

Von Willebrand Disease

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THE STORY IN ONE SENTENCE

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“Von Willebrand disease happens when you don't have enough or the right kind of a special protein that helps stop bleeding. This protein acts like glue to hold platelets in place at the site of an injury. Without enough good glue, bleeding takes longer to stop.”

Normal anatomy — the body's job

Von Willebrand factor (VWF) is a large sticky protein made by endothelial cells (the cells lining blood vessels) and stored in platelets. When a blood vessel is injured, VWF is released and unfolds into long strands that stick to the exposed collagen (structural protein) in the vessel wall. Platelets then attach to these VWF strands, forming the first layer of a blood clot. VWF also carries and protects factor VIII (a clotting protein needed for the next steps of clot formation).

BODY'S JOB

VWF works like double-sided tape at a gift-wrapping station: one sticky side attaches to the torn edge of the wrapping paper (the blood vessel wall), and the other sticky side holds the ribbon (platelets) in place so you can tie everything together.

1. Endothelial cells in blood vessel walls constantly make and store von Willebrand factor in tiny packages called Weibel-Palade bodies.
2. When a blood vessel is cut or injured, the endothelial cells release von Willebrand factor into the bloodstream.
3. The released von Willebrand factor unfolds and binds tightly to collagen fibers exposed in the damaged vessel wall.
4. Platelets flowing past the injury site attach to the von Willebrand factor strands through a receptor called GP1b on their surface.

5. More platelets attach to each other and to the von Willebrand factor, building a platelet plug at the injury site.
6. Von Willebrand factor also protects factor VIII from being destroyed, keeping it available to help form the final fibrin mesh that strengthens the clot.

What breaks

In von Willebrand disease, the body either doesn't make enough von Willebrand factor, or the factor is made incorrectly so it doesn't work well. Sometimes the protein is released too quickly from storage, or it breaks down too fast in the bloodstream. The result is that platelets can't stick properly to injured blood vessel walls, and factor VIII levels drop because it's not protected, so both the initial platelet plug and the later clot formation are weak.

CLINICAL TERM

Von Willebrand disease results from quantitative deficiency (not enough VWF protein) or qualitative defects (abnormal VWF structure or function) caused by mutations in the VWF gene on chromosome 12. Type 1 involves partial quantitative deficiency with 20-50% of normal VWF levels. Type 2 involves qualitative defects where VWF is present but doesn't bind properly to platelets, collagen, or factor VIII. Type 3 is a complete absence of VWF due to homozygous (inheriting two abnormal copies) or compound heterozygous (two different abnormal copies) mutations.

How the body compensates

The body has limited ability to compensate for missing or defective von Willebrand factor because there is no backup protein that can do its job. Mild cases may show some compensation through increased platelet production and enhanced platelet activation pathways, but these adaptations cannot fully replace VWF function. Severe bleeding episodes trigger general clotting responses, but the initial platelet plug remains weak.

1. {'step': 'Bone marrow increases platelet production', 'detail': 'Megakaryocytes (platelet-making cells) in the bone marrow produce more platelets to try to overcome poor adhesion, though this rarely raises platelet counts above normal.'}
2. {'step': 'Platelets become more sensitive to activation signals', 'detail': 'Circulating platelets may respond more aggressively to thrombin (a clotting enzyme) and ADP (a platelet activator), attempting to clump together even without proper adhesion to vessel walls.'}
3. {'step': 'Blood vessels constrict more strongly', 'detail': 'Injured vessels release more vasoconstrictor (vessel-narrowing) chemicals like serotonin and thromboxane to reduce blood flow through the damaged area and decrease bleeding.'}

4. {'step': 'Remaining von Willebrand factor is used more efficiently', 'detail': 'In Type 1 disease where some VWF is present, the available protein may be released more readily from storage sites and circulate longer before breakdown.'}
5. {'step': 'Alternative adhesion pathways activate', 'detail': 'Platelets attempt to use backup receptors like GP6 and integrin alpha-2-beta-1 to bind directly to collagen, though these pathways work much more slowly without VWF.'}
6. {'step': 'Factor VIII replacement from extravascular sources', 'detail': 'Small amounts of factor VIII produced outside blood vessels (in liver sinusoidal cells and other tissues) enter circulation, though these levels remain low without VWF protection.'}

