

## ORIGINAL ARTICLE

# Desmopressin responsiveness by age in type 1 von Willebrand disease

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## Abstract

**Background:** Patients with type 1 von Willebrand disease (VWD) undergo a desmopressin (DDAVP) responsiveness challenge at diagnosis to assess whether DDAVP reverses their coagulation deficits. Current practice assumes DDAVP responsiveness remains constant over the lifetime. In patients with type 1 VWD, VWF-related parameters increase with age. This study explores whether DDAVP responsiveness also differs with age in this population.

**Methods:** We conducted a retrospective chart review of 106 patients enrolled at our center since 1990. Our primary outcome was DDAVP responsiveness at 1 hour after DDAVP challenge. Locally weighted scatterplot smoothing fit and Spearman correlation coefficients were used to study the relationship between age and DDAVP responsiveness. For female participants, we used the Kruskal-Wallis test to compare absolute and relative changes in DDAVP responsiveness at various ages.

**Results:** We had 79 patients (56 female) with type 1 VWD with at least 1 DDAVP challenge. In women with type 1 VWD, the absolute change in DDAVP responsiveness did not vary significantly with age (VWF:antigen [Ag],  $-0.08$ ,  $P = .56$ ; VWF:ristocetin cofactor [RCo],  $-0.16$ ,  $P = .26$ ; low-molecular-weight component of factor VIII [FVIII:C],  $-0.01$ ,  $P = .93$ ), nor did the relative change in DDAVP responsiveness (VWF:Ag,  $-0.03$ ,  $P = .86$ ; VWF:RCo,  $-0.25$ ,  $P = .09$ ; FVIII:C,  $-0.14$ ,  $P = .34$ ). The data plot suggested a relationship.

**Conclusion:** In women with type 1 VWD, DDAVP responsiveness may vary over the life cycle. Our exploratory findings are limited by our retrospective data, cross-sectional design, and small sample. Future studies should investigate the relationship between age and DDAVP responsiveness prospectively to evaluate whether there is clinical utility in rechallenging postpubertal female patients with type 1 VWD.

## KEYWORDS

deamino arginine vasopressin, hemorrhage, hemostasis, von Willebrand disease, women

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### Essentials

- In patients with type 1 von Willebrand disease (VWD), VWF-related parameters increase with age.
- We investigated whether desmopressin responsiveness also varies with age in these patients.
- The only age-related DDAVP response we found was a trend toward enhanced responsiveness in peripubertal women.
- Future studies should prospectively study the clinical implications of this laboratory phenomenon.

## 1 | INTRODUCTION

Von Willebrand factor (VWF), a multimeric glycoprotein, plays an important role in primary hemostasis by promoting platelet plug formation. VWF is also important for secondary hemostasis, as it extends the half-life of factor VIII (FVIII) by preventing degradation, excessive activation, and consumption.<sup>1</sup> VWF is genetically coded as a large polypeptide that is cleaved into multimeric subunits that later recombine to form a functional unit.<sup>1</sup> Defects in VWF quantity (type 1, relative; type 3, absolute) or function (type 2) lead to von Willebrand disease (VWD), an inherited bleeding disorder found in approximately 0.1% of the population worldwide.<sup>2</sup>

Patients with VWD may receive treatments that boost VWF-independent hemostatic pathways, such as tranexamic acid,<sup>3</sup> or receive therapy targeting VWF activity itself.<sup>4</sup> Targeted therapies include VWF-containing concentrate and vasopressin. VWF-containing concentrate is highly effective at preventing life-threatening hemorrhage,<sup>5,6</sup> but there are important pressures to find alternatives to blood products, which leads many physicians to use desmopressin (DDAVP), an arginine d-amino derivative of the hormone vasopressin. DDAVP is a safe, inexpensive, and effective alternative in most patients that mimics endogenous vasopressin by stimulating VWF and FVIII release from the vascular endothelium.<sup>7</sup>

Patients with VWD type 1 have adequate stores of relatively well-functioning VWF and therefore can theoretically boost their hemostatic response following administration of DDAVP.<sup>8,9</sup> In practice, patients with genetically similar disease can differ dramatically in their response to DDAVP administration, with some patients normalizing their VWF levels, while others remain close to or at baseline.<sup>10,11</sup> To mitigate the risk created by unknown variation in responsiveness, patients with VWD type 1 routinely undergo a DDAVP responsiveness challenge, usually at the time of diagnosis, to determine whether they will benefit from DDAVP as therapy for future bleeding or prophylaxis for procedures. For most patients, this occurs before age 18, and subsequent care assumes that a patient's responsiveness remains constant over their lifetime.<sup>12</sup> Consequently, most patients are never retested, unless there is concern about a drug administration error, and those who failed to respond during their initial challenge are treated as nonresponders indefinitely. Patients with VWD types 2A, 2B, 2M, and 3 are typically not challenged or treated with DDAVP because DDAVP administration may stimulate worsening thrombocytopenia (type 2B) or because the underlying pathophysiology cannot be corrected by exogenous DDAVP (type 2A, type 2M, type 3).

