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SUPPLEMENT ARTICLE

von Willebrand disease and von Willebrand factor

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Abstract

Summary: Progress in both basic and translational research into the molecular mechanisms of VWD can be seen in multiple fields.

Genetics of VWD: In the past several decades, knowledge of the underlying pathogenesis of von Willebrand disease (VWD) has increased tremendously, thanks in no small part to detailed genetic mapping of the von Willebrand Factor (VWF) gene and advances in genetic and bioinformatic technology. However, these advances do not always easily translate into improved management for patients with VWD and low-VWF levels.

VWD and pregnancy: For example, the treatment of pregnant women with VWD both pre- and postpartum can be complicated. While knowledge of the *VWF* genotype at some amino acid positions can aid in knowledge of who may be at increased risk of thrombocytopenia or insufficient increase in VWF levels during pregnancy, in many cases, VWF levels and bleeding severity is highly heterogeneous, making monitoring recommended during pregnancy to optimize treatment strategies.

VWF and COVID-19: New challenges related to the consequences of dysregulation of hemostasis continue to be discovered. The ongoing COVID-19 pandemic has highlighted that VWF has additional biological roles in the regulation of inflammatory disorders and angiogenesis, disruption of which may contribute to COVID-19 induced vasculopathy. Increased endothelial cell activation and Weibel-Palade body exocytosis in severe COVID-19 lead to markedly increased plasma VWF levels. Coupled with impairment of normal ADAMTS13 multimer regulation, these data suggest a role for VWF in the pathogenesis underlying pulmonary microvascular angiopathy in severe COVID-19.

Conclusion: With the increased affordability and availability of next-generation sequencing techniques, as well as a push towards a multi-omic approach and personalized medicine in human genetics, there is hope that translational research will improve VWD patient outcomes.

KEYWORDS
complex trait genetics, COVID-19, pregnancy and VWD, thrombosis and hemostasis, von Willebrand disease

1 | THE *VWF* GENE

1.1 | VWD due to genetic variants within the *VWF* gene

Type 1 VWD is the most common type of VWD and is characterized by low plasma VWF levels with normal VWF structure and function, and is often transmitted in an autosomal dominant inheritance pattern. It is mainly associated with haploinsufficiency at the VWF locus. Type 1 VWD accounts for 85% of all VWD cases.[1] These patients are further subcategorized into a low-VWF phenotype or Type 1 VWD based on VWF plasma levels of 0.03–0.3 and 0.3–0.5 U ml^{-1}, respectively,[2] although these cutoffs have long been debated.[3] In fact, recent revisions on the guidelines on diagnosing VWD suggest referring to low-VWF patients with bleeding as having Type 1 VWD so as to not create a barrier to care.[4] For the purposes of this review, we will use the term "low-VWF" to refer to patients with VWF:Ag levels 0.3–0.5 U ml, as they may be genetically distinct from VWD patients in unknown ways.

Genetic variants that have been shown to be pathogenic in some way are also known as genetic mutations. VWD type 1 features mutations resulting in alterations in VWF homeostasis that are unrelated to the degradation of VWF multimers by *ADAMTS-13*. These mutations mainly affect circulating plasma VWF levels through VWF synthesis/secretion, storage and clearance. Previous studies have shown that most (~70%) mutations in the *VWF* gene that cause Type 1 VWD are missense, followed by splice-site (~9%) transcription (8%), small deletion (6%), nonsense (5%) and small insertion or duplication (2%) mutations.[5] Even synonymous mutations have been shown cause Type 1 VWD.[6] Type 2 VWD is perhaps the most genetically straightforward, as defects in VWF function are predominantly caused by mutations in specific regions of the VWF protein. Type 3 VWD is the most severe form of VWD, with affected individuals producing virtually no VWF due to homozygosity or compound heterozygosity for null alleles in the *VWF* gene. Copy number variants (CNVs) have been shown to cause all subtypes of VWD.[7]

While the description and cataloguing of genetic variants within the *VWF* gene that have been associated with all subtypes of VWD is extensive, it has become clearer in recent years that in order to get a more complete genetic picture of VWD, it is necessary to also look outside of the *VWF* gene. This is evidenced by the fact that not all low VWF or Type 1 VWD patients have characterized mutations in their *VWF* gene, adding to its genetic complexity.

