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Von Willebrand Disease: Exploring the Diagnostic and Therapeutic Challenges in Pakistan

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ABSTRACT

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, arising from either a reduced amount or impaired function of von Willebrand factor (VWF), a protein vital to normal clot formation. This article examines the condition in detail, outlining its biological basis, symptoms, diagnostic difficulties, and available treatment options. Particular focus is placed on the situation in Pakistan, where unique challenges shape patient outcomes. The discussion also addresses the development of alloantibodies in some patients, exploring how these immune responses affect treatment success and quality of life. Psychosocial factors and dietary patterns, especially within the Pakistani context, are considered as additional influences on disease management. Worldwide, VWD often remains undetected because its symptoms can vary widely and resemble those of other bleeding disorders. In Pakistan, the problem is aggravated by low public awareness, limited access to diagnostic tools, and financial constraints, all of which lead to late diagnosis and inadequate care. Timely identification and appropriate medical intervention are critical for improving prognosis. The review underscores the need to strengthen diagnostic infrastructure, increase the reach of specialized care, and make effective therapies more accessible, particularly in underserved regions. Advances in genetic research and new treatment options, including the possibility of gene therapy, offer hope for better disease control in the future. The article concludes by urging reforms in healthcare systems, greater educational outreach, and focused measures to close existing gaps in the detection and management of VWD in Pakistan.

1. INTRODUCTION

Von Willebrand disease (VWD) is the one of the most common inherited bleeding disorders, with global prevalence estimating to approximately 0.1% of the population (Bowman *et al.*, 2010). First report of the disease date back to 1926 by a Helsinki researcher Erik von Willebrand. He observed the condition in several members of a family

living on an island in Finland (Nilsson, 1984). Later, in 1981 Nyman and colleagues revisited the family and classified the individuals based on the severity of their condition: disease with mild symptoms as type 1 VWD, and with severe symptoms as type 3 VWD (Nyman *et al.*, 1981). In general, in Type 1 VWD, partial quantitative deficiency of von Willebrand factor (*VWF*) occurs, while Type 3 VWD is characterized by a virtually complete absence of *VWF*, leading to more severe bleeding

symptoms. The underlying cause of VWD is the deficiency or low quantities of multimeric plasma glycoprotein termed as von Willebrand factor (*VWF*). This glycoprotein plays a crucial role in blood clotting. It has two key functions: it binds to the clotting factor VIII, and stabilizes it, which is essential for clotting. It plays a key role in blood clotting by drawing platelets to sites of vessel injury. Once there, platelets provide a platform for fibrin formation and the activity of clotting factors, allowing a stable clot to develop (Altaf *et al.*, 2008).

In its mature form, VWF exists as multimers of varying lengths, from just two subunits to well over a hundred. Production begins with single monomers, which undergo glycosylation, link in pairs to form dimers, and then assemble into large multimeric chains. This architecture creates multiple binding sites that enable VWF to interact with both platelets and endothelial cells. Depending on its composition, the molecular size can range from roughly 500 kDa to more than 10,000 kDa, making it the largest soluble protein in human plasma (Lenting *et al.*, 2015). Post-translational changes, such as proteolytic cleavage, can alter its size, resulting in a mixture of intact and cleaved forms in circulation. The VWF gene is located on chromosome 12p13.2, spread across 52 exons and about 180 kb of DNA. There is also a partial pseudogene on chromosome 22q11.2, about 21–29 kb in length, which corresponds to exons 23–34 of the functional gene. This pseudogene is unprocessed but can interfere with genetic analysis of VWF (Dent *et al.*, 1991), (Mancuso *et al.*, 1989; Kuwano *et al.*, 1996). People with von Willebrand disease (VWD) tend to have recurrent bleeding episodes, most often affecting mucocutaneous sites. This can include heavy menstrual bleeding, gastrointestinal hemorrhage, frequent nosebleeds, and oral bleeding. Excessive bleeding is also common after surgery, dental extractions, injuries, or

childbirth. In women, prolonged or heavy menstrual bleeding is often a key sign of VWD. In mild cases, bleeding usually follows significant injury, but in severe disease, even a small cut, or no clear injury at all, can lead to considerable blood loss. Symptoms can change over time, influenced by age, pregnancy, physical activity, and stress (Sanders *et al.*, 2015). In women, prolonged and heavy bleeding during menstruation is a key indicator of VWD. In cases of mild VWD, excessive bleeding typically occurs after significant injuries, while in more severe forms of the disease, even minor cuts or no apparent injury can lead to substantial bleeding. The severity of symptoms can change over time, often influenced by factors like age, pregnancy, physical activity, and stress (Philipp and Kadir, 2000; Dilley *et al.*, 2001; Shankar *et al.*, 2002; Goodeve *et al.*, 2007; Touré *et al.*, 2007; Tabrizchi and Sani, 2014; Bowman and Rizvi, 2018).