It is well known that in individuals without VWD, VWF levels increase with age,<sup>12,13</sup> likely suggestive of an age-related tendency toward thrombosis. Various authors<sup>13-15</sup> have found that VWF levels also rise with age in patients with type 1 VWD. These observations led us to hypothesize that DDAVP responsiveness, in patients with type 1 VWD, may also differ with increasing age. The objective of the current study is to explore the relationship between age and DDAVP responsiveness in patients with type 1 VWD.

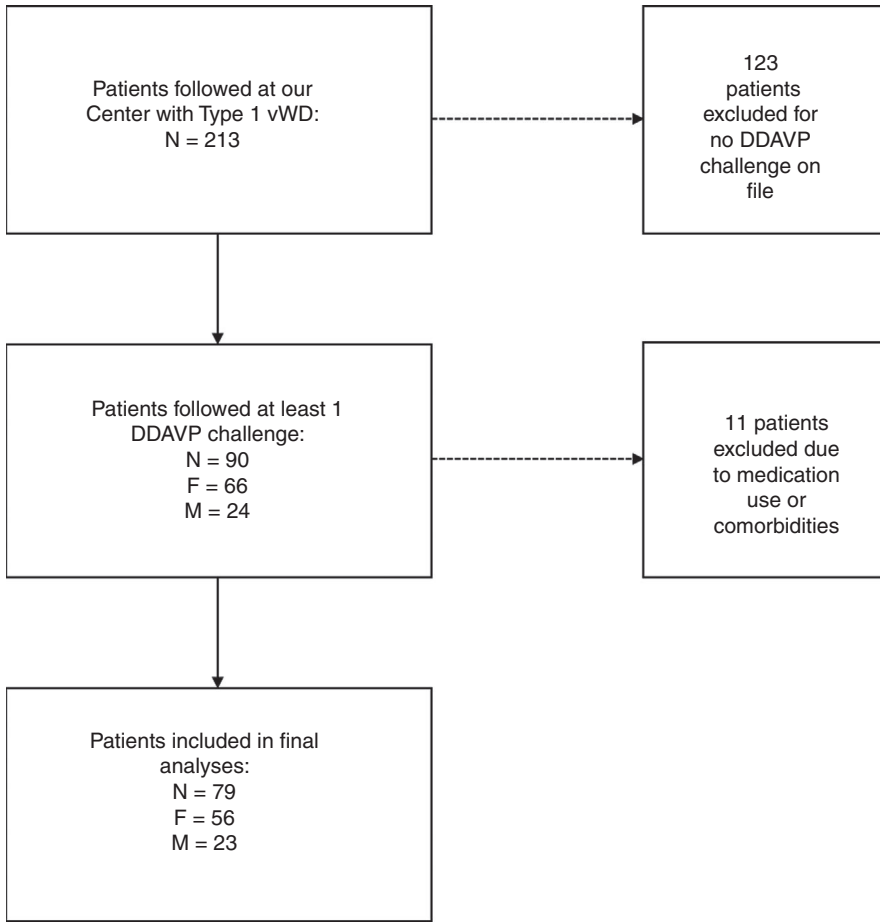
## 2 | METHODS

### 2.1 | Study design and participants

We conducted a retrospective chart review of DDAVP responsiveness in patients with type 1 VWD followed at the largest Canadian Hemophilia Treatment Center at St. Michael's Hospital in Toronto, Ontario, from 1990 to 2016 (see Figure 1). Patients included ranged from age 18 to 72 at the time of data extraction, but their historical pediatric data were included if available, which would have been collected at the requisite pediatric tertiary care center, most commonly The Hospital for Sick Children in Toronto, Ontario. One reviewer (HS) performed manual data extraction from all patient charts to be used for the current study. A separate reviewer (NG) performed the analyses to reduce bias.

