 (17%)	9 (19%)
	2-5	13 (27%)	5 (10%)
	6-10	6 (12%)	–
	>10	21 (44%)	–
Joint bleed treatment	VWF concentrate	44 (92%)	–
	Desmopressin	10 (21%)	–
Relevant comorbidity¶	n (%)	3 (6%)	5 (10%)

VWD: von Willebrand disease; JB: joint bleed; n.: number; y: years; med: median; IQR: 25-75% interquartile range; IU/dL: units per deciliter; VWF:Ag: von Willebrand factor antigen level; VWF:Act: VWF activity level; FVIII:C: Factor VIII level. *Based on centrally determined [n=94, data from the Willebrand in the Netherlands (WiN) study] or historic VWD type (n=4, as known in the hemophilia treatment center). †Centrally measured: based on 72 patients for whom plasma was available at times of WiN inclusion and after exclusion of pregnant patients and those who had received clotting factor concentrate (CFC) or desmopressin less than 72 hours before the laboratory assessment. ‡Based on medical file data and information provided by the participants during the study visit. ¶5 controls (2 gout, 1 psoriatric arthritis, 1 congenital flexion contraction elbows, 1 elbow fracture) and 3 patients (1 septic arthritis knee, 1 psoriatric arthritis, 1 ankle fracture).

ity <30 IU/dL[8]) from all hemophilia treatment centers in the Netherlands were eligible. Joint bleeds were verified if we found medical file documentation of treatment with clotting factor or desmopressin for at least one joint bleed. VWD patients without prior treated joint bleeds were included as controls (VWD controls). These VWD controls were primarily selected from the WiN cohort and matched 1:1 to the VWD-JB patients for age, sex and, if possible, on FVIII or otherwise on VWF activity (*Online Supplementary Table S1*).[4] The goal of the case-control design was to distinguish joint bleed-related arthropathy from other causes of joint deterioration, such as age-related osteoarthritis or subclinical joint bleeding. The absence of documented treatment for joint bleeds in the medical files at inclusion was regarded as "no clinically relevant joint bleeds". Exclusion criteria were inability to give informed consent, recent joint bleeding without complete recovery, and lack of available medical files. Restricted motion due to another musculoskeletal disorder [e.g. gout or rheumatoid arthritis (RA), excluding age-related osteoarthritis] was regarded as relevant musculoskeletal comorbidity.

Primary outcome parameters for joint health assessment

Participants were invited for a half-day visit to the hemophilia treatment center, and underwent physical examination and measurements. Joint X-rays were performed. One experienced physiotherapist conducted the Hemophilia Joint Health score (HJHS, 0-30/joint, total range 0-124) in all participants. The HJHS has been developed to analyze joint outcome in hemophilia.[9] It is an 11-item scoring tool to assess joint health of elbows, knees and ankles that includes range of motion, crepitus on motion, swelling, muscle atrophy, pain, joint strength, and global gait. Range of motion reference values to calculate the HJHS were derived from Soucie *et al.*[10] For the analyses, we dichotomized the HJHS≥10 as 'arthropathy' based on our interobserver reliability results in VWD and because this cut-off value has also been used in hemophilia to define arthropathy.[11,12]

X-rays were taken from all ankles, knees and elbows with prior bleeds, the contralateral joints of the VWD-JB patients, and from the ipsilateral joints of the matched VWD controls. X-rays were scored by one radiologist according to Pettersson (PS, 0-13 points per joint), using a consensus atlas.[13] We defined a PS>3 of one or more joints as 'radiological arthropathy', based on the Limits of Agreement of the PS joint in hemophilia patients.[14]

All participants were asked to complete the Hemophilia Activity List (HAL, normalized score: 0-100). This questionnaire has been developed to analyze self-perceived functional abilities in hemophilia.[15,16] The HAL total and three component sub scores ['upper extremity activities' (HAL upper), 'basic lower extremity activities' (HAL lowbas) and 'complex lower extremity activities' (HAL lowcom)] were calculated. A score of 100 means no func-

Table 2. Arthropathy, functional abilities and contextual factors compared between the von Willebrand disease-joint bleeds (VWD-JB) patients and VWD controls.