2. PATHOPHYSIOLOGY AND BIOSYNTHESIS

The *VWF* gene encodes a protein made up of 2,813 amino acids. This protein includes a 22-amino acid signal peptide, followed by a large propeptide of 741 amino acids, known as von Willebrand antigen II, and a mature subunit that consists of 2,050 amino acids (Figure 1) (Sadler *et al.*, 1985; Bonthron *et al.*, 1986). Remarkably, over 95% of the protein's structure consists of domains that share similarities with those found in other proteins. The sequence of these structural domains is organized as follows: D1, D2, D', D3, A1, A2, A3, D4, B1, B2, B3, C1, C2, and CK (Figure 2). Additionally, the *VWF* protein undergoes significant glycosylation, featuring 12 N-linked and 10 O-linked oligosaccharides. Notably, some N-linked oligosaccharides carry ABO blood group determinants, which exhibit distinct characteristics (Titani *et al.*, 1986; Matsui *et al.*, 1992).



Von Willebrand factor (*VWF*) synthesis occurs in the endothelial cells and megakaryocytes (Nachman *et al.*, 1977). The process begins in the endoplasmic reticulum, where pro*VWF* forms disulfide dimers linked by 90 amino acid "cysteine knot" (CK) domains at their carboxyl ends (Meitinger *et al.*, 1993). These pro*VWF* dimers are then transported to the Golgi apparatus for further processing. In the Golgi, additional inter-subunit disulfide bonds are formed between the D3 domains, leading to the creation of multimers that can exceed 20 mDa in size (Dong *et al.*, 1994). The pro*VWF* propeptide is crucial in this process, as it exhibits protein disulfide isomerase-like functions that aid in the formation of disulfide bonds in the typically acidic environment of the

Golgi, which would not favour such processes under normal conditions (Mayadas and Wagner, 1992). Post-translational modifications that occur in the Golgi include the proteolytic cleavage of the *VWF* propeptide and the completion of N-linked and O-linked glycosylation, along with the sulfation of specific N-linked oligosaccharides (Rehemtulla and Kaufman, 1992; Vischer and Wagner, 1994). Mature *VWF* multimers are secreted from endothelial cells to Weibel-palade, *VWF* stored in the granules (Vischer and Wagner, 1994). Finally, mature *VWF* multimers are secreted from endothelial cells and stored in Weibel-Palade bodies within granules.

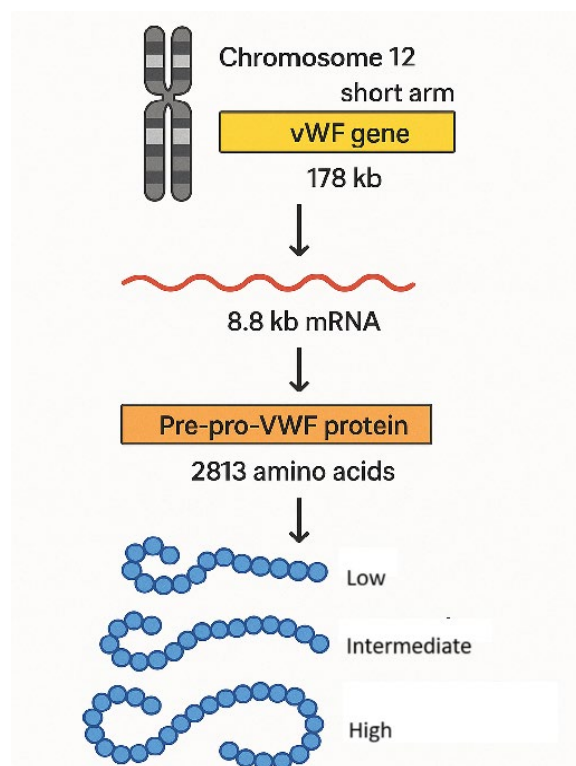


Figure 1. The figure indicates the position and biosynthesis of the *VWF* gene on chromosome 12. A *VWF* gene is 178Kb in size go into transcription and form mRNA of 8.8Kb. After translation a ~2813 amino acid residue protein is formed which is 300-350 kDa in size. The *VWF* protein has low, intermediate and high molecular weight multimers