All patients met the following clinical criteria, used at our center, for the diagnosis of type 1 VWD: VWF:antigen (Ag) level <0.5 U/mL, VWF:ristocetin cofactor (RCo) activity <0.5 U/mL, normal distribution of multimers, and a positive personal and/or family history of excessive bleeding. Confirmatory genetic testing was available for all participants and categorically excluded a type 2 VWD defect. More conservative definitions of type 1 VWD were not applied given our limited sample size and also because this definition is clinically accepted at our institution and at many other bleeding disorder-focused institutions. Frequency of previous bleeding episodes requiring DDAVP was not available due to the retrospective nature of the study. Patients were included if they had undergone at least 1 DDAVP challenge in their lifetime. When patients had 2 challenges, we included data from the most recent record or the record that had more complete data for laboratory results.

We excluded patients on medications known to impact VWF and FVIII levels (ie, hormonal contraception, hormone replacement therapy,  $\beta$ -blockers, thyroid replacement) and patients with types 2A, 2B, 2M, and 3 VWD due to contraindication or lack of benefit with DDAVP. No patients had VWD type 2N. We planned to exclude results if patients were pregnant, admitted to the hospital (ie, acutely ill and/or receiving



**FIGURE 1** Flow diagram of patients followed at our center included in the study. DDAVP, desmopressin; VWD, von Willebrand disease

hemostatic therapy), or received DDAVP or factor replacement in the 4 days preceding the responsiveness challenge, as these conditions are known to alter plasma VWF-related measurements. However, no patients met these clinical criteria for exclusion. All patients who met the above criteria were included in the study.

## 2.2 | Data

We extracted all available laboratory results on file for study participants for: VWF:Ag level, VWF:RCo activity, and low-molecular-weight component of FVIII (FVIII:C) activity. For DDAVP challenges, patients received intravenous or subcutaneous DDAVP dosed at 0.3  $\mu\text{g}/\text{kg}$ , with a dose-cap applied to patients weighing  $>100$  kg. We could not perform subgroup analyses by DDAVP formulation due to the small sample size. We included plasma levels of VWF:Ag, VWF:RCo, and FVIII:C at any of the following available time points: prior to administration (ie, at baseline) and then at 1 hour and 4 hours after administration. We did not include levels at 2-hour administration because this value was not consistently documented. We did not have access to data on innate VWF clearance. We designated the pre-DDAVP values as the patient's baseline, but these may not reflect historical nadir levels used to establish the diagnosis of VWD. Patients were excluded if the above data points were missing from their chart.

## 2.3 | DDAVP responsiveness definitions

We applied 2 definitions of DDAVP responsiveness: (i) absolute change in VWF:Ag, VWF:RCo, and FVIII:C levels from baseline to post-DDAVP administration, defined as post-DDAVP levels minus baseline levels; and (ii) relative change in VWF:Ag, VWF:RCo, and FVIII:C levels from baseline to post-DDAVP administration, defined as post-DDAVP levels divided by baseline levels. Categorical definitions of responsiveness exist in the literature,<sup>16</sup> but we chose not to use them as we wanted to explore the age relationship with continuous responsiveness before applying clinical criteria.

## 2.4 | Outcomes

Our primary outcomes were absolute and relative change in DDAVP responsiveness at 1 hour after challenge.

## 2.5 | Analyses

Analyses were stratified by sex to control for the impact of estrogen on VWF and FVIII:C levels and by age due to the known variation in estrogen levels over the life span in women. The relationships between age and DDAVP responsiveness (at 1 hour and at 4 hours)

were explored by creating scatterplots using locally weighted scatterplot smoothing fit and estimating Spearman correlation coefficients. Second, for female patients, we used the Kruskal-Wallis test to compare absolute and relative changes with respect to selected age categories based on literature estimates of when childhood, puberty,<sup>17</sup> childbearing,<sup>18</sup> and perimenopause<sup>19</sup> take place in North America (ages 0-10.0 years, 10.1-20.0 years, 20.1-47.0 years; and  $\geq 47.1$  year, respectively). SAS 9.4 (SAS Institute Inc, Cary, NC, USA) was used for all analyses.

### 3 | RESULTS

Of the 213 patients at our center with type 1 VWD, only 90 had undergone 1 ( $n = 77$ ) or 2 ( $n = 13$ ) DDAVP challenges. The time between challenges ranged from 233 days to 21.9 years (median, 10 years, interquartile range, 6.3-11.1 years). Of the 90

patients, 11 (12.2%) were using medications known to affect test results (Advair [ $n = 1$ ], hormonal contraception [ $n = 6$ ],  $\beta$ -blockers ( $n = 2$ ), thyroid replacement [ $n = 2$ ]), and were excluded from the analyses. The final analysis sample included 79 patients (56 females [70.9%] and 23 males [29.1%]), with age at challenge ranging from 142 days to 65.3 years (mean [standard deviation] = 24.1 [15.1]). The distribution of baseline characteristics by sex is displayed in Table 1.

