

Von Willebrand disease in the elderly: clinical perspectives

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Abstract: Von Willebrand disease (VWD) is an inherited bleeding disorder that affects up to 1% of the population. In most cases, VWD results from a mutation in the von Willebrand Factor (VWF) gene, which alters the amount and function of VWF, a key glycoprotein in both primary and secondary hemostasis. A comprehensive analysis of patients with VWD should include VWF activity, antigen levels, platelet function, and a careful bleeding history. Treatment options include antifibrinolytics, desmopressin, and VWF replacement therapy. VWF levels fluctuate due to age, stress, environmental exposures, and pharmacologic treatment. Treatment guidelines exist to treat and prevent bleeding for patients undergoing surgery and medical procedures, but often these must be reevaluated in the setting of age-related comorbidities including cardiovascular events, venous thrombosis, and malignancy. In addition, many age-related complications are associated with a secondary acquired von Willebrand syndrome (AVWS), including malignancies, hypothyroidism, cardiovascular diseases, and cardiac replacement devices. The current literature is limited by a lack of older patients in clinical trials. Larger studies are needed to determine if age-related comorbidities affect VWD patients at different frequencies than the general elderly population. There is also a significant need for registry-based studies to evaluate many age-related comorbidities in VWD patients.

Keywords: von Willebrand disease, acquired von Willebrand syndrome, bleeding disorders, aging

Introduction

Von Willebrand disease (VWD) was initially described in 1924 by Erik von Willebrand in a small family cohort with unusual bleeding and deaths resulting from menorrhagia. In the century since the initial clinical pathology was described, multiple genetic and phenotypic variants of VWD have been identified and treatment methods have been developed. VWD is now characterized as an autosomal bleeding disorder with a prevalence in up to 1% of the population,^{1,2} although the symptomatic prevalence is approximately 1:10,000.³⁻⁵ The bleeding patterns of VWD most often involve bleeding on mucosal surfaces such as epistaxis, dental bleeding, menorrhagia, and significant bruising. Bleeding patterns are different based on age. In children, bleeding is most often characterized by bruising and epistaxis, while adults more commonly develop hematomas, menorrhagia, and wound bleeding.^{6,7} The severity of bleeding depends greatly on the quantity and quality of von Willebrand factor (VWF). Some patients experience only minor bleeding with procedures or menses, while others have significant regular hemorrhages requiring prophylaxis with hemostatic agents.⁸ As they age, patients with VWD experience age-related health comorbidities and may require interventions for heart disease, cancer, orthopedic fractures, and other diseases. In addition, changes in hemostasis occur as part of normal aging and may influence the risk

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of bleeding and thrombosis in these patients. Increases in procoagulant factors and fibrinogen, decreases in endogenous anticoagulant factors, and altered platelet activation have all been described in aging.⁹

The purpose of this review is to describe age-related complications in VWD, how they impact the disease, and how these can be mitigated.

VWD overview

VWD is a disorder of VWF, a large multimeric glycoprotein with molecular weights that range from approximately 500–20,000 kDa. VWF binds to the glycoprotein GPIb α on the surface of platelets that results in platelet tethering in addition to platelet adherence to vessel wall collagen.¹⁰ It also functions as a carrier molecule for FVIII, protecting FVIII from proteolysis and prolonging its half-life in circulation.^{10,11} Mutations in VWF have been described that affect platelet binding, collagen binding, secretion, and synthesis. However, mutations do not always identify patients with VWD. Approximately 30% of patients with type 1 VWD do not have a candidate mutation identified.^{12,13} Conversely, low levels of VWF have been identified in patients without a clinical bleeding disorder, making the diagnosis of VWD especially challenging in less severe cases.¹⁴ The current classification systems of VWD involve a description of the VWF antigen and activity levels, platelet binding tests, VWF-propeptide levels, and VWF multimer analysis (Table 1).^{15,16} It should also be noted that many types of acquired von Willebrand syndrome (AVWS) exist and can be related to diseases more commonly encountered in the elderly, which is described below in more detail.