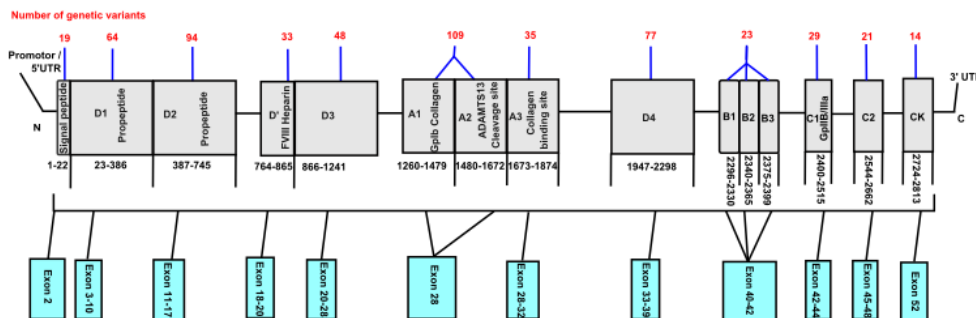


Figure 2. Schematic cartoon showing the 2813 amino acids present in the VWF protein. The VWF gene is made up of 52 exons and 51 introns that undergo transcription and form mRNA of 8830 nucleotides. The transcribed mRNA consists of a 22 bp long signal peptide followed by the 2791 residue mature VWF protein

3. PREVALENCE IN PAKISTAN

VWD is an inherited disorder that can be passed from parents to offspring through various inheritance patterns. The most common form, Type 1 VWD, and many cases of Type 2 VWD follow an autosomal dominant inheritance pattern, meaning a single copy of the altered gene from either parent can cause the condition. In contrast, Type 3 VWD and some rare forms of Type 2 (e.g., Type 2N) are inherited in an autosomal recessive manner, where both copies of the gene—one from each parent—must be mutated for the disease to manifest. These inheritance patterns influence both the severity of the disease and the likelihood of transmission to offspring. It is estimated that 1% of the global population suffers from VWD; however, research has shown that 9 out of 10 patients remain undiagnosed. In developed countries, government registries are actively involved in allocating resources for individuals with bleeding disorders through tertiary care centers. These centers provide services, ensure accurate diagnosis, offer medical facilities for patients, and focus heavily on patient education.

In Pakistan, a developing South Asian country, there are no proper government registries or tertiary healthcare centers dedicated to managing bleeding disorders. The matter of fact is that, in Pakistan, comprehensive studies on VWD are not present, but few tertiary care centers published approximately 3.18-7.74% prevalence among all inherited bleeding disorders (Saeedi *et al.*, 2001). Consequently, the exact prevalence of VWD and its subtypes in Pakistan is unknown due to frequent misdiagnosis and underdiagnosis of the disease. Some trust foundations and transfusion centers work with patients affected by inherited bleeding disorders, but challenges remain. Another cause of misdiagnosis is the variability among laboratory tests across different labs, with these variations depending on the availability of specific diagnostic tests. To address these issues, great care is required when interpreting diagnostic results. Additionally, the diagnosis must be based on the combined results of multiple screening tests along with confirmatory test reports. In Pakistan, limited access to specific testing is a major reason why many patients are misdiagnosed with haemophilia or Bernard-Soulier syndrome, based on incorrect results.



from factor VIII levels and platelet aggregation assays, respectively (Adil and Qureshi, 2008).

4. CLINICAL PRESENTATION

To know the pathogenesis of von Willebrand disease (VWD), it is necessary to know the molecular pathogenic mechanisms of VWD in all three types. As VWD has very diverse types and type II is also divided into subtypes leads to complicated pathogenesis. This is the major hurdle in the diagnosis of correct type of VWD. To understand the exact pathogenesis of VWD is helpful in the treatment.

- **Type 1:** Type 1 VWD is a partial quantitative defect of *VWF* that is based on the level of protein deficiencies while the function of the protein remains the same. In this type, the level of FVIII also falls in the same manner, but normally its level is approximately 1.5 times higher than the level of *VWF* in the blood (Favaloro, 2011b). The average *VWF* level in the plasma of the local population is 100 IU/dL, and it has a normal reference range between 50-200 IU/dL. Only 5% of individuals detect low levels of 50 IU/dL and are included in VWD, while others have slightly low levels and remain undiagnosed (Sadler *et al.*, 2006). Mild bleeding symptoms are commonly observed, including menorrhagia and prolonged nosebleed time. However, diagnosing type 1 is a difficult process due to the linkage between different levels of *VWF* and symptoms of the disease (Yawn *et al.*, 2009).
- **Type 2:** Type 2 VWD is a qualitative defect of VWD in which, *VWF* level in plasma is ineffective, and the FVIII level may also be low or normal. Functional defects play an important role in the categorization of different subtypes of type 2 VWD (Sadler *et al.*, 2006).
 - **Subtype 2A:** The 2A class of type 2 is categorized based on the absence or deficiency of the large molecular weight subunit of *VWF*, which is a biologically active form. It is caused by either faulty assembly or an accelerated in vivo proteolysis process (Sadler *et al.*, 2006). Subtype 2A VWD is traditionally considered a common type, but recent evidence suggests that subclass 2M is a common variant among the population (Favaloro, 2011b). Based on reported data, subclass 2A accounts for 40-80% of all type 2 VWD cases (Favaloro, 2015).
 - **Subtype 2B:** In 2B VWD, *VWF* performs hyperactive or hyper adhesive functions (Sadler *et al.*, 2006). In this condition, the absence of typical haemostatic triggers leads to spontaneous platelet binding, as well as clearance from the blood circulation, causing a loss of HMW *VWF*. Sometimes, this condition leads to mild thrombocytopenia. Type 2B VWD is known to be a rare form among all types of 2 VWD, accounting for less than 5% of cases, often with normal FVIII levels (Favaloro, 2011b).
 - **Subtype 2M:** In this type of VWD, *VWF*-dependent platelet adhesion is reduced, irrespective of defective or deficient HMW *VWF* multimers (Sadler *et al.*, 2006). Several scientists and clinicians face difficulty in the diagnosis of 2M VWD, and it represents a wide heterogeneous group of *VWF* defects. An exclusion strategy is used for the identification of 2M VWD among all types (Favaloro, 2011a). Subclass 2M comprises 20-50% of all types of 2 VWD cases (Favaloro, 2011b).
 - **Subtype 2N:** In subclass 2N of VWD, defects occur in *VWF*, leading to improper FVIII binding (Sadler *et al.*, 2006). This is similar to type 3 VWD, where early