DDAVP responsiveness mean absolute changes were positive at 1 hour and 4 hours for both males and females; DDAVP responsiveness mean relative changes indicate postchallenge levels were at least twice as high as baseline levels at 1 hour and 4 hours for both males and females (Table 2).

The relationships between absolute change in DDAVP responsiveness at 1 and 4 hours after challenge and age at challenge are illustrated in Figure 2A-C. There is a lot of variability in the data and an apparent peak between 20 and 30 years in women.

**TABLE 1** Baseline characteristics of patients with VWD type 1 prior to administration of a DDAVP challenge

Characteristic	Female (N = 56)	Male (N = 23)	No. missing
Blood type O, n (%)	28 (66.7)	13 (92.9)	23
Comorbidities, <sup>a</sup> n (%)	0	1 (4.4)	0
Age at DDAVP challenge, y, mean (SD)	22.6 (12.6)	27.7 (19.7)	0
Baseline VWF:Ag, U/mL, mean (SD)	0.44 (0.18)	0.27 (0.15)	5
Baseline VWF:RCo, U/mL, mean (SD)	0.39 (0.17)	0.25 (0.13)	3
Baseline FVIII:C, U/mL, mean (SD)	0.70 (0.29)	0.49 (0.32)	4

Abbreviations: FVIII:C, low-molecular-weight component of factor VIII; SD, standard deviation; VWD, von Willebrand disease; VWF:Ag, von Willebrand factor:antigen; VWF:RCo, von Willebrand factor:ristocetin cofactor.

<sup>a</sup>Comorbidities included type 2 diabetes mellitus. Note that all other patients with comorbidities were already excluded due to medication use.

**TABLE 2** Plasma levels of VWF:Ag, VWF:RCo, and FVIII:C, and DDAVP responsiveness at 1 h and 4 h after challenge

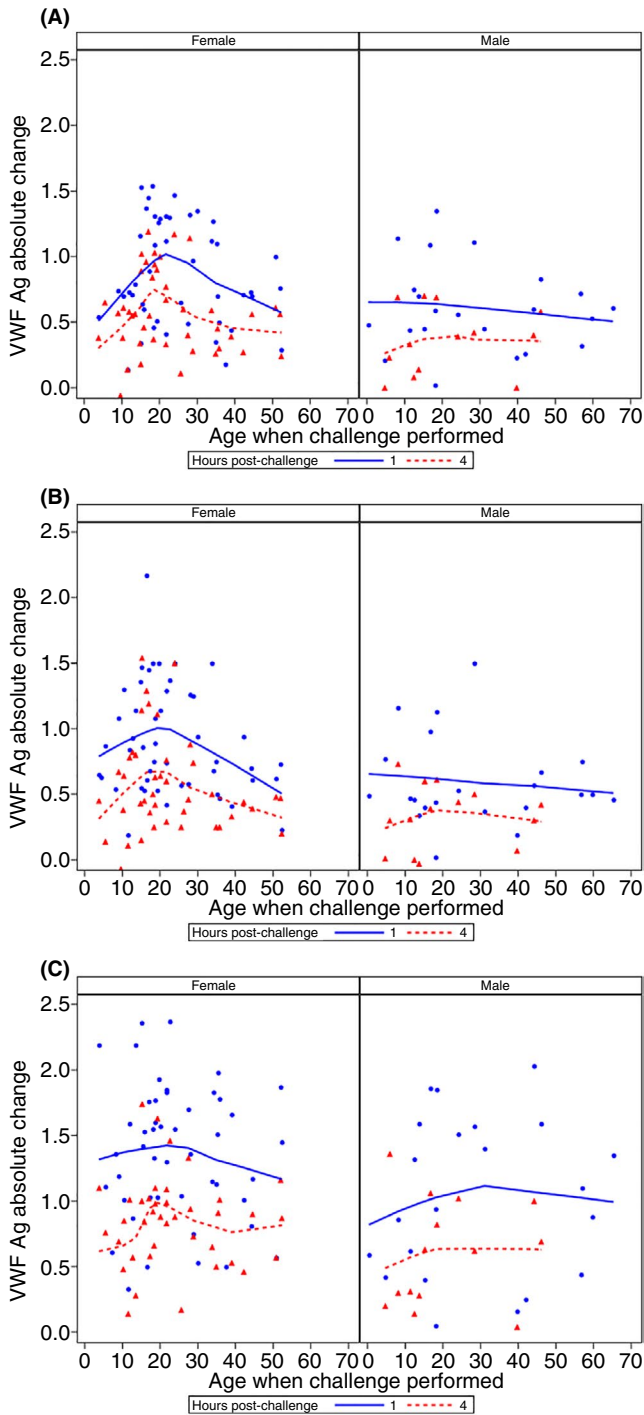
Hours post challenge	VWF:Ag		VWF:RCo		FVIII:C	
	Female	Male	Female	Male	Female	Male
At 1 h, n	46	22	48	22	47	22
Plasma levels, U/mL, mean (SD)	1.30 (0.49)	0.88 (0.44)	1.28 (0.49)	0.85 (0.43)	2.07 (0.60)	1.49 (0.71)
DDAVP responsiveness absolute change, mean (SD)	0.87 (0.40)	0.61 (0.34)	0.90 (0.41)	0.60 (0.34)	1.37 (0.51)	1.04 (0.61)
DDAVP responsiveness relative change, mean (SD)	3.30 (1.57)	3.96 (2.42)	4.05 (2.91)	3.72 (1.78)	3.28 (1.18)	4.21 (3.04)
At 4 h, n	43	13	42	14	40	14
Plasma levels, U/mL, mean (SD)	1.03 (0.45)	0.64 (0.39)	0.96 (0.47)	0.58 (0.33)	1.57 (0.53)	1.13 (0.69)
DDAVP responsiveness absolute change, mean (SD)	0.58 (0.31)	0.36 (0.26)	0.57 (0.37)	0.33 (0.24)	0.83 (0.38)	0.60 (0.41)
DDAVP responsiveness relative change, mean (SD)	2.30 (0.59)	2.12 (0.59)	2.62 (1.25)	2.25 (0.80)	2.22 (0.69)	2.14 (0.48)