1.2 | VWD due to genetic variants outside the *VWF* gene

Family studies have put the heritability of VWF levels around 30%.[8] However, twin studies have put estimates of the heritability of VWF plasma levels as high as 75%,[9] with 30% of the genetic variance explained by the effect of ABO blood type and only ~5% explained by variation in the VWF gene itself.[10] Environmental factors such as pregnancy, exercise, aging or even exposure to cigarette smoke and air pollution have also been shown to contribute to variation in VWF levels.[11,12]

As VWF:Ag levels in people with blood group O have are known to be 25%–30% lower than in people with blood groups A, B and AB, people with blood group O are overrepresented among VWD patients, comprising 77% of all VWD patients even though they make up only 45% of the general European-American population. Other modifier genes besides *ABO* have also been identified, including *CLEC4M*, *STXBP5* and *STAB2*[13–15] (Table S1).

Approximately 35% of VWD type 1 patients do not have a known likely causative variant in the *VWF* gene,[16] and a previous linkage study found that only 41% of families with VWD type 1 had linkage to the VWF locus.[17] This figure is even lower in low-VWF patients, whose VWF levels are more often explained by synthesis/secretion and not overactive clearance.[18] After discovering only half of their Type 1 patients had any variants in the *VWF* gene, one group concluded that due to incomplete penetrance and variable expressivity "…mutation screening of the *VWF* gene has limited general utility in genetic diagnostic and family studies in Type 1 VWD."[19] This is also seen in Type 3 VWD, where one study found that in approximately 15% of Type 3 VWD patients, two null mutations in the *VWF* gene were not observed, suggesting other genes may play a role.[20]

Taken together, the current state of the literature on VWD type 1 and low-VWF is indicative of a complex disorder with multiple genetic risk factors. As with other disorders, the more severe cases are enriched for putatively causative mutations, in this case in the *VWF* gene. However, the low-VWF cases represent a milder form of the disorder, which necessarily will have a more complicated genetic basis that more often involves variants in other genes besides *VWF*.

While a handful of genome-wide association studies (GWAS) of plasma VWF levels have been performed and have successfully identified several non*VWF* and non*ABO* loci,[21] these do not detect associations with rare variants. One study attempted to look for rare variants associated with VWF:Ag levels,[22] however they only had exome chip data and did not find any new genes involved.

As a class, rare variants (<5% population frequency) constitute the majority of genetic variation and are four times more likely to be deleterious.[23] In a recent study, we show that the burden of rare nonsynonymous variants significantly predicts VWF:Ag levels, even after controlling for known and predicted pathogenic variants. This suggests that additional variants, either in *VWF* or elsewhere in the genome are affecting VWF:Ag levels. This also suggests that patients with higher VWF:Ag levels as well as fewer rare nonsynonymous *VWF* variants could benefit from whole genome sequencing to discover the cause of their bleeding.[24]

As the field moves towards more consistent usage of next-generation sequencing techniques to look at rare and ultra-rare variants as well as techniques to obtain an even more detailed genetic picture such as structural variation analysis, noncoding DNA analysis and analysis of various epigenetic markers, we should expect to see an increase in associations between variants in genes other than *VWF* and *ABO* and VWF:Ag levels and related phenotypes. Unlike common variant associations in which large sets of highly correlated

SNPs spanning many kilobases of the genome are often implicated in disease risk, rare variant association analysis has the power to implicate specific variants and genes, enabling more rapid translation of findings into treatments. The same is true of copy-number variation and expression analyses. By combining these methods, we will be able to work towards our goal of explaining a greater proportion of the heritability of VWF:Ag levels and VWD, as well as increase our overall understanding of the disease process.