		VWD-JB patients n=48	VWD controls n= 48	*P*
Mean CFC use*	Median IU FVIII/kg/y (IQR)	51 (1.3-188)	0 (0-0)	<0.01
CFC prophylaxis¶	n (%)	13 (27%)	1 (2%)	<0.01
because of JB	n (%)	11 (23%)	–	
Surgery in large joints‡	Overall n (%)	22 (46%)	10 (21%)	<0.01
	Because of JB n (%)	9 (19%)	–	–
BMI	Mean (range)	26 (18-49)	25 (17-37)	0.28
HJHS total	Median (IQR)	5 (1-15)	1.5 (0-5)	<0.01
HJHS ≥ 10	n (%)	19 (40%)	5 (10%)	<0.01
PS >3	n (%)	12 (25%)	2 (4%)	<0.01
PS >3 ankle	n (%)	9 (19%)	1 (2%)	<0.01
PS >3 knee	n (%)	5 (10%)	1 (2%)	0.09
PS >3 elbow	n (%)	2 (4%)	0	0.15
HAL total	Median (IQR)	88 (69-98)	100 (87-100)	<0.01
HAL upper	Median (IQR)	93 (82-100)	100 (91-100)	0.01
HAL lowbas	Median (IQR)	87 (53-100)	100 (86-100)	<0.01
HAL lowcom	Median (IQR)	80 (44-100)	100 (77-100)	<0.01
HAL total <95	n/total (%)	32/48 (67%)	16/46 (35%)	<0.01
Figure 8 (sec)				
Preferred speed	Median (range)	15 (10-25)	14 (11-24)	0.24
Maximum speed	Median (range)	11 (8-20)	10 (8-20)	0.71
Joint pain§	Overall n (%)	29 (60%)	23 (48%)	0.22
VAS mean **	Median (IQR)	3.5 (1-5.7)	2.1 (1.4-4.7)	0.39
VAS >3 joint	n (%)	17 (35%)	9 (19%)	0.07
D-AIMS2affect	Anxiety median (range)	13 (7-24)	12 (5-22)	0.33
	Mood median (range)	12 (5-22)	9 (5-17)	0.87
IPA	Sum score median (range)	1.93 (0-11)	0.97 (0-14)	0.14

VWD: von Willebrand disease; JB: joint bleeds; CFC: clotting factor concentrate; IU: units; IQR: 25-75% interquartile range; BMI: Body Mass Index; HJHS: Hemophilia Joint Health Score; VAS: Visual Analog Scale pain scale (total range 0-10 cm); PS: Pettersson score; sec: seconds; IPA: Impact on Participation and Autonomy questionnaire. HAL: Hemophilia Activity List questionnaire; DAIMS2affect: Dutch Arthritis Impact Measurement Scales-2. *In units Factor VIII/kg/year calculated over five years (2005-2009), based on medical file data (n=90). ¶Currently or in the past; defined as at least 1 regular CFC infusion per week for at least 45 consecutive weeks. §Chronic joint pain, not related to a recent joint bleed. ‡Knee, ankle, elbow, shoulder or hip surgery. **N=27 patients and n=21 controls.

tional limitations. For statistical analyses, the total HAL score was dichotomized into 'no functional limitations' (>95) and 'some functional limitations' (<95). This threshold was chosen as it was the median HAL score in patients with severe hemophilia.[7] We recently validated both the HJHS and HAL in VWD.[12]

Secondary outcome parameters

All participants were asked to perform the modified Figure 8 walk test[17] and to complete the Impact on Participation and Autonomy questionnaire (IPA, 31 items with 0-4 points per item on five domains: 0=very good, 4=bad; IPA sum score of mean scores per item range 0-20).[16,18] Participants were also requested to complete the affect component of the Dutch Arthritis Impact Measurement Scales-2 (D-AIMS2affect), asking questions on anxiety and depression ranging from 5 (never) to 25 (always) for both components, as well as the McGill Pain Questionnaire-Dutch Language Version.[19,20] The mean Visual Analog Score (VAS 0-10 cm) for pain was calculated from the minimum and maximum VAS reported in this questionnaire. A mean VAS of more than 3 in joints (chronic joint pain, not related to a recent joint bleed) was considered as clinically-relevant joint pain. Body Mass Index (BMI) was calculated after measuring body weight and height during the study visit. Data on the cumulative number of joint bleeds, history of joint surgery, use of prophylaxis (defined as at

Table 3. Characteristics, functional abilities and contextual factors compared within the von Willebrand disease-joint bleed (VWD-JB) patients with *versus* without arthropathy (HJHS ≥10 or PS >3 of one or more joints).