Note: DDAVP responsiveness absolute change is measured as the difference between levels at 1 h or 4 h and levels at baseline.

DDAVP responsiveness relative change is measured as the postchallenge levels divided by baseline levels.

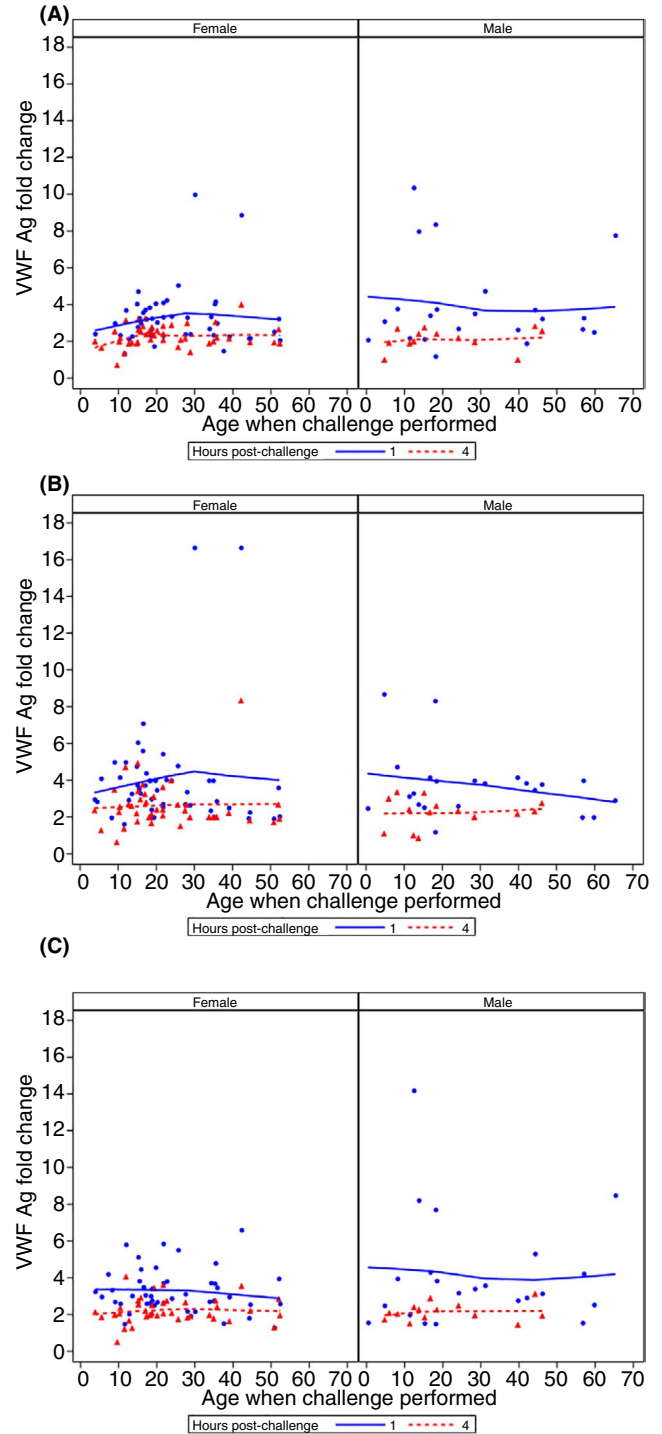
Abbreviations: DDAVP, desmopressin; FVIII:C, low-molecular-weight component of factor VIII; SD, standard deviation; VWD, von Willebrand disease; VWF:Ag, von Willebrand factor:antigen; VWF:RCo, von Willebrand factor:ristocetin cofactor.