2 | PREGNANCY MANAGEMENT IN WOMEN WITH VON WILLEBRAND DISEASE

Clinical manifestations in von Willebrand disease (VWD) are mainly represented by muco-cutaneous and soft tissue bleeding and the severity of bleeding symptoms is variable mostly depending on the degree of von Willebrand factor (VWF) and factor VIII (FVIII) reduction. However, the burden of the disease is greater in affected women because of physiological events (menstruation, pregnancy and parturition) that may result in excessive bleeding even in normal women. FVIII and VWF may attain very high levels during pregnancy in normal women, while in VWD patients the pattern is highly heterogeneous and careful evaluation is needed especially in those with more severe clinical and laboratory phenotype.

In general, VWD patients should be monitored for VWF activity and FVIII at least once during the third trimester of pregnancy.[25] A progressive increase of FVIII and VWF occurs in most women with type 1 VWD, with levels >50 U/dl in the third trimester[26] and in the MCMDM-1VWD study no difference of bleeding risk at parturition was observed compared to their normal relatives.[27] Women with baseline of VWF and FVIII levels >30 U/dl, suggesting type 1 VWD or low VWF category, usually achieve levels >50 U/dl at the end of pregnancy.[26,28] However, women with low VWF attaining these at parturition, but significantly lower compared to normal women, may have significant bleeding, requiring blood transfusion in 22 % of them.[29] This again suggests the need for close surveillance of these women and that probably endogenous levels >100 U/dl are required.[29] Treatment options for delivery management should ideally be planned at beginning of pregnancy and the results with previous treatment(s), including desmopressin-trial, should be available and carefully reviewed.[26,29] Women with basal levels <20 U/dl usually have a lesser increase since most of these women carry DNA variants associated with increased VWF clearance or decreased synthesis or variants that alone or in compound heterozygosity are not associated with the achievement of safe hemostatic levels.[29,30] Since the genetic background (which is highly predictive of FVIII and VWF changes during pregnancy in most cases[31]) is not available for most of these patients, careful monitoring during pregnancy or at least during the third trimester is highly recommended to identify those who will need specific treatment.

Retrospective data does not suggest the presence of an increased risk of abortion in VWD women, especially with type 1 VWD, the most frequent and least severe type.[27] In a large case-control study, no increased risk of placental abruption, preterm delivery, fetal growth restriction or stillbirth was observed.[32] The need for villocentesis/amniocentesis in VWD can be successfully and safely covered with desmopressin in responsive women but measurement of FVIII and VWF after desmopressin in these circumstances is advisable to confirm adequate response. Those with severe phenotypes should be treated with VWF concentrate for a couple of days.

In general, invasive management of delivery with ventouse or rotational forceps should be avoided because of the risk of bleeding for the potentially affected neonate.[33,34] Women who require or desire epidural anesthesia should have FVIII and VWF levels >50 U/dl,[25] although no definite evidence about the best threshold is available.[34]

The use of utero-tonic agent soon after delivery is recommended similarly to normal women to reduce the risk of bleeding.[34]

The risk of bleeding of primary postpartum hemorrhage is more than 50% when FVIII and VWF activity levels are <50 U/dl in the third trimester,[26,35,36] and it may remain even if they are treated with VWF concentrate to achieve levels >100 U/dl.[33,37]

Tranexamic acid (1 g iv following umbilical clamping and then 1 g orally every 8 h up to 2 weeks) is generally recommended in women with type 1 VWD and preferably also in those with types 2 and 3.[25] In type 1 pregnant women with FVIII and/or VWF levels lower than 30 U/dl at time of parturition and with evidence of a remarkable positive response, the administration of desmopressin preferably after umbilical clamping to avoid neonate hypotension[29] and for 3–4 days thereafter is required,[31,34] especially if midline episiotomy is required. Monitoring FVIII and VWF levels is advisable, especially when repeated doses are given, together with urinary output and fluid restriction to avoid the risk of hyponatremia.[26,34] The same approach, with fewer infusions, can be applied to those with VWF >30 and <50 U/dl. The use of VWF/FVIII concentrates may be advisable, especially when close surveillance of the patient is not easily available. In this case 40–60 IU/kg VWF is administered during the late stage of labor together with tranexamic acid. Replacement therapy is repeated once daily for at least three days, preferentially extending the period of treatment up to 5–7 days for cesarean section. Oral tranexamic acid should be continued for 7–15 days.[25]