		VWD-JB and arthropathy n=19	VWD-JB no arthropathy n=29	*P*
Sex	Males (n,%)	7 (37%)	22 (76%)	<0.01
	Females (n,%)	12 (63%)	7 (24%)	
Age (y)	(median, range)	50 (28-64)	44 (18-78)	0.38
VWD subtype	Type 1	3	5	0.90
	Type 2	4	17	0.01
	Type 3	12	7	0.01
Levels (IU/dL; med, IQR)†	VWF:Ag	1 (0-50)	13 (7-30)	0.75
	VWF:Act	0 (0-19)	6 (0-12)	0.90
	FVIII:C	5 (1-51)	26 (10-42)	0.36
JB sites & cum n.	n (%)			
Elbow		6 (32%)	12 (41%)	
Elbow >5 JB		2 (11%)	0	0.07
Knee		13 (68%)	25 (86%)	
Knee >5 JB		4 (21%)	3 (10%)	0.30
Ankle		16 (84%)	21 (72%)	
Ankle >5 JB		13 (68%)	6 (21%)	<0.01
Mean CFC use*	Median IU FVIII/kg/y (IQR)	343 (79-821)	18 (0-73)	<0.01
CFC prophylaxis¶	n (%)	12 (63%)	1 (3%)	<0.01
because of JB	n (%)	11 (58%)	0	
Surgery in large joints‡	Overall n (%)	12 (63%)	19 (66%)	0.05
	Because of JB n (%)	9 (47%)	0	<0.01
HJHS total	Median (IQR)	16 (14-26)	2 (0.3-4)	<0.01
HAL total	Median (IQR)	70 (49-78)	95 (88-100)	<0.01
HAL upper	Median (IQR)	88 (71-93)	100 (91-100)	<0.01
HAL lowbas	Median (IQR)	50 (37-83)	97 (87-100)	<0.01
HAL lowcom	Median (IQR)	53 (24-71)	89 (73-100)	<0.01
HAL total <95	n/total (%)	32/48 (67%)	16/46 (35%)	<0.01
Figure 8 (sec)				
Preferred speed	Median (range)	16 (15-20)	14 (13-15)	<0.01
Maximum speed	Median (range)	12 (11-13)	9.7 (9.2-11)	<0.01
Joint pain§	Overall n (%)	17 (89%)	12 (41%)	<0.01
VAS mean **	Median (IQR)	3.5 (3.1-6.3)	0.3 (0.0-1.1)	<0.01
VAS >3 joint	n (%)	13 (68%)	4 (14%)	<0.01
D-AIMS2affect	Anxiety median (range)	13 (10-17)	13 (10-16)	0.90
	Mood median (range)	10 (8-12)	9 (7-11)	0.14
IPA¥	Sum score median (range)	6.1 (2.5-8.6)	0.9 (0-2.4)	<0.01

VWD: von Willebrand disease; JB: joint bleeds; y: year; IQR: interquartile range; cum: cumulative; CFC: clotting factor concentrate; IU: units; n: number: HJHS: Hemophilia Joint Health Score; HAL: Hemophilia Activity List questionnaire; VAS: Visual Analog Scale pain scale (total range 0-10 cm). *In units factor VIII/kg/year calculated over five years (2005-2009), based on medical file data (n=44). §or in the past; defined as at least 1 regular CFC infusion per week for at least 45 consecutive weeks. †Centrally measured: based on 34 patients of whom plasma was available at time of Willebrand in the Netherlands (WiN) study inclusion and after exclusion of pregnant patients and those who had received CFC or desmopressin less than 72 hours before the laboratory assessment. §Chronic joint pain, not related to a recent joint bleed. ‡Knee, ankle, elbow, shoulder or hip surgery. **Based on n=17 arthropathy patients and n=26 patients without arthropathy. ¥N=12 and n=27, respectively; med: median; sec: seconds; DAIMS2affect: Dutch Arthritis Impact Measurement Scales-2.

least 1 regular clotting factor infusion per week for at least 45 consecutive weeks, currently or in the past), and total clotting factor use (in units factor VIII/kg/year calculated over 5 years), were retrieved from the medical files and verified by the principal investigator (KG) by asking the participants during the study visit. The cumulative lifetime number of joint bleeds was categorized as a history of 0, 1, 2-5, 6-10 or >10 joint bleeds, based on medical file data and verified by asking the participants during the study visit.