protein cleavage occurs, resulting in FVIII loss that consequently leads to bleeding, similar to what happens in haemophilia A. It is also one of the rare forms of type 2 VWD, affecting less than 5% of all patients (Favaloro, 2011b).

- **Type 3:** It is the most severe and rare type among all cases of VWD in developing countries, with a prevalence of less than 5%. In this type, *VWF* is absent, and consequently, the level of FVIII in the plasma is also reduced, accounting for less than 10 IU/dL. Due to consanguinity and underdiagnosed mild bleeding disorders, there is a high prevalence rate of about 60% in underdeveloped countries (Favaloro, 2011b).
- **Acquired von Willebrand syndrome (AVWS):** It is an underdiagnosed, rare haemorrhagic disorder that shares similar clinical and laboratory parameters with the congenital form of von Willebrand disease (VWD). However, it occurs in individuals who have a negative family history of the disease and no genetic basis for VWD (Shetty *et al.*, 2011). AVWS is an acquired syndrome with multiple causative factors, including quantitative *VWF* deficiency; for example, hypothyroidism is hypothesized to result in reduced *VWF* production (Federici *et al.*, 2013). It may also be caused by increased clearance of *VWF* from the immune system, such as through autoantibodies. In transformed or cancer cells, this mimic type 1 VWD. Similarly, qualitative defects may also contribute to AVWS; for example, aortic stenosis and plasma cell disorders can induce the removal of selective high-molecular-weight multimers of *VWF*, mimicking type 2A VWD (Favaloro, 2015).

5. DIAGNOSIS OF VWD

VWF quantity is measured through different initial tests, which depend on the phenotype of the patient, but some confirmatory tests are also needed to confirm the types and subtypes. If the *VWF*: RCo/*VWF*: Ag ratio is decreased in patients, then *VWF* multimer distribution should be evaluated because the normal distribution of multimers signals a diagnosis of type 2M, while the loss of HMW multimers leads toward a diagnosis of type 2A or 2B VWD. To assess the multimers, the agarose gel electrophoresis technique is used, but most laboratories do not use this technique due to time consumption (Ruggeri and Zimmerman, 1980). Multimer assessment can be replaced by the collagen binding assay of *VWF* to identify HMW multimers and type 2M VWD (Favaloro, 2009). Type 2B VWD is confirmed by the platelet binding (*VWF*: PB) assay, in which spontaneous binding increases with platelets, confirming type 2 VWD. Commercially available platelets are used with patient plasma to identify the increased binding ability in type 2B (Roberts and Flood, 2015).

Low-dose ristocetin-induced platelet aggregation (Id-ripa) is another confirmatory test for the diagnosis of VWD. The low dose of ristocetin, which is approximately ≤ 0.6 mg/mL, is sufficient for spontaneous aggregation compared to the normal dose of ≥ 1 mg/mL in type 2 and platelet-type VWD patients. VWD variants can be differentiated based on *VWF*: PB or through genetic analysis. However, the identification of type 2B VWD is necessary because these patients avoid desmopressin treatment, although type 2A and 2B have similar features, such as symptoms occurring in the deficiency of HMW multimers and a decreased *VWF*: RCo/*VWF*: Ag ratio. The diagnosis of platelet-type VWD is needed because patients require platelet transfusion treatment (Roberts and Flood, 2015). *VWF*: FVIII binding (*VWF*: FVIIIb) is a



confirmatory test for type 2N VWD, in which *VWF* is extracted from the patient's plasma and demonstrates its binding ability with recombinant FVIII. Type 2N VWD has a specific defect in FVIII binding with *VWF* (Nishino *et al.*, 1989).