Domino effect

1. Von Willebrand factor is absent, deficient, or structurally abnormal — Inherited gene mutations prevent normal production, storage, or release of functional VWF protein from endothelial cells and platelets.
2. Platelets cannot adhere to injured blood vessel walls — Without VWF to bridge platelets to exposed collagen, platelets slide past the injury site instead of sticking and forming the initial hemostatic (bleeding-stopping) plug.
3. Primary hemostasis fails and bleeding time prolongs — The first phase of clotting depends on a platelet plug forming within 1-3 minutes; without VWF this takes 10-30 minutes or longer, allowing continued oozing from cuts and injuries.
4. Factor VIII levels drop due to lack of carrier protein — VWF normally protects factor VIII from rapid enzymatic breakdown; without this protection, factor VIII is cleared from blood in 2 hours instead of 12, dropping levels to 5-40% of normal.
5. Secondary hemostasis is also impaired — Low factor VIII weakens the intrinsic coagulation pathway (one of the clotting cascades), reducing thrombin generation and fibrin mesh formation needed to strengthen the clot.
6. Mucosal and soft tissue bleeding becomes frequent — Areas with high blood flow and friable (easily damaged) tissue—nose, mouth, GI tract, uterus—bleed easily and persistently because weak clots break apart under normal blood flow pressure.
7. Chronic or recurrent bleeding leads to iron deficiency anemia — Repeated bleeding episodes, especially heavy menstrual periods (menorrhagia) in women, cause ongoing iron loss exceeding dietary intake, dropping hemoglobin (oxygen-carrying protein) to 7-10 g/dL or lower.
8. Rare but life-threatening bleeding (hemorrhage) occurs with major trauma or surgery — In Type 3 disease or severe Type 2 variants, complete absence of functional VWF means no primary hemostasis at all, leading to uncontrolled bleeding into joints (hemarthrosis), muscles, or brain after injuries that would be minor in healthy individuals.

Symptoms · what the patient feels, and why

- Easy bruising: Low von Willebrand factor (VWF, a clotting protein) prevents platelets (clotting cells) from sticking to blood vessel walls, so even minor bumps cause bleeding under the skin
- Frequent nosebleeds lasting more than 10 minutes: Nasal blood vessels are fragile and without adequate VWF to plug tiny breaks, bleeding continues longer than normal
- Heavy menstrual bleeding requiring pad or tampon change every 1–2 hours: Uterine (womb) blood vessels cannot form stable clots during menstruation without sufficient VWF, so the endometrium (lining) sheds with excessive blood loss
- Prolonged bleeding after dental extraction or surgery: Surgical wounds need platelet plugs held together by VWF; deficiency allows the plug to fall apart and bleeding to restart hours or days later
- Blood in stool or black tarry stools: Gastrointestinal (stomach and intestine) bleeding from angiodysplasia (abnormal blood vessels) or ulcers cannot clot properly without VWF
- Joint swelling and pain: Hemarthrosis (bleeding into joints) occurs in severe type 3 VWD where factor VIII (another clotting protein carried by VWF) is also very low
- Excessive bleeding after minor cuts lasting more than 15 minutes: Small skin wounds normally stop bleeding in 5–10 minutes; VWF deficiency delays formation of the initial platelet plug
- Bleeding in the mouth or gums with routine tooth brushing: Oral mucosa (mouth lining) has rich blood supply and constant minor trauma; without VWF, tiny vessels bleed easily

Focused exam

- Multiple bruises (ecchymoses) (bruises) larger than 3 cm on arms and legs in different stages of healing: Large bruises without remembered trauma suggest impaired primary hemostasis (initial clotting step) from platelet or VWF dysfunction
- Pinpoint bleeding spots (Petechiae) (tiny red or purple dots) on the soft palate or lower legs: Pinpoint bleeding spots (Petechiae) indicate bleeding from capillaries (smallest blood vessels) and can signal a low platelet count (thrombocytopenia) (low platelet count) or severe VWF deficiency, but are less common in VWD than in platelet disorders
- Pale conjunctivae (eye lining) and pale palmar creases: Pale skin (Pallor) suggests anemia (low hemoglobin) from chronic blood loss due to heavy menses or gastrointestinal bleeding
- Swollen, warm knee or elbow with decreased range of motion: Hemarthrosis causes joint damage and suggests severe type 3 VWD with factor VIII below 10 percent, requiring immediate factor replacement

- Active a nosebleed (epistaxis) (nosebleed) from the anterior nasal septum: Direct visualization identifies the bleeding site for cauterization or packing and confirms mucosal bleeding pattern typical of VWD
- A fast heart rate (Tachycardia) (heart rate above 100) and orthostatic low blood pressure (hypotension) (blood pressure drop when standing): These vital sign changes indicate significant acute blood loss (more than 15 percent of blood volume) requiring immediate intravenous fluids and possible transfusion