The genetics and synthesis of VWF

The genetics of VWD are complicated and not fully predictive of bleeding phenotypes. The VWF molecule consists

of 178 kb located on the short arm of chromosome 12 and contains 52 exons. The mature secreted glycoprotein consists of 2,050 amino acids and 4 types of repeat domains to which binding to FVIII, platelet glycoprotein GPIb α , collagen, and integrin α IIB β 3 have been mapped.¹⁷ As a functional assay, VWF ristocetin cofactor (VWF:RCo) levels <30 U/dL are strongly associated with a clinical bleeding phenotype and the presence of an identified VWF mutation in type 1 VWD.¹² Other genetic factors that influence VWF levels, including the “platelet type” of VWD¹⁸ (*GP1BA* mutation) and the ABO blood groups.¹⁹ Newer associations between VWF antigen levels and polymorphisms in non-VWF genes have been identified by genome wide association studies, including polymorphisms in secretory protein genes, such as *STAB5*, *STX2*, and *STXBP5*.²⁰ Some of these variations correlate with patient reported bleeding.^{21,22} For example, annexin A2 (ANXA2) is involved in trafficking of Weibel–Palade bodies (WPBs) by a cAMP-dependent mechanism.²³ ANXA2 is also a key mediator in the trafficking of VWF from the WPB to the endothelial cell surface, and its absence results in impaired endothelial secretion in response to histamine.²⁴ ANXA2’s role as a modifier of clinical disease requires further research.

Both endothelial cells and megakaryocytes synthesize VWF. Endothelial cells store VWF in the WPB, and megakaryocytes store VWF in α -granules. Initial synthesis of VWF occurs in the endoplasmic reticulum, where VWF is synthesized as a propolypeptide. During activation, the signal peptide is cleaved, allowing VWF subunits to dimerize and enter the Golgi network. VWF then assembles into multimers that are directed to the storage organelles.²⁵ The large and ultra-large multimers that are stored in WPBs or platelet α -granules are then secreted by either a constitutive or agonist-controlled mechanism.^{26,27} In circulation, large VWF multimers are cleaved by the metalloprotease

Table 1 Summary of classification of VWD (based on NHLBI classification)

Type	Description	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	VWF:RCo/VWF:Ag ratio	Multimers
Type 1	Partial quantitative VWF deficiency	<30	<30	Low or normal	>0.5–0.7	Normal pattern, reduced VWF
Type 2A	Reduced VWF-dependent platelet adhesion	<30	<30–200	Low or normal	<0.5–0.7	Loss of HMWM
Type 2B	Increased VWF affinity for platelet GP 1b; reduced platelets	<30	<30–200	Low or normal	<0.5–0.7	Loss of HMWM
Type 2M	Reduced VWF-dependent platelet adhesion	<30	<30–200	Low or normal	<0.5–0.7	Normal HMWM
Type 2N	Reduced VWF binding affinity for FVIII	30–200	30–200	Significantly reduced	>0.5–0.7	Normal HMWM
Type 3	Complete deficiency of VWF	<3	<3	Significantly reduced	Not applicable	Absent HMWM
Normal		50–200	50–200	Normal	>0.5–0.7	Normal HMWM

Abbreviations: HMWM, high molecular weight multimers; NHLBI, National Heart, Lung, and Blood Institute; FVIII, factor VIII; VWD, von Willebrand disease; VWF:Ag, von Willebrand factor antigen; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin activity.

ADAMTS13 (A Disintegrin-like and Metalloprotease with Thrombospondin Type one repeat motifs, member 13) into smaller molecular forms.²⁸ The importance of ADAMTS13 in pathophysiology is demonstrated in both congenital and acquired forms of thrombotic thrombocytopenic purpura (TTP), where failure of appropriate VWF multimer cleavage from a deficiency of ADAMTS13 can lead to vessel thrombosis, hemolytic anemia, and platelet consumption.²⁹

Diagnosis and assessing bleeding severity in VWD

The diagnosis of VWD requires both laboratory and clinical evaluations (Table 1).¹⁶ An initial evaluation consists of prothrombin time and activated partial thromboplastin time, assessment of VWF activity (ristocetin cofactor; VWF:RCo), VWF antigen (VWF:Ag), and factor VIII activity. Further testing includes multimer analysis, the VWF-collagen binding assay, and VWF propeptide antigen levels, which can assist in refining the diagnosis. The clinician encountering a patient with a history of VWD will want to identify the VWD subtype, the bleeding phenotype, and obtain past and current coagulation studies of the patient. Bleeding may still be difficult to predict based on the laboratory analysis, and VWF:RCo can be poorly predictive of bleeding.^{14,30} Bleeding assessment scores have been utilized in both the hemophilia and VWD populations to address the limits of laboratory testing and more appropriately quantify the bleeding risk.^{31–33} Bleeding scores have the potential to predict bleeding phenotype, determine need for treatment, and distinguish between subtypes.^{34,35} Most bleeding scores