VWF propeptides (*VWFpp*) can be assessed in type 1C, also known as clearance defect, which has an increased ratio of *VWFpp/VWF*: Ag that is also observed in some type 2 variants. *VWFpp* can be checked through ELISA, which is not accessible in all laboratories. Another way to measure the clearance defect is through the desmopressin response; in this assay, an elevated level of *VWF*: Ag is observed after 1 hour, but the *VWF* level decreases with desmopressin treatment after 4 hours (Haberichter *et al.*, 2006). The large size and multimeric globular nature of the *VWF* gene are major hurdles in the genetic analysis of *VWF*. DNA sequencing focuses on some specific variants of VWD; for example, in type 2 VWD, there is difficulty in interpretation through confirmatory laboratory tests. A large number of sequence variations data of type 2 VWD is reported by the International Society on Thrombosis and Hemostasis (Roberts and Flood, 2015).

6. RELATIONSHIP OF ABO BLOOD GROUP WITH *VWF*

ABO blood group determinants have an indirect relationship with platelet von Willebrand factor (*VWF*). Their oligosaccharide sequences are not present on the N-glycan of platelet *VWF* but are expressed on the surface of other glycolipids and glycoproteins. Glycoproteins such as GPIb, IIa, IIIa, IV, V, and platelet endothelial cell adhesion molecule 1 express ABO determinants on their surfaces. *VWF* plays a crucial role at the site of injury by creating a meshwork between collagen and specific receptors present on the surface of platelets.

Under adverse conditions, *VWF* binds with platelet surface complexes like GPIb-IX-V and GPIIb-IIIa. This indicates that specific oligosaccharide sequences of the ABO blood group are expressed on these surface complex receptors and influence haemostasis (Zhong *et al.*, 2015). When *VWF* binds under stress conditions, it is able to connect subendothelial collagen with the specific receptors on platelets. ABO(H) determinants are expressed on these surface complex receptors and impact haemostasis (Zhong *et al.*, 2015).

Additionally, the expression of ABO on GPIb influences the interaction of glycoproteins with *VWF*. To investigate this influential effect, Dunne *et al.* examine the translocation dynamics of blood group O and other blood groups over *VWF* through comparative analysis. They find a significant decrease in the interactive ability of blood group O with *VWF* under specified conditions. In comparison to other blood groups, type O has a reduced ability to adhere stably to *VWF*. Analytical modelling suggests that differences among ABO platelet types depend on alterations in GPIb and *VWF* interactions, although the exact mechanism remains unknown (Dunne *et al.*, 2019).

7. INHIBITOR DEVELOPMENT

Patients with von Willebrand disease (VWD) face another challenge in treatment: the production of alloantibodies. The prevalence of alloantibody production ranges from 5.8% to 9.5% in these patients (Iorio *et al.*, 2008). Inhibitor development against *VWF* is rare and occurs mainly in severe type 3 VWD, while patients with type 1 and type 2 VWD do not typically develop alloantibodies (Mannucci and Federici, 1995). Early investigations suggest that *VWF* alloantibodies are produced only in patients with gene deletions, either partial or complete. However, in the 1970s, a patient with a nonsense mutation also



developed anti-*VWF* antibodies. Later studies confirm that nonsense mutations, frameshift mutations, and primarily partial and complete gene deletions are associated with inhibitor development (James *et al.*, 2013).

Currently, there are no specific laboratory techniques to identify alloantibodies. Some general assays are available that work through mixing studies, based on the inhibition of platelet-dependent function of *VWF*. It is suggested to evaluate collagen binding and FVIII binding functions of *VWF* to assess inhibitors (Berntorp *et al.*, 2012). *VWF* alloantibodies are independent of time and temperature; therefore, assays are conducted at 37°C with a 15- to 120-minute incubation period. The titer of the antibody is measured in Bethesda units. Recently, laboratories have used ELISA for the detection of alloantibodies, which serves as a sensitive assay. However, false positive results can occur, leading to ambiguity. To resolve this issue, it is preferred to use laboratories with experience in both screening ELISA and functional mixing studies (Siaka *et al.*, 2003).