Sample size

A sample size of 50 VWD-JB patients and 50 VWD controls would be sufficient to detect a difference in joint function of 8 points in the HJHS, with a power of 80%, and significance level of 5% (2-sided). When the inter-rater variability is taken into account, differences of more than 7-10 points in the total HJHS are likely to represent clinically significant differences.[12,21,22] With a sample size of 50 in each group we would be able to detect a difference of 17% in the proportion of patients with 'radiological arthropathy' and with 'some functional limitations', with a power of 80% and significance level of 5% (1-sided) based on an estimated prevalence of 5% in the control group.

Statistical analysis

For statistical analysis, we used IBM SPSS v.23. To evaluate normal distribution of continuous scores, we used Q-Q plots. Mann-Whitney U and χ^2 tests were used to compare continuous values and proportions, respectively. To explore whether BMI, relevant musculoskeletal comorbidity, and anxiety or mood (D-AIMS2affect) could explain a difference in HJHS between the VWD-JB patients and VWD controls, we used multivariable negative binomial regression analysis because of the skewed distribution and excess of zeros of the HJHS on its continuous scale.[23] Multivariable logistic regression analysis was performed to explore whether these determinants could explain possible differences in the occurrence of 'radiological arthropathy' and functional limitations (PS>3 and HAL total <95 as dependent variable, respectively). We used logistic regression analysis to explore whether FVIII, type 3 VWD, higher age, age at the first joint bleed, or the cumulative number of joint bleeds were associated with arthropathy (HJHS≥10 or PS>3) within the VWD-JB group and whether arthropathy was associated with clinically relevant joint pain (VAS mean >3) within the whole study cohort.

Table 4. Associations between the Hemophilia Joint Health Score (HJHS), Pettersson Score (PS) and Hemophilia Activity List (HAL) and co-variables. A. Among 48 von Willebrand disease-joint bleed (VWD-JB) patients compared to 48 VWD controls (independent variable).

Dependent variable	Co-variable	Rate ratio	95% CI	*P*
HJHS	–	2.5	1.6-3.9	<0.01
	BMI	2.4	1.6-3.8	<0.01
	D-AIMS2-affect	2.9	1.9-4.7	<0.01
	Relcom*	2.8	1.8-4.3	<0.01
		Odds ratio		
PS >3	–	7.7	1.6-36	0.01
	BMI	7.7	1.6-37	0.01
	D-AIMS2-affect	8.8	1.8-43	<0.01
	Relcom*	8.5	1.7-42	<0.01
HAL <95	–	3.8	1.6-8.8	<0.01
	BMI	3.6	1.5-8.6	<0.01
	D-AIMS2-affect	4.6	1.9-12	<0.01
	Relcom*	4.0	1.7-9.4	<0.01

B. Among 48 VWD-JB patients: exploration of possible predictors of arthropathy.

Dependent variable	Co-variable	Odds ratio	95% CI	*P*
HJHS ≥10	FVIII <10 IU/dL[¥]	4.6	1.3-16	0.02
	Type 3 VWD	5.1	1.5-18	0.01
	Type 3 VWD & FVIII[¥]	6.9	0.8-57	0.07
	Age	1.0	1.0-1.1	0.28
	Age 1[th] JB<10 y	2.2	0.7-7.4	0.19
	No. joint bleeds[#]	2.2	1.2-4.0	0.01
	No. joint bleeds[#] & FVIII[¥]	2.1	1.0-4.1	0.04
	> 5 joint bleeds in at least one joint	7.9	2.0-31	<0.01
PS >3	FVIII <10 IU/dL[¥]	10	1.9-53	<0.01
	Type 3 VWD	7.8	1.8-35	<0.01
	Type 3 VWD & FVIII[¥]	6.8	0.6-84	0.14
	Age	1.0	1.0-1.1	0.34
	Age 1[th] JB <10 y	3.8	1.0-15	0.06
	No. joint bleeds[#]	3.9	1.4-11	<0.01
	No. joint bleeds[#] & FVIII[¥]	3.4	1.2-10	0.02
	> 5 joint bleeds in at least one joint	17	2-149	0.01