are able to distinguish between healthy patients and those with symptomatic VWD.^{31,33} The International Society of Hemostasis and Thrombosis (ISTH) has also developed a bleeding assessment tool (BAT) that has been used in patients with bleeding disorders.³⁶ Additional advances in laboratory testing, such as whole blood ristocetin-induced platelet aggregometry also have the potential to improve the diagnosis of VWD and inform the bleeding risk.³⁷

At this time, there is no validated bleeding assessment score designed specifically for the elderly population, and although patients over 65 have been included in clinical studies, they have not been represented as a unique population. Development of a bleeding assessment score in elderly patients is an area for further exploration.

Treatment of VWD

Treatment of VWD is generally based on symptoms and bleeding severity. Most VWD patients fall into milder subtypes like VWD type 1, and thus most often require episodic treatment. Treatment goals are to increase circulating VWF activity and reduce bleeding (Table 2). Desmopressin (DDAVP), a vasopressin analog, binds to vasopressin receptors on the surface of endothelial cells, thereby increasing intracellular calcium, promoting trafficking of WPB to the endothelial cell plasma membrane, which then triggers the release of VWF, FVIII, and other coagulation proteins. The net result is an increase in circulating VWF and FVIII, and improved systemic hemostasis. The release of VWF and FVIII normally occurs within 30–60 minutes of its administration, and usually provides a durable hemostatic

Table 2 Current therapies for VWD

Name of treatment	Mechanism	Route	Use
Desmopressin (DDAVP)	Increased secretion of VWF and FVIII from endothelial cells	IV, SC, ^a IN	Mostly used in type 1 disease and some type two forms. Relative contraindication in type 2B. Ineffective in type 3. Ineffective (tachyphylaxis) after repeat dosing, fluid restriction to prevent hyponatremia.
Humate P	Plasma-derived VWF and FVIII concentrate (VWF:RCo: FVIII ratio 2.4:1)	IV	Acute treatment of bleeding in severe forms of VWD, prophylaxis against bleeding in severe disease.
Wilate	Plasma-derived VWF and FVIII concentrate (VWF:RCo: FVIII ratio 1:1)	IV	Acute treatment of bleeding in severe forms of VWD, prophylaxis against bleeding in severe disease.
Alphanate	Plasma-derived VWF and FVIII concentrate (VWF:RCo: FVIII ratio 1:3)	IV	Acute treatment of bleeding in severe forms of VWD, prophylaxis against bleeding in severe disease.
Vonvendi	Recombinant VWF produced in cell lines	IV	Acute treatment of bleeding in severe forms of VWD.
Aminocaproic acid	Inhibits fibrinolysis	PO, IV	Prevention and treatment of minor bleeding, especially mucosal surfaces. ^b
Tranexamic acid	Inhibits fibrinolysis	PO, IV	Prevention and treatment of minor bleeding, especially mucosal surfaces. ^b

Notes: ^aIn some geographies; ^bMay be used in combination with DDAVP.

Abbreviations: FVIII, factor VIII; IN, intranasal; IV, intravenous; PO, oral; SC, subcutaneous; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin activity.

response that lasts for 4–6 hours. The optimal increase in VWF is associated with bleeding control in 70% of cases of VWD, albeit with some interpatient variability.^{38,39} DDAVP also releases tissue plasminogen activator (tPA) from the WPB.⁴⁰ DDAVP therefore increases circulating hemostatic factors but may also increase fibrinolysis. Antifibrinolytic treatments are often used in conjunction with DDAVP to improve hemostasis. This approach has been used successfully in multiple congenital bleeding disorders.⁴¹

In more severe cases of VWD, prophylaxis with a VWF-containing concentrate is desirable to prevent bleeding (Table 2). The prophylactic strategy involves administration of VWF replacement factors on a regular basis to maintain active trough levels of VWF and FVIII in circulation. The strategy is similar to hemophilia treatment, where factor concentrates are regularly administered to reduce joint bleeding and its associated long-term morbidity.^{42,43} Symptomatology in VWD is more variable than hemophilia; joint bleeding is less common and mucosal surface bleeding can be the predominant bleeding pattern.⁴⁴ Prophylaxis with VWF concentrates significantly reduces mucosal and joint bleeding rates.^{44–46} A recombinant VWF concentrate has also been developed that is effective at stabilizing FVIII⁴⁷ and controlling bleeding events.⁴⁸