The relationships between relative change in DDAVP responsiveness at 1 and 4 hours after challenge and age at challenge are illustrated in Figure 3A-C. A few extreme outliers in females are noted.



**FIGURE 2** Absolute desmopressin responsiveness versus age for females (left) and males (right). (A) VWF:Ag change at 1 h and 4 h after desmopressin challenge. (B) VWF:RCo change at 1 h and 4 h after desmopressin challenge. (C) FVIII:C change at 1 h and 4 h after desmopressin challenge. FVIII:C, low-molecular-weight component of factor VIII; VWF:Ag, von Willebrand factor:antigen; VWF:RCo, von Willebrand factor:ristocetin cofactor

In women with type 1 VWD, the correlations between continuous age and VWF-related responsiveness to DDAVP at 1 hour were small. For absolute change, the correlations were: VWF:Ag,  $-0.08$ ,  $P = .56$ ; VWF:RCo,  $-0.16$ ,  $P = .26$ ; FVIII:C,  $-0.01$ ,  $P = .93$ ;



**FIGURE 3** Fold change in desmopressin responsiveness versus age for females (left) and males (right). (A) Fold VWF:Ag change at 1 h and 4 h after desmopressin challenge. (B) Fold VWF:RCo change at 1 h and 4 h after desmopressin challenge. (C) Fold FVIII:C change at 1 h and 4 h after desmopressin. FVIII:C, low-molecular-weight component of factor VIII; VWF:Ag, von Willebrand factor:antigen; VWF:RCo, von Willebrand factor:ristocetin cofactor

and for relative change, the correlations were: VWF:Ag,  $-0.03$ ,  $P = .86$ ; VWF:RCo,  $-0.25$ ,  $P = .09$ ; FVIII:C,  $-0.14$ ,  $P = .34$ . Likewise, correlations were small at 4 hours after DDAVP challenge. For absolute change: VWF:Ag,  $-0.06$ ,  $P = .70$ ; VWF:RCo,  $-0.08$ ,  $P = .61$ ; FVIII:C,  $0.07$ ,  $P = .65$ ; and for relative change: VWF:Ag,  $0.12$ ,  $P = .43$ ; VWF:RCo,  $-0.11$ ,  $P = .49$ ; FVIII:C,  $0.09$ ,  $P = .57$ . In men with type 1 VWD, none of the correlations between age at challenge and any of the DDAVP responsiveness parameters was significant.

The distribution of relevant age categories in female patients was as follows: 8 (14.3%) between 0 and 10 years, 22 (39.3%) between 10.1 and 20 years, 23 (41.1%) between 20.1 and 47 years, and 3 ages  $\geq 47.1$  years. The median and interquartile range of DDAVP responsiveness at 1 hour among the 4 age categories is displayed in Table 3. Our data do not support differences in relative DDAVP responsiveness at 1 hour between the age categories.

## 4 | DISCUSSION

In our retrospective exploratory study, females of peripubertal age demonstrated a trend toward enhanced responsiveness to DDAVP administration that declines toward menopause that did not reach statistical significance. We did not observe any trend towards an age-related change in DDAVP responsiveness in males.

