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Hidden behind thromboinflammation: revealing the roles of von Willebrand factor in sickle cell disease pathophysiology

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Purpose of review
This review provides an update on the pathophysiology of sickle cell disease (SCD) with a particular focus on the dysregulation of the von Willebrand factor (VWF) - ADAMTS13 axis that contributes to its pathogenesis. In discussing recent developments, we hope to encourage new and ongoing discussions surrounding therapeutic targets for SCD.

Recent findings
Within the last 5 years, the role of VWF in the pathophysiology of SCD has been further elucidated and is now a target of study in ongoing clinical trials.

Summary
The pathophysiology of SCD is multifaceted, as it involves systemwide vascular activation, altered blood rheology, and the activation of immune responses and coagulative pathways. The presence of VWF in excess in SCD, particularly in its largest multimeric form, greatly contributes to its pathogenesis. Understanding the molecular mechanisms that underly the presence of large VWF multimers in SCD will provide further insight into the pathogenesis of SCD and provide specific targets for therapy.

Keywords
ADAMTS13, pathophysiology, sickle cell disease, thrombosis, vaso-occlusion, von Willebrand factor

INTRODUCTION

Sickle cell disease (SCD) has long been characterized as a chronic and debilitating haematologic disease with widely varied symptomatology. At the origin of SCD is a point mutation in the beta-globin gene, which encodes for haemoglobin. This mutation results in the generation of haemoglobin S (HbS), which polymerizes upon oxygen unloading. These polymers subsequently stretch and puncture the red blood cell (RBC) membrane, causing it to adopt the characteristic 'sickled' morphology. These molecular and cellular interactions have system-wide thromboinflammatory implications [1,2], namely, vascular occlusion (VOC), a hallmark of SCD pathology. Although the available therapeutic options for SCD have significantly reduced the frequency and severity of symptoms endured by patients, acute crises stemming from chronic and widespread thromboinflammation still occur [3–9]. von Willebrand factor (VWF) plays a primary role in the thromboinflammatory response and is widely known to be elevated in SCD patients, though, no available SCD therapies target it.

Over the last three and a half decades, there have been over 50 articles investigating VWF in SCD, with nearly 30% of them published within the last couple of years. Examining the role of VWF in the context of SCD is imperative, since, for decades, VWF elevation in patients with SCD was considered to occur solely as a secondary effect of widespread endothelial activation. Recent findings have suggested VWF as a key player in the pathogenesis of SCD, through its role in mediating VOC [10,11▪▪,12▪▪]. This suggests that VWF is the 'missing piece', linking the occurrence of inflammation and thrombosis in SCD.

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KEY POINTS

- VWF is a key player in the pathophysiology of SCD via its mediation of VOC and potentially thromboembolic events.
- Correction of VWF - ADAMTS13 axis dysregulation in SCD largely reduces VOC and subsequent acute organ damage and is currently under investigation in a clinical trial (NCT03997760).
- Further exploration of thrombotic and coagulative pathways should be conducted to identify improved means for SCD treatment.

In this review, we will discuss the recent findings that have investigated the role of VWF in SCD pathophysiology, which have also become the basis for ongoing clinical trials.