VWF and aging

It has been demonstrated that VWF levels increase with age by approximately 1% per year^{49–51} in the healthy population and in mild forms of VWD. In addition, patients older than 55 have increases in VWF circulating half-lives and increased secretion.¹⁹ The highest levels of circulating VWF can be seen in healthy centenarians.⁵²

VWF levels do not change with age in severe forms of VWD, including types 2 and 3. In addition, it is not clear whether age-related increases in VWF observed in mild VWD affect the bleeding phenotype.^{53,54} VWD is therefore considered a lifelong bleeding condition that may require ongoing treatment.

In general, patients without bleeding disorders accumulate risk factors based on organ systems (cardiovascular disease, osteoporosis, hypothyroidism), molecular cell signaling and stem cell clonal populations (malignancies), and motor functions (fall risk, tremors) as they age. In addition, age represents an independent risk factor for venous thrombosis. All of these comorbidities combined with the common consequences of aging have significant impact on aging patients with VWD.

VWD and cardiovascular events

Cardiovascular disease represents a leading cause of morbidity and mortality in the adult population in most developed

countries.⁵⁵ Risk factors for arterial disease in the general population have also been associated with VWF including smoking, glycemic control,⁵⁶ elevated triglycerides, and blood pressure, and aortic stiffness.⁵⁷

A large number of animal models have shown that VWF deficiency may have a protective effect against atherosclerosis and arterial thrombosis risk in both small and large arteries.⁵⁸ Studies in humans have been less clear, however, with most trials showing only modest reductions in atherosclerosis.^{59–63} While arterial thrombosis has been reported in VWD,⁶⁴ its incidence is low, especially in younger populations.⁶⁵ Cohort studies have yielded conflicting results on the degree of protection against arterial disease in VWD.^{65,66} Some studies have also demonstrated that patients with VWD have a reduced risk of both cerebrovascular and peripheral vascular diseases.⁶⁷

The treating clinician should not assume that a patient is at low risk for cardiovascular events because of a history of VWD, as both male and female patients with VWD have developed acute coronary syndrome (ACS).⁶⁸ ACS should be managed as it would be in otherwise healthy patients. Percutaneous interventions and coronary artery bypass grafting have been performed^{69–71} although a hematologist should be available for consultation as perioperative bleeding is a known risk in this setting.⁶⁸ VWD patients with ACS can also be managed medically without increased mortality in select patients.⁶⁸ Aspirin, statins, and other therapies for cardiovascular disease can be given in VWD, although caution must be exercised with antiplatelet agents, direct oral acting anticoagulants (DOACs), and warfarin, as these drugs carry an additional bleeding risk.

VWD and venous thrombosis

Elevated levels of VWF have been associated with increased risk for venous thromboembolism (VTE) in healthy populations, leading to speculation that VWD patients may be protected from VTEs.⁷² However, the degree of risk reduction is not clear and some reports have suggested patients with VWD are not protected against VTE.⁶⁵ Both deep vein thrombosis and pulmonary emboli have been reported in all types of VWD.^{64,73} In clinical practice, the risk of VTE should not be considered negligible, even in the setting of an inherited bleeding disorder like VWD. When planning for a major surgery, patients with VWD should be appropriately evaluated for thromboprophylaxis to reduce the risk of post-operative VTE.⁷⁴

Age is also a risk factor for VTE, and it should be suspected in the appropriate clinical context in elderly patients with VWD. DOACs have been demonstrated to have equal efficacy to

vitamin K antagonists (VKA) like warfarin and with improved safety in the elderly thrombosis population.⁷⁵ Each VTE treatment should be individualized to the patient. There are no consensus guidelines for the selection and use of anticoagulation in patients with VWD, but DOACs have been suggested for use in other bleeding disorders because of their shorter half-life and improved safety profile compared to VKAs.⁷⁶

VWD and malignancy

To date, the available literature on VWD and malignancy risk is limited. In general, these patients should be considered to be similar to age and risk factor-adjusted healthy individuals in the general population, provided they did not contract viruses associated with contaminated blood products such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV), and that the diagnosis of VWD is a primary diagnosis and not AVWS.