CI: Confidence Interval; HJHS: Hemophilia Joint Health Score; no.: number; PS: Pettersson score; HAL: Hemophilia Activity List questionnaire; FVIII: historically lowest Factor VIII level; D-AIMS2: Dutch Arthritis Impact; JB: joint bleed; Relcom: relevant comborbidity. BMI: Body Mass Index. *Possible restricted motion due to a musculoskeletal disorder for other medical reasons (excluding age-related osteoarthritis). [¥]Historically lowest FVIII level. [#]Cumulative number of joint bleeds categorized (see Table 1).

Results

Baseline characteristics

In total, 119 patients were screened for participation: 19 patients did not want to participate and 4 were excluded on the basis of the exclusion criteria (n=1) or because they did not meet the inclusion criteria (n=3). A total of 48 VWD-JB patients and 48 VWD controls were included with a mean age of 46 years (range 18-80). Most patients had participated actively in the WiN study (95%: 44 of 48 VWD-JB patients and 47 of 48 VWD controls).[2] Baseline characteristics are presented in Table 1. Despite matching, the median FVIII and VWF levels were lower in the VWD-JB group, compared to the VWD control group (Table 1 and *Online Supplementary Table S1*). This was due to the wide range in age and clotting factor levels within the original WiN cohort, the low correlation between VWF and FVIII levels, and the relatively limited size of 804 subjects.[2] Furthermore, due to the matching of clotting factor levels instead of subtype, more VWD-JB patients had type 3 VWD (19 *vs.* 3 VWD controls, *P*<0.01) (Table 1).

Body structure and function: occurrence and severity of arthropathy

The VWD-JB patients were four times more likely to have developed arthropathy compared to the VWD controls (HJHS≥10 or PS>3 of one or more joints: OR 3.8, 95%CI: 1.4-10). This difference became somewhat stronger after correcting for the unverified joint bleeds in the control group (OR 6.8, 95%CI: 1.8-25). Arthropathy, as detected by HJHS≥10, occurred in 40% of the VWD-JB patients compared to 10% of the VWD controls (OR 5.8 95%CI: 2.0-17, *P*<0.01). VWD-JB patients had more severe and more often radiological joint abnormalities compared to the controls, especially in the ankles (*Online Supplementary Table S2*). Arthropathy based on X-rays (PS>3 of one or more joints) was found in 25% of the VWD-JB patients compared to 4% of the VWD controls (OR 7.7 95%CI: 1.6-37, *P*=0.01). None of the VWD-JB patients had a PS>3 in a contralateral joint without prior bleeds.

Self-perceived functional abilities and Figure 8 walk test

VWD-JB patients reported more functional limitations in the HAL, compared to the VWD controls (median HAL total score 88 *vs.* 100) (Table 2). Some functional limitations (HAL total score <95) were reported by 67% of the VWD-JB patients compared to 35% of the controls (HAL total <95, OR 3.8; 95%CI: 1.6-8.8, *P*<0.01). No significant difference in performance according to the modified Figure 8 walk tests was found between the VWD-JB patients and VWD controls (Table 2). However, the VWD-JB patients with arthropathy did perform worse on the Figure 8 test compared to those without arthropathy (Table 3).

IPA, environmental and personal factors, joint pain

No significant differences in the IPA score (participation questionnaire) and level of anxiety or mood were found between the VWD-JB patients and VWD controls (Table 2). However, the VWD-JB patients with arthropathy had a lower score on the IPA compared those without arthropathy, corresponding to less social participation (Table 3).

Clotting factor prophylaxis because of joint bleeds was used by 58% (11 of 19) of the VWD-JB patients with arthropathy (HJHS≥10). BMI, relevant musculoskeletal comorbidity or mood/anxiety did not influence the difference in arthropathy between the VWD-JB patients and VWD controls in multivariable analysis (Table 4A).