8. DIETARY INFLUENCE ON VWD

Diet plays a significant role in overall health and can influence the risk of arterial and venous thrombosis. Studies have shown that individuals who follow a low-fat, high-fiber diet have a reduced risk of thrombosis. Research has also established a direct link between a healthy diet and improved haemostasis. The primary function of the haemostatic system is to prevent excessive bleeding and haemorrhage following blood vessel injuries, which is achieved through a series of steps. In primary haemostasis, platelets adhere to the injury site and aggregate, while secondary haemostasis involves a coagulation cascade that converts soluble fibrinogen into insoluble fibrin, activating and aggregating more platelets. The final step is

fibrinolysis, where the fibrin network is systematically degraded (Pieters and De Maat, 2015). Von Willebrand factor (*VWF*) plays a crucial role in primary haemostasis. The relationship between dietary energy and haemostasis can be seen through the effects of obesity and weight reduction, which serve as important indicators. Increased adiposity is associated with higher levels of *VWF*, fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and plasminogen (Faber *et al.*, 2009). Alcohol consumption also influences platelet aggregation, though its exact effect on platelet function remains unclear. While alcohol, particularly red and white wine, may act as a platelet function inhibitor, it has also been shown to enhance platelet activation (Ruf, 2004). One hypothesis suggests that alcohol causes partial platelet activation and degranulation, resulting in platelets circulating in a state unable to contribute to plug formation. (Salem and Laposata, 2005). For patients with bleeding disorders, particularly those with VWD, alcohol intake should be avoided to reduce the risk of platelet dysfunction. Dietary fats also affect platelet function and, consequently, haemostasis. The impact of dietary fats on platelet function is determined by the length and saturation of fatty acids. Long-chain fatty acids have been shown to increase platelet aggregation at injury sites, while medium- and short-chain fatty acids result in lower aggregation (Phang *et al.*, 2011). Micronutrients also play a vital role in platelet function. For example, Vitamin C enhances platelet activation, while Vitamin E inhibits platelet adhesion and aggregation. Phytochemicals such as garlic, licorice, chili, green tea extracts, soy, turmeric, ginger, lettuce, and parsley can also support platelet activity. Additionally, fruits like tomatoes, grapefruit, melons, and strawberries contribute to the regulation of haemostasis (Phang *et al.*, 2011). In Pakistan, there is a lack of awareness regarding the importance of a healthy diet and exercise, leading to inadequate health



outcomes. Due to widespread illiteracy, many people do not pay attention to their dietary habits, which are crucial in certain medical conditions.

9. GENETIC AND ENVIRONMENTAL INFLUENCE ON VWD

The whole genome-wide association studies reveal that some additional genes, such as *STXBP5*, *SCARA5*, *STAB2*, *TC2N*, *STX2*, and *CLEC4M*, rather than *VWF* and *ABO*, also impact *VWF* and FVIII levels (Smith *et al.*, 2010). The mentioned specific genes collectively account for 12.8% of the variability in *VWF* levels in plasma. The identified variants, predominantly situated within introns, influence gene expression by altering mRNA splicing patterns or may be linked with variants in the *VWF* coding region that modify protein function (Swystun and Lillicrap, 2018). Some other genes that are associated with quantitative *VWF* levels in the plasma are *PDHB/PXK/KCTD6*, *SLC39A8*, *FCHO2/TMEM171/TNPO1*, *HLA*, *GIMAP7/GIMAP4*, *OR13C5/NIPSNAP*, *DAB2IP*, *C2CD4B*, *RAB5C-KAT2A*, *TAB1/SYNGR1*, and *ARSA*. Functional analysis provides additional support for the association of all loci on *VWF* with the exception of *ARSA* and *DABIP* genes. Some responsible silencing genes that exhibit a noticeable alteration in *VWF* levels are involved in vesicle transportation, exocytosis, intracellular signaling, and the inflammatory response. These newly identified loci primarily impact the regulation of *VWF* release from endothelial cells and megakaryocytes. However, further confirmation and validation are required for these associations. Most *VWF* loci that belong to quantitative traits are classified into genes that help regulate the glycosylation process. These respective genes are also responsible for the secretion of *VWF* from endothelial cells and the clearance of *VWF* (Sabater-Lleal *et al.*, 2019).

VWD patients are influenced by different environmental, pathological, hormonal and genetic factors. Level of *VWF* in plasma influences physiological conditions i.e., menorrhagia, pregnancy, age, exercise, circadian rhythm. Environmental factors including cigarette smoking and air pollution also influence the *VWF* levels in plasma. Although *VWF* levels influenced by environmental factors but studies proved that genetic factors has great influence and VWD is highly heritable disease (Swystun and Lillicrap, 2018). In case of Pakistan, unfortunately patient do not know about their disease and due to lack of awareness environmental factors also take great part. Likely heavy bleeding during menorrhagia, or postpartum leads to death and they were unaware about their disease. Severity of the disease has increased with the passage of time and age.

10. PSYCHOSOCIAL INFLUENCE OF VWD

Inherited bleeding disorders can arise from platelet dysfunction and a lack of aggregation, with von Willebrand disease (VWD) being one such condition (Paroskie *et al.*, 2014). While both males and females can be affected equally by VWD, females often face additional challenges due to the menstrual cycle and childbirth. Diagnosis of VWD in women is particularly difficult, as heavy menstrual bleeding is the most common symptom, affecting up to 80% of cases (Lavin *et al.*, 2018). This condition has a significant impact on the quality of life, disrupting daily activities, work, and leading to iron deficiency due to blood loss. Preventing early hysterectomy and other invasive procedures, as well as improving a patient's quality of life, depends on timely and appropriate treatment. Alongside medical care, raising public awareness and ensuring that patients receive informed counselling from healthcare providers are essential steps.