Diagnostics · every test answers a question

- Von Willebrand factor antigen (VWF:Ag) → How much von Willebrand protein is circulating in the blood?
- Von Willebrand factor activity (VWF:RCO or VWF:GPIbM) → Does the VWF protein work properly to bind platelets?
- Factor VIII activity → Is the level of factor VIII clotting protein normal?
- VWF multimer analysis → Are the different sizes of VWF molecules present in the correct pattern?
- Complete blood count (CBC) → Is the patient anemic from blood loss, and is the platelet count normal?
- Bleeding time or PFA-100 (platelet function analyzer) → How long does it take for a small skin wound to stop bleeding?
- Blood type (ABO typing) → Does the patient have type O blood, which naturally has lower VWF levels?
- VWF:FVIII binding assay → Can VWF properly bind and protect factor VIII?

Treatment logic

- Desmopressin (DDAVP) given intravenously, subcutaneously, or intranasally before procedures → Stimulates release of stored VWF from endothelial cells (blood vessel lining) into circulation, raising VWF and factor VIII levels 3-5 fold within 30-60 minutes
- VWF/factor VIII concentrate infusion for major bleeding or surgery → Directly replaces missing VWF and factor VIII proteins, restoring normal clotting within minutes; used when DDAVP is ineffective or contraindicated
- Tranexamic acid oral or intravenous → Blocks plasmin (enzyme that breaks down clots), stabilizing clots already formed in mucous membranes like mouth, nose, and uterus for 6-8 hours per dose

- Hormonal contraceptives (combined oral pills, levonorgestrel IUD, or depot medroxyprogesterone) for heavy menstrual bleeding → Thins the endometrium (uterine lining) and reduces menstrual blood loss by 40–50 percent; estrogen in combined pills also raises VWF levels by 20–30 percent
- Avoidance of antiplatelet drugs (aspirin, NSAIDs, clopidogrel) and anticoagulants unless absolutely necessary → Prevents additional impairment of platelet function and clotting cascade, reducing bleeding risk in daily life
- Red blood cell transfusion for symptomatic anemia from acute bleeding (hemorrhage) → Restores oxygen-carrying capacity and blood volume within hours, reversing a fast heart rate (tachycardia), fatigue, and orthostatic symptoms when hemoglobin drops below 7 g/dL or patient is unstable

Medications

Desmopressin · Synthetic vasopressin analog

Desmopressin is a man-made copy of vasopressin, a hormone that normally controls urine output. When given to people with VWD, it binds to receptors on the cells lining blood vessels. This triggers those cells to squeeze out stored VWF into the bloodstream very quickly. The VWF level can triple or more within 30 minutes.

1. Desmopressin binds to V2 receptors on endothelial cells
2. Receptor activation triggers cyclic AMP (cAMP), a signaling molecule inside the cell
3. cAMP causes Weibel-Palade bodies (storage sacs of VWF) to move to the cell surface
4. Weibel-Palade bodies fuse with the cell membrane and release VWF into the blood
5. Released VWF carries factor VIII with it, raising both clotting proteins together

SAFETY WATCH

Low sodium (Hyponatremia) (low blood sodium) from water retention—limit fluids to 1 liter for 24 hours after dose in adults, monitor sodium in children and elderly · Contraindicated in type 2B VWD because it releases abnormal VWF that clumps platelets and can cause dangerous a low platelet count (thrombocytopenia) · Can trigger seizures if sodium drops below 125 mEq/L, especially in children under 2 years old · Trial dose recommended before surgery to confirm patient responds with 3-fold rise in VWF

Von Willebrand factor/factor VIII concentrate (human plasma-derived) · Clotting factor replacement (examples: Humate-P, Wilate, Alphanate)

This medicine contains real VWF and factor VIII proteins purified from donated human blood plasma. When infused into a vein, the proteins immediately circulate and fill in what is missing.

The VWF molecules stick to platelets and blood vessel walls at injury sites. They also carry and protect factor VIII so it lasts longer in the blood. Both proteins work together to form strong clots.