Clinically relevant joint pain (VAS mean >3 of ≥1 joints) was reported by 36% of the VWD-JB patients compared to 19% of the VWD controls (OR 2.4 95%CI:0.9-6.1, *P*=0.07) (Table 2). Within the VWD-JB patients, arthropathy HJHS≥10 was strongly associated with clinically relevant joint pain (OR 18 95%CI: 3.9-84, *P*<0.01). Arthropathy PS>3 showed a weaker association with clinically relevant joint pain in the VWD-JB patients (OR 3.6 95%CI: 0.93-14, *P*=0.06). Fifty-nine percent (10 of 17) of the VWD-JB patients with clinically relevant joint pain used or had used pain medication for joint pain.

Predictors of arthropathy

Within the VWD controls, the patients with arthropathy HJHS≥10 were significantly older compared to the VWD controls with HJHS<10 (median age 63 *vs.* 46 years, *P*=0.03). In contrast, this age difference was not found within the VWD-JB patients (median age 50 in the VWD-JB patients with arthropathy *vs.* 44 in those without arthropathy, *P*=0.38) (Table 3). More females than males had arthropathy within the VWD-JB patients (Table 3). The occurrence of arthropathy within the VWD-JB patients was associated with the cumulative number of joint bleeds. A low FVIII level less than 10 IU/dL at VWD diagnosis (in all 19 type 3, one type 2, and 3 type 1 VWD-JB patients) was also associated with the occurrence of arthropathy. Type 3 VWD was associated with arthropathy, but not independent from FVIII levels (Table 4B). Patients who had their first joint bleed under the age of 11 years showed a trend towards the occurrence of 'radiological arthropathy' more often compared to the VWD-JB patients who had their first joint bleed over ten years of age (OR 3.8; 95%CI: 1.0-15, *P*=0.06). The VWD-JB patients who had a history of more than 5 joint bleeds in at least one joint (n=25 of 48) were also significantly more likely to have developed arthropathy (Table 4B). In a logistic regression model, the difference in the occurrence of arthropathy between the patients and controls was dependent on bleeding and not on FVIII levels: after adjustment for a history of more than 5 joint bleeds in at least one joint the OR changed from 3.8 to 1.8 (95%CI: 1-12, *P*=0.36), but it remained stable after adjustment for historically lowest FVIII level at 3.5 (95%CI: 1.3-9.5, *P*=0.02).

Discussion

This nested case-control study demonstrates that 40% of patients with VWD and documented treatment for joint bleeds (VWD-JB patients) have arthropathy at physical examination (HJHS ≥10) and 25% 'radiological arthropathy' of ankles, knees or elbows (PS>3). Arthropathy occurred significantly less often in matched patients with VWD who had never received treatment for a joint bleed (10% HJHS≥10 and 4% PS>3). Arthropathy is related to clinically relevant joint pain and less social participation. The VWD-JB patients also reported significantly more functional limitations in the HAL question-

naire, compared to the VWD controls. Within the VWD-JB patient group, the most important predictors of the development of arthropathy were a FVIII level <10 IU/dL and the cumulative number of joint bleeds.

Comparing VWD-JB patients to matched VWD controls without a relevant history of joint bleeds allowed us to get a good impression of the consequences of joint bleeds in VWD, independently of the burden of VWD itself and age-related osteoarthritis. More X-rays were taken from the VWD-JB patients compared to VWD controls, which could have led to a potential overestimation of the difference in the occurrence of 'radiological arthropathy' between the two groups. However, only one of the VWD controls had a PS>3 not related to joint bleeding. None of the VWD-JB patients had a PS>3 based on X-rays of a contralateral joint without a history of joint bleeds.

For the first time, we used the HJHS to measure arthropathy in VWD. The HJHS has been validated to assess joint outcome in hemophilia.[22] The cut off of HJHS≥10 to define arthropathy has been used in hemophilia patients with a lower mean age of 25 years.[11] We found a median HJHS of 10 in VWD patients with a history of more than 5 joint bleeds within our validation study (on the same VWD cohort) which supports the rationale of a similar cut off for arthropathy in VWD.[12] Nevertheless, we also observed 5 cases of arthropathy HJHS≥10 within the VWD controls, associated with older age. A higher cut off to define arthropathy would lead to loss of sensitivity. However, the incidence of osteoarthritis increases with age, especially after 50 years of age.[24] An age-specific HJHS cut off to define arthropathy could be the subject of further study.