Cohort studies suggest that solid tumors are significantly more common than hematologic malignancies in VWD patients. More severe cases of VWD were also associated with exposure to HCV, likely from VWF concentrate exposure, and with an increased risk of hepatocellular carcinoma and non-Hodgkin lymphoma.⁷⁷ Interestingly, increased rates of malignancy were seen in type 2 VWD compared to other types, leading the authors to speculate that a qualitative difference in VWF may be an important component in malignancy. In support of this hypothesis, experimental animal data has suggested that a reduction in VWF reduces metastases of tumor cells.⁷⁸ This has yet to be confirmed in a clinical setting. In small clinical studies, it does not appear that cancer risk is related to VWF antigen levels but may be related to qualitative VWF defects and perturbed angiogenesis that could affect cancer metastasis.⁷⁷

Hemophilia patients exposed to HCV and HIV have increased risk of malignancies related to these exposures,

such as hepatocellular carcinoma and lymphoma.^{79,80} Treatment plans for malignancies in patients with hemophilia can be successfully customized to reduce bleeding risk related to chemotherapy-induced thrombocytopenia.⁸¹ VWD patients are exposed less frequently to VWF-containing concentrates compared with hemophilia patients, and therefore have historically had lower exposure to HCV and HIV, although the natural history of chronic viral infection and subsequent risk of malignancies are similar.^{77,82} The bleeding risks in VWD associated with treatments of malignancies can be minimized when performed in conjunction with specialty centers.⁷⁷ The incidence of chronic viral infections with HIV and HCV from plasma concentrate exposure and the subsequent malignancy risk will decrease in current generations of patients who are receiving high purity concentrates or recombinant products. Longitudinal studies are needed to provide more insight into VWD malignancy risks.

Acquired AVWS and aging

It is important to distinguish a patient with congenital VWD who has developed a malignancy, especially a hematologic malignancy, from a patient who has developed AVWS from a malignancy. The distinction is relevant to treatment strategies, since treating an underlying malignancy may also restore functional VWF in cases of AVWS.

AVWS is a syndrome that predominantly occurs in older patients and is almost always encountered in the setting of an underlying disorder (Table 3).⁸³ Most patients with AVWS have a hematologic neoplasm or a form of cardiac disease where perturbed blood flow leads to loss of VWF multimers. In addition, medications including ciprofloxacin⁸⁴ and valproic acid⁸⁵ have been implicated in reducing VWF secretion. A longitudinal bleeding history is important to distinguish a new AVWS from a patient with congenital VWD and an accompanying diagnosis of cancer, both of

Table 3 Pathophysiology associated with acquired von Willebrand syndrome

Disorder	Pathophysiology
Hypothyroidism	Reduced synthesis and secretion of VWF
Lymphoproliferative disorders (lymphoma, myeloma, MGUS, Waldenstrom's macroglobulinemia)	Antibody-mediated clearance of VWF
Myeloproliferative disorders (myeloproliferative neoplasias)	Shear-mediated loss of larger and ultra-large VWF multimers
Solid tumor malignancy	Adsorption of VWF onto tumor cells
Autoimmune disorders (SLE)	Antibody-mediated clearance of VWF
Cardiac valve disease/malformation	Shear-mediated loss of larger and ultra-large VWF multimers
Cardiac assist devices (eg, LVAD)	Shear-mediated loss of larger and ultra-large VWF multimers
Idiopathic	Various
Drug induced (see text)	Reduced synthesis and secretion of VWF (valproic acid), increased proteolysis (ciprofloxacin)

Abbreviations: LVAD, left ventricular assist device; MGUS, monoclonal gammopathy of uncertain significance; SLE, systemic lupus erythematosus; VWF, von Willebrand factor.

which can be seen more commonly in populations over 60. The diagnosis of AVWS can be challenging, since different etiologies result in different mechanisms whereby VWF is lost and can be broadly divided into immune-mediated clearance of VWF, adsorption, and shear stress.⁸⁶ In the acute setting, bleeding can be managed by treatments similar to congenital VWD. Treating the underlying condition often restores circulating VWF.