Wide heterogeneous patterns are observed in patients with type 2 VWD. In type 2 A, multimer abnormalities usually do not correct and VWF:RCo remains markedly reduced.[31] These patients require treatment with FVIII/VWF concentrates.[37] All concentrates are equally effective and safe, but the choice should be based according to the associated levels of FVIII and local availability. In presence of high FVIII levels and low VWF observed in women with type 2 VWD, a concentrate with low FVIII is advisable and FVIII and VWF monitoring is recommended during treatment, as well as with the other concentrates.[25,26,34] Similar doses as reported with type 1 should be used. In case of cesarean section, antithrombotic prophylaxis for a few days should be considered until daily treatment with concentrate.[25] Recombinant VWF is now available in the USA and in a few EU countries, but no data about its use in pregnancy are available.

Thrombocytopenia is the most important associated hemostatic change observed in type 2B VWD women during pregnancy,[38,39] but its severity is strongly dependent on the specific VWF amino acid change, with some variants resulting in normal platelet counts (e.g., p.Pro1266Leu) and others with severe thrombocytopenia (e.g., p.Arg1308Cys and p.Met1316Val).[38] Thus, platelet count should be also closely monitored during pregnancy in women with this type. In some women with platelet count <30,000/μl, platelet transfusion has been used.[39] While this approach seems reasonable when invasive procedures are needed, its true clinical benefit remains unproven because of the rarity of the disorder.

Women with type 2M VWD often show a significant correction of FVIII and VWF:Ag, while VWF:RCo does not reach levels of 50 U/dl, similar to the pattern observed after desmopressin and thus factor replacement should be used,[26] as already discussed for type 2A and 2B VWD.

In type 2N, normalization of FVIII, which is more reduced compared to VWF, usually occurs during pregnancy in most heterozygous and some homozygous women, again overlapping the pattern after desmopressin.[26,40] Responsive women can be safely managed with this agent in case of bleeding complications. In unresponsive women, during labor and before epidural anesthesia, 50 IU/kg of VWF should be administered, followed by 30–40 IU/kg/daily for at least 3 days. Daily monitoring of FVIII and VWF activity is recommended during the same period.

Women with type 3 VWD typically do not show any increase of FVIII and VWF during pregnancy. VWF/FVIII concentrates may be required during pregnancy to control intermittent vaginal bleeding and at delivery or for Cesarean section.[25,26,36] Patients on prophylaxis with a VWF concentrate prior to pregnancy should continued it throughout the pregnancy to avoid all types of bleeds, with increasing doses appropriate for weight gain. Cesarean section should be reserved only for the usual obstetrical indications. Replacement therapy should be prolonged up to 5–7 days to maintain FVIII (and possibly VWF) levels >50 U/dl.[25,26,33]

FVIII and VWF fall to baseline levels soon after delivery[26] and thus oral antifibrinolytic agents, as suggested above, can be used during this period to prevent delayed postpartum bleeding and heavy lochia. Tranexamic acid appears to decrease the risk of delayed bleeding and to be safe during lactation.[25,26] However, significant delayed bleeding may occur, especially in the more severe cases treated for a short period, requiring treatment with desmopressin or FVIII/VWF concentrates.[25,26,31]

3 | VON WILLEBRAND FACTOR IN COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for coronavirus disease 2019 (COVID-19). This global pandemic has already involved more than 265 million cases. In the majority of cases, COVID-19 runs a mild clinical course.[41] However, approximately 10% to 20% of patients develop severe COVID-19 characterized by progressive bilateral pneumonia that can progress to acute respiratory distress syndrome (ARDS). Risk factors associated with increased COVID-19 severity include older age, male sex, ethnicity, hypertension and diabetes.[42,43] Despite the fact that it has already been responsible for more than 5 million deaths, the pathogenesis underlying severe COVID-19 remains incompletely understood. However, a dysregulated host immune response likely plays a key role.[43] The SARS-CoV-2 virus gains entry into airway epithelial cells via ACE2 receptors. Intracellular viral replication then leads to pneumocyte death, alveolar macrophage activation, and secretion of pro-inflammatory cytokines. In a minority of infected individuals, SAS-CoV-2 triggers excessive monocyte and T cell recruitment into the alveoli, together with the generation of high local levels of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6 and IL-8).[43]