Recall and information bias, including misclassification of joint symptoms for joint bleeds, probably hampered the reliability of the data on the cumulative number of joint bleeds.[25] The occurrence of unverified joint bleeds in 14 VWD controls led to an underestimation of the difference in the occurrence of arthropathy between the VWD-JB patients and VWD controls. Further study is needed to find a better threshold for severity of joint bleeds to cause arthropathy than verification by documentation on treatment for joint bleeds. The strong association between a HJHS≥10 and clinically relevant joint pain could partly be explained by assigning points for joint pain in the HJHS assessment (max. 1 point for each of 6 joints).

This study is the first to report functional consequences of joint bleeds in VWD. It appears that the prevalence of arthropathy due to joint bleeds in the total population of patients with moderate to severe VWD is less than 6%, since 44 of the VWD-JB patients within the current study were selected from the original WiN cohort (n=804). However, not all eligible WiN patients participated in the current study. Literature on joint damage due to joint bleeds is scarce in VWD and arthropathy has not been well defined.[5] More studies on arthropathy should be conducted in other VWD cohorts to confirm the validity of our results.

In hemophilia, progressive arthropathy predominantly occurs when patients report more than 5 joint bleeds before the start of prophylaxis.[26] A history of more than 5 treated joint bleeds was also associated with arthropathy in the current study, which is in accordance with the findings of our cross-sectional study.[4] As in hemophilia, we found VWD arthropathy mostly in the ankle joints (19% of VWD JB patients had a PS ankle >3).[22] In mild and moderate hemophilia, ankle arthropathy, less strictly defined as a PS>0, occurred in 48% of the patients and was also associated with FVIII levels less than 10 IU/dL and with ankle bleeding at a young age.[27]

The HJHS is suitable to detect arthropathy in VWD and physiotherapists should be involved in patient care after joint bleeds, as in hemophilia, to obtain complete recovery.[28] To get a better impression of the prevalence of arthropathy in VWD, upfront joint assessment is needed in future population studies on VWD, especially those VWD patients with type 3 VWD, low FVIII levels, and those who received prior treatment for joint bleeds.

The VWD patients with the poorest joint outcome were also the most heavily treated patients. Fifty-eight percent of the patients with an HJHS≥10 had used clotting factor prophylaxis. However, the association of arthropathy with clinically relevant joint pain, lower health-related quality of life,[4] functional limitations and less social participation, suggests that there might be room for more intensive treatment of joint bleeds in VWD. In accordance with the ICF model, this should include a rehabilitation program aimed at full functional recovery. It remains to be determined whether more intensive prophylaxis to prevent arthropathy and improve participation in VWD would be cost-effective.[29]

In conclusion, arthropathy as detected by the Hemophilia Joint Health Score occurs in almost half of VWD patients treated for joint bleeds; this is consistent with more radiological joint abnormalities compared to matched VWD controls without a relevant history of joint bleeds. VWD patients with arthropathy reported more functional limitations and less social participation compared to those without arthropathy, and clinically relevant joint pain in the majority of cases.

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References

1. Leebeek FW and Eikenboom JC. Von Willebrand's Disease. N Engl J Med. 2016;375(21):2067-2080.
2. de Wee EM, Sanders YV, Mauser-Bunschoten EP, et al. Determinants of bleeding phenotype in adult patients with moderate or severe von Willebrand disease. Thromb Haemost. 2012;108(4):683-692.
3. Jansen NW, Roosendaal G, Lafeber FP. Understanding haemophilic arthropathy: an exploration of current open issues. Br J Haematol. 2008;143(5):632-640.
4. van Galen KP, Sanders YV, Vojinovic U, et al. Joint bleeds in von Willebrand disease patients have significant impact on quality of life and joint integrity: a cross-sectional study. Haemophilia. 2015;21(3):e185-e192.
5. van Galen KP, Mauser-Bunschoten EP, Leebeek FW. Hemophilic arthropathy in patients with von Willebrand disease. Blood Rev. 2012;26(6):261-266.
6. Jette AM and Keysor JJ. Disability models: implications for arthritis exercise and physical activity interventions. Arthritis Rheum. 2003;49(1):114-120.
7. Fischer K, Nijdam A, Holmstrom M, et al. Evaluating outcome of prophylaxis in