Recognizing abnormal bleeding early greatly increases the likelihood of an accurate diagnosis, reduces long-term complications, and lessens the emotional and social burden of the disease (Kulkarni, 2015). For individuals with von Willebrand disease (VWD), mental health can be an overlooked but critical aspect of management. Emotional stress, particularly acute stress, may worsen the condition by triggering fibrinolysis and disrupting platelet function. In countries such as Pakistan, limited public understanding of bleeding disorders means that many cases remain undetected, often until a serious medical event occurs. In some Muslim communities, routine circumcision in boys can reveal a bleeding disorder early in life, but girls and women frequently go undiagnosed.

Cultural expectations and social norms add further complications, as many women feel unable to discuss menstrual or reproductive health issues openly, even with medical professionals. This reluctance can delay diagnosis and treatment, contributing to higher mortality among women with VWD. The additional pressures of anxiety, stigma, and strained relationships can place a heavy burden on mental well-being. Addressing these cultural and psychological challenges is therefore as important as treating the physical symptoms.

11. MANAGEMENT

Assessing the severity of VWD involves both clinical evaluation and patient history. Standardized bleeding score tools are used to document personal and family bleeding patterns. In cases of musculoskeletal bleeding, more common in type 3 VWD but also seen in types 1 and 2, the joints and muscles are carefully examined. Patients who have received plasma or clotting factors are routinely screened for HIV, hepatitis B, and hepatitis C. Iron deficiency, especially

prevalent among women, is also checked, and female patients are specifically evaluated for menorrhagia (Demers *et al.*, 2006). Correctly identifying the type and subtype of VWD is essential, as treatment approaches differ. For type 3 disease, prophylactic therapy is often tailored to specific circumstances. Long-term prophylaxis is generally recommended for patients who experience severe bleeding episodes, heavy menstrual bleeding, joint and muscle hemorrhages, or gastrointestinal bleeding (Berntorp, 2008). Patients diagnosed with severe bleeding, severe menorrhagia, joint and muscle bleeding, and gastrointestinal tract bleeding are recommended long-term prophylaxis (Oldenburg, 2011).

Different strategies are used to treat VWD and address the severity of the disease, including recombinant *VWF* concentrates as replacement treatment. Desmopressin (DDAVP), an antifibrinolytic agent, is effective in promoting the secretion of *VWF* from endothelial cells or megakaryocytes. This treatment is highly effective for patients suffering from mucosal tissue bleeding in VWD. Hormonal regulation therapy is effective in managing severe menorrhagia in female patients (James, 2009). In replacement therapy, patients receive commercially available plasma-derived *VWF*-containing FVIII concentrates or various recombinant *VWF* products (Schneppenheim, 2011).

Replacement therapy with *VWF*/FVIII concentrates is recommended for patients experiencing severe bleeding episodes, those with a short half-life of *VWF*, or type 3 VWD patients who are unresponsive to desmopressin (DDAVP). DDAVP functions by mobilizing endogenous *VWF* from Weibel-Palade bodies and facilitating its movement in the endothelium (Ruggeri *et al.*, 1982). Some endothelial cells have receptors for vasopressin and its analogue DDAVP, which are antidiuretic hormones that aid in the exocytosis of *VWF* by binding to specific receptors



(Kaufmann *et al.*, 2000). This mechanism leads to 3- to 5-fold increases in *VWF* levels, containing a major proportion of *VWF* multimers, which is effective in type 1 VWD and some cases of type 2 VWD (Federici *et al.*, 2004). DDAVP plays an important role in managing bleeding episodes in mild types of VWD, but it is ineffective for type 3 VWD patients, as they cannot produce *VWF*. Similarly, it may not be useful for treating type 2B VWD patients due to associated thrombocytopenia (Holmberg *et al.*, 1983).

Indirect treatments are also employed to manage VWD and reduce bleeding episodes. Fibrinolytic inhibitors, such as tranexamic acid, can be effective in reducing bleeding. Contraceptive pills may also serve as hormonal treatment and are particularly helpful for menorrhagia (Greaves and Watson, 2007). VWD presents significant challenges in obstetric conditions, as *VWF* levels remain high throughout pregnancy, especially in the last three months. Women with elevated *VWF* levels during pregnancy are at higher risk of complications, and postpartum bleeding poses an additional challenge since *VWF* levels decrease rapidly after delivery. To manage these issues, extra care must be given to patients, and bleeding disorder centers should have expertise in perinatal management (Varughese and Cohen, 2007). In male infants, circumcision should occur in the presence of pediatric haemostasis, and desmopressin should be given to children under two years old as a precaution (Berntorp and Federici, 2024).