As lymphoproliferative and myeloproliferative disorders are more common in elderly populations, bleeding symptoms should be closely evaluated in patients with these diagnoses. AVWS is associated with lymphoproliferative diseases, and most commonly monoclonal gammopathy of uncertain significance (MGUS). The mechanism of action in this AVWS subtype is the development of an anti-VWF antibody that can induce both a loss of function and increased clearance of VWF.⁸⁷ Both IgG and IgM types of MGUS have been described in relation to AVWS. DDAVP and VWF concentrates agents have been used to control bleeding, although these treatments can be subject to rapid clearance. Immunosuppression has also been used to treat the underlying MGUS syndrome.⁸⁸ The MGUS AVWS subtype appears to respond to intravenous immunoglobulins (IVIG) that binds the autoantibody. IVIG has been demonstrated to restore plasma VWF levels and control bleeding.^{89,90}

Additional lymphoproliferative disorders have been described, including Waldenstrom's macroglobulinemia (WM) which responded to chemotherapy and plasmapheresis, and marginal zone lymphoma, which responds to chemotherapy.⁹¹ In WM, the IgM paraprotein binds VWF and clears it from circulation. Bleeding symptoms do appear to improve with plasmapheresis.

Myeloproliferative disorders have also been described in association with AVWS. In essential thrombocythemia, characterized by an excess of platelets, high molecular weight multimers (HMWM) adsorb onto the surface of activated platelets removing VWF from circulation. Cyto-reduction with hydroxyurea has been shown to reverse this deficit in some cases.⁹¹ Chronic myeloid leukemia has also been associated with AVWS and loss of HMWMs. The pathophysiology of this disorder is likely also related to thrombocytosis and has demonstrated responsiveness to tyrosine kinase inhibitor therapy.

The reports of solid tumors and AVWS are few and constitute a small minority of AVWS (5%). The mechanism of AVWS in solid tumors remains incompletely understood. Several solid tumor subtypes have been associated with tumor expression of GP Ib or IIb/IIIa receptors, suggesting

the pathology could be related to VWF binding onto the cell surfaces.⁹² AVWS has also been reported in nephroblastoma and Wilms tumor, where hyaluronic acid has been postulated with loss of VWF.⁹³ A case of AVWS in prostate cancer was also reported without a clear pathophysiologic explanation.⁹⁴ In general, AVWS in these cases has responded to the chemotherapy treatments used for the underlying malignancy.

Acquired VWS and left ventricular assist devices (LVADs)

The diagnosis of Heyde's syndrome, characterized by gastrointestinal bleeding from angiodysplasia in the setting of native valve aortic stenosis (AS), is a shear-related loss of VWF that causes both bleeding, and loss of vessel wall integrity. The severity of AS also correlates with more significant loss of VWF and predicts mortality and requirement for surgical valve replacement.⁹⁵ AVWS related to valve shear forces may resolve with valve replacement although there can be recurrences.⁹⁶ In addition, new onset gastrointestinal bleeding from angiodysplasia in older adults has been associated with AVWS.⁹⁷ Gastrointestinal bleeding from angiodysplasia in an elderly patient should prompt an evaluation for AVWS, especially in the setting of cardiac valve disease.

At least two cases of octogenarians with AS and epistaxis related to loss of VWF multimers have been reported in the literature, demonstrating that AS bleeding may occur on different mucosal surfaces.⁹⁸ AVWS related to shear stress has also been reported in congenital heart diseases.⁹⁹ Circulatory assistance devices such as LVADs can also cause loss of HMWM and result in bleeding and angiodysplasia. LVAD bleeding is similar to that observed in Heyde's syndrome.^{100,101} In many cases, both VWF:RCo and VWF:Ag levels remain normal.^{100,102,103} Furthermore, the degree of pulsatility is linked to bleeding events.¹⁰⁴ It is currently recommended that LVAD settings be altered to improve shear and therefore bleeding,^{100,105} although it is to be noted that there is no robust data in the published literature to support this recommendation.¹⁰¹

AVWS and thyroid disease

The elderly population is susceptible to hypothyroidism, with an estimated prevalence as high as 4.4%.¹⁰⁶ Hypothyroidism accompanied by AVWS can occur at any age, although it has been described as a more common issue in older adults and the prevalence of AVWS in hypothyroidism is approximately 33%.¹⁰⁷ Bleeding symptoms correlate with both VWF:RCo and VWF:Ag resembling type 1 VWD. Interestingly, thyroid hormone levels do not appear to correlate with severity of

disease. In one prospective cohort, treatment with thyroid hormone replacement over a median of 5 months resulted in normalization of VWF and resolution of bleeding symptoms in almost all cases.¹⁰⁷ When it is urgent to raise VWF levels prior to completion of thyroid replacement, DDAVP can be used to increase VWF in circulation.¹⁰⁸ Laboratory evaluation of thyroid function should accompany any new case of VWD or AVWS to rule out easily reversible causes.