haemophilia: objective and self-reported instruments should be combined. Haemophilia. 2016 Feb 8 [Epub ahead of print]
8. de Wee EM, Leebeek FWG, Eikenboom JCJ. Diagnosis and Management of von Willebrand Disease in The Netherlands. Semin Thromb Hemost. 2011;37(5):480-487.
9. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. Haemophilia. 2006;12(5):518-525.
10. Soucie JM, Wang C, Forsyth A, et al. Range of motion measurements: reference values and a database for comparison studies. Haemophilia. 2011;17(3):500-507.
11. Fischer K, Steen CK, Petrini P, et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. Blood. 2013;122(7):1129-1136.
12. van Galen KP, Timmer M, de Kleijn P, et al. Joint Assessment in Von Willebrand Disease: Validation of the Haemophilia Joint Health Score and Haemophilia Activities List. Thromb Haemost. 2017 May 11 [Epub ahead of print]
13. Foppen W, van der Schaaf IC, Beek FJ, Verkooijen HM, Fischer K. Scoring haemophilic arthropathy on X-rays: improving inter- and intra-observer reliability and agreement using a consensus atlas. Eur Radiol. 2016;26(6):1963-1970.
14. Foppen W, van der Schaaf IC, Beek FJ, Verkooijen HM, Fischer K. Scoring haemophilic arthropathy on X-rays: improving inter- and intra-observer reliability and agreement using a consensus atlas. Eur Radiol. 2016;26(6):1963-1970.
15. 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(5):565-571.
16. van Genderen FR, Westers P, Heijnen L, et al. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List. Haemophilia. 2006;12(1):36-46.
17. Nijdam A, Foppen W, de Kleijn P, et al. Discontinuing early prophylaxis in severe haemophilia leads to deterioration of joint status despite low bleeding rates. Thromb Haemost. 2016;115(5):931-938.
18. Cardol M, de Haan RJ, van den Bos GA, de Jong BA, de Groot IJ. The development of a handicap assessment questionnaire: the Impact on Participation and Autonomy (IPA). Clin Rehabil. 1999;13(5):411-419.
19. van der Kloot WA, Oostendorp RA, van der Meij J, van den Heuvel J. [The Dutch version of the McGill pain questionnaire: a reliable pain questionnaire]. Ned Tijdschr Geneeskd. 1995;139(13):669-673.
20. de Joode EW, van Meeteren NL, van den Berg HM, de Kleijn P, Helders PJ. Validity of health status measurement with the Dutch Arthritis Impact Measurement Scale 2 in individuals with severe haemophilia. Haemophilia. 2001;7(2):190-197.
21. Feldman BM and Pullaneyagum E. Response to 'Limits of agreement between raters are required for use of HJHS 2.1 in clinical studies'. Haemophilia. 2015; 21(1):e71.
22. Fischer K and de Kleijn P. Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: exploring reliability and validity. Haemophilia. 2013;19(6):944-950.
23. den Uijl IE, Fischer K, van der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. Haemophilia. 2011;17 (1):41-44.
24. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum. 1995;38(8):1134-1141.
25. Ceponis A, Wong-Sefidan I, Glass CS, von Drygalski A. Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patients. Haemophilia. 2013;19(5):790-798.
26. Kreuz W, Escuriola-Ettingshausen C, Funk M, Schmidt H, Kornhuber B. When should prophylactic treatment in patients with haemophilia A and B start?--The German experience. Haemophilia. 1998;4(4):413-417.
27. Ling M, Heysen JP, Duncan EM, Rodgers SE, Lloyd JV. High incidence of ankle arthropathy in mild and moderate haemophilia A. Thromb Haemost. 2011;105(2):261-268.
28. de Kleijn P, Gilbert M, Roosendaal G, Poonnose PM, Narayan PM, Tahir N. Functional recovery after bleeding episodes in haemophilia. Haemophilia. 2004;10 Suppl 4:157-160.
29. Abshire TC, Federici AB, Alvarez MT, et al. Prophylaxis in severe forms of von Willebrand's disease: results from the von Willebrand Disease Prophylaxis Network (VWD PN). Haemophilia. 2013;19(1):76-81.