Accumulating evidence suggests that hemostatic dysfunction and microvascular thrombosis also play important roles in severe COVID-19.[43,44] Early reports from China reported a characteristic coagulopathy in COVID-19 with significantly elevated fibrin degradation D-dimer levels and prolonged prothrombin times (PT).[45] These abnormalities were seen on admission, suggesting they represented an early feature of SARS-CoV-2 infection.[45,46] Importantly, progressive increases in D-dimers and PT were observed in patients who did not survive.[45,46] In particular, high rates of pulmonary embolism (PE) >30% were seen in COVID-19 patients requiring ICU support despite the use of thromboprophylaxis. The concept that hemostasis contributes to COVID-19 pathogenesis was further supported by postmortem studies which reported disseminated microthrombi and hemorrhagic necrosis throughout the lung vasculature in COVID-19 patients.[47,48] Thrombi were identified in precapillary arterioles, alveolar capillaries and postcapillary venules. The clots were composed predominantly of platelets and fibrin, but also had associated megakaryocytes and evidence of NETosis.[48] Autopsy studies further demonstrated that severe COVID-19 was associated with significant endotheliopathy.[47,48] This included disruption of normal intercellular junctions leading to enhanced endothelial cell (EC) barrier permeability, significantly increased EC apoptosis, and enhanced intussusceptive angiogenesis within the lungs. Although early studies reported intracellular SARS-CoV-2 virus within EC, more recent data suggest that EC are resistant to direct infection. Instead, the endotheliopathy associated with severe COVID-19 is likely driven through indirect mechanisms including complement activation, pro-inflammatory cytokines, platelet activation, and hypoxia. Collectively, these findings demonstrate that coagulopathy, and in particular lung-centric vasculopathy, play major roles in COVID pathogenesis.[49]

von Willebrand factor is a large multimeric plasma sialoglycoprotein that plays key roles in normal hemostasis. In addition, recent studies have described additional novel biological roles for VWF in regulating inflammatory disorders, angiogenesis and cancer metastasis. VWF synthesized within EC is either secreted in the blood vessel lumen, or stored within Weibel Palade bodies (WPB) together with the VWF propeptide (VWFpp). In keeping with the concept that severe

COVID-19 is associated with marked EC activation, markedly elevated plasma VWF antigen (VWF:Ag) and activity (VWF:RCo and VWF:CB) levels have been observed in patients with severe COVID-19.[50–53] Plasma factor VIII (FVIII:C) levels were also significantly increased.[51] Particularly high VWF and FVIII levels (~ 8-fold) were observed in COVID-19 patients requiring ICU support.[50,51] Consistent with acute EC activation and WPB exocytosis, plasma VWFpp levels were also markedly elevated.[50,52] The absolute VWF:Ag and VWFpp levels in patients with SARS-CoV-2 were much higher than those previously observed in patients with other clinical conditions associated with fulminant EC activation (e.g. *Plasmodium falciparum* cerebral malaria).[50,54] Importantly, plasma VWF and VWFpp levels also both correlated significantly with COVID-19 severity.[50,52] Together, these data suggest that VWF:Ag and/or VWFpp may be useful biomarkers of SARS-CoV-2 disease severity.