VWD and osteoporosis, fracture risk, and falls

The discovery of the RANK (Receptor Activator of Nuclear Factor-kappa B), RANK ligand (RANKL), osteoprotegerin (OPG) axis led to a greater understanding of bone growth and remodeling by osteoblasts and osteoclasts. In addition, coagulation proteins have been identified in this physiologic axis. The FVIII-VWF complex inhibits osteoclastogenesis *in vitro*,¹⁰⁹ and a deficit of FVIII in WPBs results in increased RANKL activity which in turn leads to increased bone resorption. In a FVIII deficiency mouse model, animals have reduced bone mineral density and impaired biomechanical strength even in the absence of bleeding.¹¹⁰ Furthermore, population studies suggest hemophilia and VWD patients to have an increased risk of fractures and lower bone mineral density,^{111,112} and that this relationship is proportional to the degree of the factor deficiency. Although VWF deficiency has not been extensively studied in relation to bone mineral density, both animal models and clinical observations suggest coagulation factor deficiencies contribute to bone loss. Exercise programs, balance exercise, and home safety programs have been shown to reduce rates of falling in the general elderly population,^{113,114} and these recommendations should be applied to patients with bleeding disorders. An ongoing study has suggested both physical therapy and occupational therapy programs in older patients with hemophilia are feasible, and would be reasonable options for patients with VWD.¹¹⁵ An interesting study in hemophilia patients indicated overall a reduced risk of falls, presumably because of an increased level of caution when ambulating and avoidance of fall risks.¹¹⁶ More studies on the risk and management of osteoporosis and falls in elderly VWD patients are needed.

Dental procedures

Dental procedures are important in elderly patients, including denture replacement and extractions. Proper dental hygiene in geriatric patients improves nutrition, functional status, and quality of life. VWD is a significant risk factor for bleeding with dental work and appropriate use of antifibrinolytics,

DDAVP, and VWF concentrates as well as good intraoperative hemostasis is of particular importance.⁴¹ In general, dental surgery can be accomplished in elderly patients using a similar approach to younger individuals.¹¹⁷ Dental issues remain an increasing concern in older patients,¹¹⁸ and oral health is a significant component of quality of life in elderly patients, therefore standards of care for general patients should be leveraged wherever possible for elderly patients with VWD.¹¹⁹

Conclusion

Elderly patients are often under-represented in clinical trials, and trials involving patients with bleeding disorders are not different in this respect.^{120,121} VWD and AVWS are bleeding disorders with diverse relationships to aging populations. A significant amount of data exists comparing VWF parameters between pediatric patients and adults, but data in older adult age cohorts are lacking. While some milder types of VWD may demonstrate increases in VWF levels over time, the more severe phenotypes do not appear to change, which highlights the point that VWD is a lifelong diagnosis and treatment plans need to be carefully established. The use of VWD prophylaxis in severe disease forms has been associated with a decrease in annual bleeding rates. Chronic conditions that increase over an individual's lifespan also alter bleeding and thrombotic risk, as well as the risk for different types of trauma, surgery, and medications. VWD patients are not entirely protected from thrombotic conditions or atherosclerosis, and wherever possible standards of care for cardiovascular disorders, malignancies, and other diseases should be followed. Elderly patients are also more likely to develop AVWS, given the age-association of most malignancies, AS, and the need for circulatory support devices. The clinician should therefore remain alert to new bleeding symptoms in elderly patients as it may be related to an underlying change in VWF.

This article sought to address some of the open questions in the elderly VWD and AVWS patients. In addition, many questions exist for the elderly population with bleeding disorders that will require longitudinal cohort studies. For example, the burden of cognitive impairment has not been studied. Common frailty measurements have not been validated in inherited bleeding disorders. Finally, in older adults with limited mobility, the incidence, healing rates, and management of pressure ulcers have not been evaluated. It remains important for longitudinal registry studies of bleeding disorders include larger numbers of older adults with VWD to more fully understand the disease complexity related to age.

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