Laboratory studies demonstrate that estrogen directly stimulates endothelial cells to produce VWF.<sup>20</sup> Our findings, while not statistically significant, are suggestive of this well-documented relationship between estrogen exposure and enhanced coagulation, which has also been demonstrated by females with VWD who experience increases to their VWD-related parameters while taking oral estrogen

therapy.<sup>21</sup> Our study is the first to explore an association between DDAVP responsiveness and age in female patients with type 1 VWD.

Our study has limitations that warrant discussion. As a retrospective study, we relied on data points already existing in our database, and many missing data points make it difficult to properly characterize our population. For example, many patients did not have a bleeding assessment tool (BAT) score on file; therefore, we did not include these values in our baseline characteristics. Likewise, because our study was cross sectional, rather than longitudinal, it does not investigate intra-individual variation in DDAVP responsiveness over the life span. The age at which VWD is diagnosed is likely suggestive of the clinical severity, with those who have more severe disease and lower levels presenting earlier, rather than absolute levels changing with age. For this reason, prospective studies that follow levels within individuals over time are needed. Given the wide variability in the bleeding phenotype of type 1 VWD, it is important to study this relationship longitudinally. Furthermore, our study, along with many other studies on rare inherited bleeding disorders, was limited by a small sample size, and thus we were unable to perform many important subgroup analyses, such as baseline VWD and formulation of DDAVP received. We are particularly limited in our number of patients falling into the 0-10 and  $\geq 47$  categories, and therefore our conclusions are based on the trends we observed in patients aged 10-47 years old. Since we chose to use a continuous definition of DDAVP responsiveness, rather than previously established cutoffs of clinically relevant changes in coagulation markers, the clinical relevance of our finding of enhanced responsiveness in women of childbearing years remains unknown.

We believe that logical next steps would be to perform a prospective study of DDAVP responsiveness in female patients and

**TABLE 3** Median and interquartile range for plasma levels of VWF:Ag, VWF:RCo, and FVIII:C, and DDAVP responsiveness at 1 h (absolute and relative change) among 4 relevant age categories

	Age categories				P value
	0-10 y	10.1-20 y	20.1-47 y	$\geq 47.1$ y	
<b>VWF:Ag</b>					
n	2	19	22	3	
Absolute change	0.64 (0.54-0.74)	0.79 (0.60-1.31)	0.85 (0.50-1.29)	0.76 (0.29-1.00)	.8016
Relative change	2.71 (2.42-3.00)	3.23 (2.35-3.74)	3.18 (2.35-4.12)	2.54 (2.07-3.24)	.6595
<b>VWF:RCo</b>					
n	5	20	20	3	
Absolute change	0.65 (0.63-0.87)	0.91 (0.65-1.40)	0.75 (0.58-1.26)	0.62 (0.23-0.73)	.2804
Relative change	2.97 (2.85-4.11)	3.88 (3.14-4.59)	3.13 (2.54-4.02)	2.05 (1.93-3.61)	.2501
<b>FVIII:C</b>					
n	5	17	22	3	
Absolute change	1.19 (1.11-1.36)	1.53 (1.03-1.76)	1.44 (1.04-1.78)	1.45 (0.57-1.87)	.9761
Relative change	3.26 (2.98-3.34)	3.03 (2.61-3.84)	2.93 (2.56-3.73)	2.59 (1.30-3.97)	.7591

Note: DDAVP responsiveness absolute change is measured as the difference between levels at 1 h or 4 h and levels at baseline.

DDAVP responsiveness relative change is measured as the post-challenge levels divided by baseline levels.

Abbreviations: DDAVP, desmopressin; FVIII:C, low-molecular-weight component of factor VIII; VWD, von Willebrand disease; VWF:Ag, von Willebrand factor:antigen; VWF:RCo, von Willebrand factor:ristocetin cofactor.

follow their responsiveness longitudinally over the life span and to investigate whether BAT scores and risk of surgical bleeding when treated with DDAVP are also dynamically affected over the life span of women with VWD.

In this exploratory study, our findings allude to a potential relationship between responsiveness to DDAVP in females with type 1 VWD around the peripubertal years. This trend is reminiscent of the well-established relationship between serum estrogen levels and coagulability.<sup>22</sup> Future studies should study this question prospectively and assess whether there is clinical utility in repeating desmopressin responsiveness testing in female patients with type 1 VWD as they enter childbearing years and as they approach menopause.

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## RELATIONSHIP DISCLOSURE

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## AUTHOR CONTRIBUTIONS

Study concept and design: all authors; acquisition of data: NG and HS; analysis/interpretation of data: NG, RN, HS, and MS; Drafting of the manuscript: NG, RN, and MS; critical revision of the manuscript: NG, RN, DL, JT, PJ, and MS; statistical analysis: NG, HS, RN, and MS.