Following EC activation, ultra-large multimers (UL-VWF) secreted from WPB can become tethered on the cell surface, leading to the formation of long platelet-decorated VWF strings. These platelet-decorated VWF strings can bind to various cell types (e.g., leucocytes, tumor cells and malaria-infected erythrocytes) and have been implicated in the pathogenesis of different types of microvascular microangiopathy.[54] Under normal conditions, VWF multimer distribution and string formation are regulated by the plasma metalloprotease *ADAMTS13*, which cleaves at Tyr1605-Met1606 in the A2 domain of *VWF*. Several studies have reported that plasma ADAMTS13 activity levels are significantly reduced in patients with severe COVID-19.[52,55,56] Although ADAMTS13 activity is reduced, absolute plasma ADAMTS13 levels remained above 30%.[52,55] Previous studies suggest that these ADAMTS13 activity levels should be sufficient to maintain normal plasma VWF multimer composition. Importantly however, because of the marked EC activation, there is also a major increase in the VWF/ADAMTS13 ratio (~ 7-fold) in SARS-CoV-2 patients compared to healthy controls.[52,55] In addition, plasma levels of a number of putative inhibitors of ADAMTS13 activity (including IL-6, TSP-1 and PF4) are significantly elevated in patients with severe COVID-19.[55] Consistent with these findings, abnormalities in plasma VWF multimer distribution have also been reported in patients with SARS-CoV-2. Several groups have reported loss of HMWM in patients with severe COVID-19.[52,55,57] This appearance is similar to that in patients with acute TTP where it is thought to be caused by consumption of hyperactive HMWM-VWF in platelet-rich microvascular thrombi. In contrast, other studies of severe COVID-19 have observed evidence of circulating pathological UL-VWF multimers.[53,56] These differing conclusions likely reflect differences in study design, as well as variations in the methodologies used to assess VWF multimer composition. Nevertheless, cumulatively these data support that the hypothesis that severe COVID-19 is associated with dysfunction in ADAMTS13-dependent regulation of VWF multimers.

A significant proportion of patients report persistent breathlessness, fatigue and decreased exercise tolerance following acute SARS-CoV-2 infection. The biological mechanisms responsible for these ongoing symptoms (so-called *"Long COVID"* syndrome) have not been defined. Interestingly however, sustained increased D-dimer levels have been reported in convalescent COVID-19 patients following the apparent resolution of their acute infection.[58,59] In addition, significantly elevated plasma VWF:Ag and FVIII:C levels have also been observed in convalescent COVID-19 patients.[59,60] For example, Fogarty et al. found VWF:Ag levels above the upper limit of normal (median 2.0 IU/mL) in 30% of patients at a median of 68 days following initial COVID-19 infection.[60] Similarly, plasma VWFpp levels were also significantly elevated in convalescent COVID-19 patients compared to controls and correlated strongly with VWF:Ag levels ($r = 0.87$; $p < 0.0001$).[60] Collectively, these data suggest that persistent EC activation is a common finding in convalescent COVID-19 patients. Further studies will be required to determine whether this endotheliopathy plays any role in the pathogenesis of Long COVID. At this time, it remains unclear whether this pathogenic significance will vary with the emergence of newer COVID-19 variants.

In conclusion, severe COVID-19 is associated with marked EC activation and WPB exocytosis. Consequently, plasma VWF levels are increased. Furthermore, physiological VWF multimer regulation by *ADAMTS13* is also impaired. The combination of markedly elevated plasma VWF levels and the presence of pathological UL-VWF multimers raises the intriguing possibility that VWF may play a direct role in the pathobiology underpinning microvascular thrombosis in severe COVID-19.

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BS, GC & JSO'D wrote the manuscript.

CONFLICT OF INTERESTS

JSO'D has served on the speaker's bureau for Baxter, Bayer, Novo Nordisk, Sobi, Boehringer Ingelheim, Leo Pharma, Takeda, and Octapharma. He has also served on the advisory boards of Baxter, Sobi, Bayer, Octapharma CSL Behring, Daiichi Sankyo, Boehringer Ingelheim, Takeda, and Pfizer. He has also received research grant funding awards from 3M, Baxter, Bayer, Pfizer, Shire, Takeda, 3M, and Novo Nordisk.

GC is on the advisory boards or is a speaker in company-sponsored symposia for Alexion, Bayer, Sanofi, Roche, Biomarin, Takeda, Novo Nordisk, Werfen, Grifols, Kedrion, LFB, Uniqure, and SOBI.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

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