VON WILLEBRAND FACTOR AND ITS ROLE IN SICKLE CELL DISEASE PATHOPHYSIOLOGY

Canonical role of von Willebrand factor

VWF is a large multimeric protein, principally stored in endothelial cells, with a fundamental role in coagulation. Upon endothelial activation, ultra-large multimers of VWF (ULVWF) are released and tethered to the endothelial membrane. ULVWF is thrombotically reactive, and when it persists in this form, it can cause widespread thrombosis, and in small vessels, haemolysis due to its large size, which enables it to shear RBCS, as seen in thrombotic thrombocytopenic purpura (TTP) [13,14]. As shown in Fig. 1a, upon its release from the endothelium, ULVWF is cleaved by, A Disintegrin and Metalloproteinase with Thrombospondin Type- 1 Motif, Member 13 (ADAMTS13), its regulatory protein, which functions to cleave ULVWF into smaller, functional multimers with dampened thrombotic reactivity, enabling it to mediate haemostasis. The absence or destruction of ADAMTS13 is the cause of ULVWF seen in TTP. In cases wherein ADAMTS13 is overactive, as found to occur in response to turbulent or chaotic flow – which can occur secondary to arterial stenosis or ventricular assistive devices (VADs) – VWF is excessively cleaved, generating low molecular weight VFW (LMW VWF) multimers that have no functional capacity for mediating homeostasis, resulting in increased bleeding events [15,16]. Tight regulation of the VWF- ADAMTS13 axis is required to maintain a homeostatic balance between bleeding and clotting, and its dysregulation in either direction can result in haemorrhage or thromboembolic events.

Dysregulation of VWF - ADAMTS13 axis in sickle cell disease

Elevated levels of VWF, predominantly in its ultra-large multimeric form, in SCD were first reported in the late 1980 s by Wick *et al.* [17,18]. High ULVWF levels continued to be reported in SCD patients through the 1990 s, and the role ULVWF had in increasing sRBC adhesion to endothelial cells and its subsequent contributions to vaso-occlusion was also described during this period [17,19]. However, these observations were often attributed to widespread endothelial activation in SCD. Leaving the mechanism underlying high plasma levels of ULVWF fragments elusive for the greater portion of the next decade.

Increased levels of ULVWF multimers in SCD patients suggested a potential deficiency of ADAMTS13 or its activity. Thus, directing initial investigations of the VWF- ADAMTS13 axis by evaluating the VWF antigen, ADAMTS13 antigen, ADAMTS13 activity levels and ratios of these factors with respect to each other, all with the purpose of pinpointing the site of dysregulation along the VWF-ADAMTS13 axis in SCD. Schnog *et al.* [20] first reported that elevated VWF antigen and activity levels exist in both asymptomatic and acute crisis SCD patients, further validating the chronic endothelial activation present in SCD. These studies also reported that the antigen levels of ADAMTS13 were not significantly deficient in SCD groups relative to healthy controls. These studies confirmed that ADAMTS13 was synthesized normally and not targeted for destruction in SCD, as it is in some forms of TTP, thus suggesting a mechanism targeting the activity levels of ADAMTS13 in SCD patients.

First, described in TTP, extracellular haemoglobin was characterized as an inhibitor of ADAMTS13 [13]. Though the extent of this inhibition was not truly appreciated until Zhou et al. [21▪▪] provided a direct mechanism by which extracellular haemoglobin inhibited VWF cleavage in SCD. Their study demonstrated that extracellular haemoglobin bound to both VWF and ADAMTS13 under static and shear conditions. However, it bound to the A2 proteolytic cleavage site of VWF with an a affinity almost three-fold higher than its binding affinity for ADAMTS13. In addition, the colocalization of VWF and extracellular Hgb was found to occur in a saturation-dependent manner. Thus, demonstrating a competitive inhibitory mechanism for ADAMTS13 activity and the dependence on high levels of haemolysis, as seen in SCD patients, especially so in acute crisis. Zhou *et al.* [21▪▪] found haemoglobin levels in healthy individuals to be approximately 24 $\pm$ 8 mg/ml, whereas in SCD patients, they were 346