1. Infused VWF binds to collagen (structural protein) exposed at sites of vascular injury
2. VWF changes shape (conformation change) to expose binding sites for platelet GPIb receptors
3. Platelets attach to VWF-coated collagen, forming the primary hemostatic plug
4. Factor VIII released from VWF participates in the coagulation cascade, generating thrombin
5. Thrombin converts fibrinogen to fibrin, creating a stable mesh that reinforces the platelet plug

SAFETY WATCH

Allergic reactions including anaphylaxis possible due to plasma proteins · Clot formation (Thrombosis) (unwanted clot formation) risk if doses are too high or in patients with cardiovascular disease · Inhibitor antibodies can develop in type 3 VWD patients (seen in 5-10 percent) who see VWF as foreign protein · Monitor VWF and factor VIII levels to ensure adequate dosing without excessive accumulation

Tranexamic acid · Antifibrinolytic (lysine analog)

Tranexamic acid is shaped like the amino acid lysine. The body uses lysine binding sites to break down clots through a process called fibrinolysis. Tranexamic acid occupies those lysine sites on plasminogen (the inactive form of the clot-dissolving enzyme plasmin). This prevents plasminogen from turning into active plasmin. Without plasmin, clots stay intact much longer, especially on mucous membranes in the nose, mouth, and uterus.

1. Tranexamic acid binds reversibly to lysine-binding sites on plasminogen molecules
2. Blocked plasminogen cannot attach to fibrin in the clot structure
3. Tissue plasminogen activator (tPA) cannot convert plasminogen to plasmin at the clot site
4. Without plasmin, fibrin strands in the clot remain intact instead of being digested
5. The stabilized clot lasts 6-8 hours longer, reducing rebleeding at mucosal surfaces

SAFETY WATCH

Contraindicated in active thromboembolic disease (DVT, PE, stroke) due to theoretical risk of stabilizing pathologic clots · Use caution in patients with history of seizures—high IV doses can lower seizure threshold · Reduce dose in chronic kidney disease because drug is cleared by kidneys · Can cause nausea when taken orally; give with food to improve tolerance

Combined oral contraceptive pills (ethinyl estradiol with progestin) · Hormonal contraceptive (estrogen-progestin combination)

Birth control pills contain two hormones: estrogen and progestin. The estrogen component increases the liver's production of VWF and factor VIII by 20–30 percent over several weeks. The progestin thins the uterine lining so less tissue sheds during periods. Together, they reduce menstrual blood loss by nearly half. The steady hormone levels also prevent ovulation (egg release), eliminating the mid-cycle hormone surge that can worsen bleeding.

1. Ethinyl estradiol stimulates hepatocytes (liver cells) to increase VWF and factor VIII gene transcription
2. Higher VWF and factor VIII levels improve hemostasis throughout the body
3. Progestin suppresses LH (luteinizing hormone) surge from the pituitary gland
4. Without LH surge, ovulation does not occur and endometrium remains thin
5. Thinner endometrium sheds less blood during withdrawal bleed (period on placebo pills)

SAFETY WATCH

Increases venous thromboembolism (VTE) risk 2–4 fold, especially in first year and in women over 35 who smoke · Contraindicated in women with migraine with aura, uncontrolled high blood pressure (hypertension), or history of VTE or stroke · May worsen high blood pressure (hypertension)—check blood pressure at follow-up visits · Small increased risk of breast cancer with long-term use, but decreases ovarian and endometrial cancer risk

Levonorgestrel intrauterine device (IUD) · Progestin-only contraceptive (intrauterine system)

The levonorgestrel IUD is a small T-shaped device placed in the uterus that slowly releases the progestin hormone levonorgestrel. The progestin acts directly on the uterine lining, keeping it very thin. Thin lining means much less tissue to shed during periods. Most women have very

light periods or no periods at all after 6–12 months. Unlike pills, it does not raise VWF levels, but it is highly effective at reducing menstrual blood loss by 90 percent or more.

1. Levonorgestrel diffuses from the IUD reservoir into the uterine cavity
2. Progestin binds to progesterone receptors in endometrial cells
3. Receptor activation suppresses estrogen-driven proliferation of the endometrium
4. Endometrial glands atrophy (shrink) and blood vessel growth decreases
5. The thin, atrophic endometrium produces minimal menstrual flow, often just spotting or none

SAFETY WATCH

Irregular spotting or bleeding common in first 3–6 months before absent periods (amenorrhea) (no periods) develops · Small risk of uterine perforation during insertion, especially in postpartum period · Ectopic pregnancy risk if pregnancy occurs with IUD in place (though overall pregnancy rate is very low) · Does not increase VTE risk like estrogen-containing contraceptives, making it safer for women with thrombophilia (clotting disorders)

Recombinant von Willebrand factor (rVWF) · Clotting factor replacement (recombinant, brand name Vonvendi)

This is VWF protein made in a laboratory using genetically engineered cells, not from human blood. The cells are programmed to produce only VWF with the correct structure. When infused, the recombinant VWF works exactly like natural VWF, binding to platelets and collagen at injury sites. It does not contain factor VIII, so factor VIII must be given separately if needed. Because it is recombinant, it carries no risk of human viruses.