12. MANAGEMENT WITH AUTOANTIBODIES

In individuals with type 3 von Willebrand disease (VWD), the almost complete absence of von Willebrand factor (*VWF*) protein triggers the formation of neutralizing alloantibodies due to the intensive management of these patients with *VWF*-containing

concentrates (Franchini and Mannucci, 2018). In type 3 VWD patients, the prevalence of these alloantibodies is estimated to be 5-10%, with a recorded incidence of 6% according to the 3WINTERS-IPS study. Most cases of *VWF* null alleles exhibit homozygosity (Pagliari *et al.*, 2023). Patients with VWD who have alloantibodies and are treated with *VWF* concentrates often show an ineffective response to treatment, and some may provoke an anaphylactic response during subsequent management with *VWF*. Although the presence of alloantibodies in patients is frequently reported, there is limited knowledge regarding their treatment. Some reports suggest that management with recombinant activated factor VII shows a good response in certain cases. Due to the short half-life of factor VII, continuous and high doses of recombinant factor VII are required to treat these patients.

Another management strategy for alloantibodies is platelet transfusions, which may offer additional benefits. It is believed that *VWF* is stored in Weibel-Palade bodies, which may be protected from alloantibodies and could potentially evade their inhibitory effects upon release at the site of vascular injury (Grossmann *et al.*, 2000).

Emicizumab is proposed as a potential treatment to prevent bleeding in type 3 VWD patients with alloantibodies, as it mimics the role of factor VIII. However, further analysis is needed to confirm the efficacy of emicizumab in patients suffering from type 3 VWD and inhibitors, as emicizumab does not act as a replacement for *VWF* function in plasma (Boyer-Neumann *et al.*, 2003).

13. SITUATION OF VWD IN PAKISTAN

VWD is one of the most prevalent bleeding disorders in South Asian countries, particularly in Pakistan. The main cause of the high frequency is the prevalence of consanguineous marriages, which are quite common in Pakistan



(Hussain and Bittles, 1998). Although the prevalence of rare bleeding disorders is very high in Pakistan compared to the worldwide prevalence, most cases remain undiagnosed. Various reasons contribute to this undiagnosed status, such as a lack of awareness, insufficient diagnostic facilities available, and, in many scenarios, low clinical suspicion. Many patients receive incorrect medication due to being misdiagnosed with haemophilia (Naz *et al.*, 2017).

Due to the mentioned limitations, there is not much data available for VWD, as there are no proper registries or hospital departments for bleeding disorders, so most of the data remains unavailable. Some foundations, like the Haemophilia Foundation, Fatmid Foundation, and Sundas Foundation, work in the Punjab region, but they primarily focus on all inherited bleeding disorders, mainly haemophilia. They do not have any correlated patient data, bleeding phenotypes of the patients, clinical data of families, or other clinical and treatment data. As Pakistan has limited resources for bleeding disorders, most of the funding is spent on infectious diseases and maternity care (Aaqil *et al.*, 2023).

The need of the day is to establish a large national study that includes less privileged and difficult-to-access areas due to certain laws of Pakistan (Khan, 2023). The establishment of large, fully equipped laboratories is needed in at least the capital cities of Pakistan, where expert staff collect accurate data from patients. All data from different cities must be gathered in a national registry or database. Awareness symposiums and campaigns are also necessary to reduce cases and ensure correct diagnosis of von Willebrand disease (VWD).

14. CONCLUSION

Von Willebrand Disease is an inherited bleeding disorder which is quite common worldwide, but the exact prevalence is

unknown in the region of Pakistan, which makes it relatively rare in Pakistan. There are limited number of cases reported in the cohort of south Asian country and most of the cases has been misdiagnosed because of unawareness and lack of facilities in the laboratories and hospitals. In this review clinical entire structure, synthesis and pathophysiology of the von Willebrand factor have been described and also gives insight information about the clinical presentations, diagnosis, and managements. This review also describes the different environmental and genetic factors that influence the disease severity and its impact on the patient's health. To conclude the study, it is very important to spread awareness about the disease, genetic counselling of the patient, building proper registries and tertiary care centers for the patients with bleeding disorders. The establishment of large, fully equipped laboratories is needed in at least the capital cities of Pakistan, where expert staff collect accurate data from patients and ensure the correct diagnosis of VWD leads to appropriate treatment recommendations.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

AL curated the concept, retrieved literature and drafted the manuscript. MAN reviewed the draft and provided logistic support. SH reviewed and revised the manuscript, provided logistic support and supervised the project.

Ethics Approval and Informed Consent

Not applicable

Availability of Data

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