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## REFERENCES

- Sadler JE, Budde U, Eikenboom JC, Favaloro EJ, Hill FG, Holmberg L, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. *J Thromb Haemost*. 2006;4(10):2103–14.
- Bowman M, Hopman WM, Rapson D, Lillicrap D, James P. The prevalence of symptomatic von Willebrand disease in primary care practice. *J Thromb Haemost* [Internet]. 2010;8(1):213–6.
- Mannucci PM. Hemostatic drugs. *N Engl J Med* [Internet]. 1998; 339(4):245–53.
- Ciavarella N, Schiavoni M, Valenzano E, Mangini F, Inchingolo F. Use of recombinant factor VIIa (NovoSeven) in the treatment of two patients with type III von Willebrand's disease and an inhibitor against von Willebrand factor. *Haemostasis* [Internet]. 1996;26(Suppl 1):150–4.
- Grossmann RE, Geisen U, Schwender S, Keller F. Continuous infusion of recombinant factor VIIa (NovoSeven) in the treatment of a patient with type III von Willebrand's disease and alloantibodies against von Willebrand factor. *Thromb Haemost* [Internet]. 2000;83(4):633–4.
- Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *J Thromb Haemost*. 2003;1(4):682–9.
- Lusher JM. Response to 1-deamino-8-D-arginine vasopressin in von Willebrand disease. *Haemostasis* [Internet]. 1994;24(5):276–84.
- Federici AB, Mazurier C, Berntorp E, Lee CA, Scharrer I, Goudemand J, et al. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. *Blood* [Internet]. 2004;103(6):2032–8.
- Mannucci PM, Lombardi R, Bader R, Vianello L, Federici AB, Solinas S, et al. Heterogeneity of type I von Willebrand disease: evidence for a subgroup with an abnormal von Willebrand factor. *Blood* [Internet]. 1985;66(4):796–802.
- Gralnick HR, Williams SB, McKeown LP, Rick ME, Maisonneuve P, Jenneau C, et al. DDAVP in type IIa von Willebrand's disease. *Blood* [Internet]. 1986;67(2):465–8.
- Ozgonenel B, Rajpurkar M, Lusher JM. How do you treat bleeding disorders with desmopressin? *Postgrad Med J* [Internet]. 2007;83(977):159–63.
- Coppola R, Mari D, Lattuada A, Franceschi C. Von Willebrand factor in Italian centenarians. *Haematologica* [Internet]. 2003;88(1):39–43.
- Rydz N, Grabell J, Lillicrap D, James PD. Changes in von Willebrand factor level and von Willebrand activity with age in type 1 von Willebrand disease. *Natalia*. 2015;21(5):636–41.
- Abou-Ismaïl MY, Ogunbayo GO, Secic M, Kouides PA. Outgrowing the laboratory diagnosis of type 1 von Willebrand disease: a two decade study. *Am J Hematol* [Internet]. 2018;93(2):232–7.
- Sanders YV, Giezenaar MA, Laros-van Gorkom BAP, Meijer K, van der Bom JG, Cnossen MH, et al. von Willebrand disease and aging: an evolving phenotype. *J Thromb Haemost* [Internet]. 2014;12(7):1066–75.
- Federici AB, Mazurier C, Berntorp E, Lee CA, Scharrer I, Goudemand J, et al. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. *Response*. 2004;103(6):2032–8.
- Addo OY, Miller BS, Lee PA, Hediger ML, Himes JH. Age at hormonal onset of puberty based on luteinizing hormone, inhibin B, and body composition in preadolescent US girls. *Pediatr Res* [Internet]. 2014;76(6):564–70.
- Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, et al. The physiology and clinical utility of anti-Müllerian hormone in women. *Hum Reprod Update* [Internet]. 2014;20(3):370–85.
- McNamara M, Batur P, DeSapri KT. Perimenopause. *Ann Internal Med*. 2015;162(3):ITC1.
- Harrison RL, McKee PA. Estrogen stimulates von Willebrand factor production by cultured endothelial cells. *Blood* [Internet]. 1984;63(3):657–64.
- Alperin JB. Estrogens and surgery in women with von Willebrand's disease. *Am J Med* [Internet]. 1982;73(3):367–71.
- Gray B, Floyd S, James AH. Contraceptive management for women who are at high risk of thrombosis. *Clin Obstet Gynecol* [Internet]. 2018;61(2):243–249.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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