1. Recombinant VWF circulates and binds to endogenous (patient's own) factor VIII in the blood
2. At sites of vascular injury, VWF attaches to exposed subendothelial collagen
3. VWF multimers unfold under shear stress (blood flow force) to expose platelet-binding sites
4. Platelets adhere to VWF via GPIb and GPIIb/IIIa receptors, forming aggregates
5. VWF-bound factor VIII is protected from degradation and participates in generating thrombin for fibrin clot

SAFETY WATCH

Clot formation (Thrombosis) risk if excessive doses used, especially in older patients or those with atherosclerosis · Infusion reactions including chest discomfort, nausea, or tingling or numbness (paresthesias) (tingling) reported in clinical trials · Monitor for development of inhibitor antibodies, though risk appears lower than with plasma-derived products · Approved only for adults with VWD in many countries; must be given with recombinant factor VIII if factor VIII is also low

Red flags

- Hemarthrosis (joint bleeding) or deep muscle a pooled collection of blood (hematoma) suggesting severe type 3 VWD with very low factor VIII
- Postpartum bleeding (hemorrhage) requiring transfusion or ICU admission
- Signs of hypovolemic shock (tachycardia, low blood pressure (hypotension), altered mental status) from acute blood loss
- New onset bleeding in older adult suggesting acquired von Willebrand syndrome from lymphoma, myeloproliferative disorder, or aortic narrowing (stenosis)

Nursing priorities

1. Assess for active bleeding and bleeding risk before any procedures or surgeries — Von Willebrand disease (VWD) is a bleeding disorder caused by low or poor-working von Willebrand factor (a protein that helps blood clot). Patients bleed longer than normal, so we must check bleeding history and current bleeding sites before invasive procedures to prevent life-threatening bleeding (hemorrhage).
2. Monitor menstrual bleeding patterns in female patients and adolescents — Heavy menstrual bleeding (menorrhagia) is often the first sign of VWD in women and girls. Excessive periods can cause anemia (low red blood cells) and fatigue. Early recognition helps start treatment and prevent complications like iron deficiency.
3. Teach patients to avoid aspirin and NSAIDs like ibuprofen — Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) stop platelets (clotting cells) from working properly. In VWD patients who already have clotting problems, these medicines increase bleeding risk significantly. Acetaminophen is safer for pain.
4. Prepare for desmopressin (DDAVP) administration in Type 1 VWD patients before procedures — Desmopressin (DDAVP) is a medicine that releases stored von Willebrand factor from blood vessel walls. It works well in Type 1 VWD (the mildest form) to temporarily raise clotting factor levels before dental work or minor surgery. Not all types respond to DDAVP.

5. Monitor for signs of intracranial bleeding after head trauma — Head injuries in VWD patients can cause bleeding inside the skull (intracranial bleeding (hemorrhage)). Watch for severe headache, confusion, vomiting, vision changes, or seizures. This is a medical emergency requiring immediate factor replacement therapy.
6. Coordinate factor replacement therapy (von Willebrand factor concentrates) for severe bleeding or Type 3 disease — Type 3 VWD is the most severe form with almost no von Willebrand factor. These patients need intravenous (IV) replacement with products containing both von Willebrand factor and factor VIII (another clotting protein). This prevents and treats serious bleeding episodes.
7. Screen for iron deficiency anemia from chronic blood loss — Repeated bleeding episodes (nosebleeds, heavy periods, gastrointestinal bleeding) deplete iron stores over time. Check hemoglobin (oxygen-carrying protein in red blood cells), hematocrit (percentage of red blood cells), and ferritin (stored iron) levels. Iron supplementation may be needed.
8. Educate patients to wear medical alert identification and inform all healthcare providers of their diagnosis — Emergency responders and dentists need to know about VWD immediately. A medical alert bracelet ensures proper treatment during emergencies and prevents use of medicines that worsen bleeding. All procedures require special planning and often preventive (prophylactic) (preventive) treatment.

Sources

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- National Hemophilia Foundation (NHF) MASAC (Medical and Scientific Advisory Council) recommendations for von Willebrand disease treatment products and protocols, 2022
- American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on von Willebrand disease in women and adolescents, 2023

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