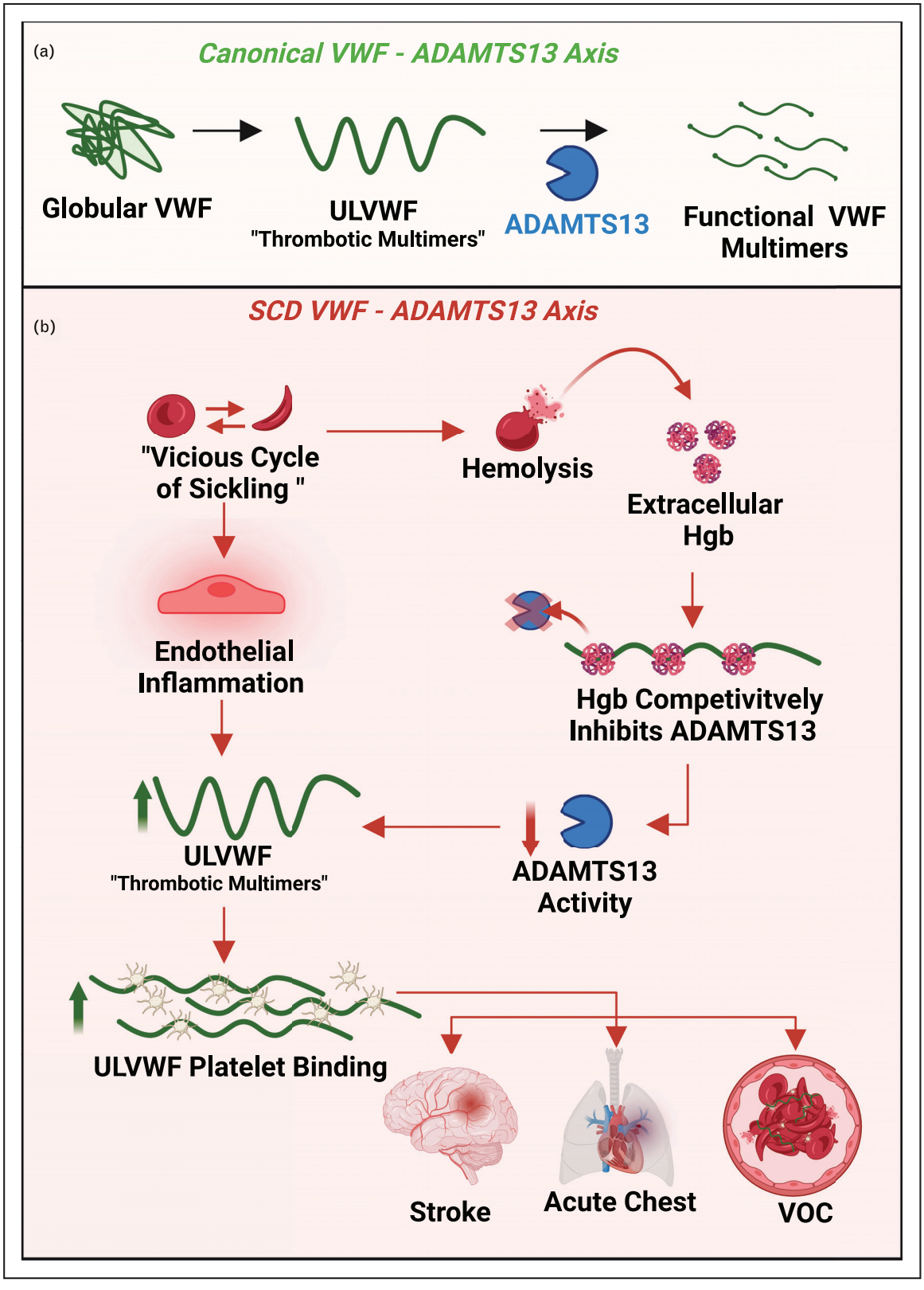

FIGURE 1. Schematic of VWF - ADAMTS13 axis in SCD. (a) Canonical pathway of VWF regulation. (b) Dysregulation of VWF - ADAMTS13 axis in SCD due to increased extracellular hemoglobin.

± 138 mg/ml. Nearly a 25% reduction in ADAMTS13 proteolytic activity was seen to occur at Hgb levels of nearly 150 mg/ml and an 80% reduction at 400 mg/ml of extracellular Hgb, levels reached when in an acute crisis. The implications of this interaction between SCD and extracellular Hgb were later reviewed by Zhou *et al.* [22], and described this mechanism to be a major contributor to the pathophysiology of SCD through its role in mediating VOC and thrombosis. As shown in Fig. 1b, the downstream implications of ADAMTS13 inhibition are increased levels of ULVWF, which are thrombotically reactive and bind platelets leading to VOC, acute chest syndrome and stroke, to name a few downstream thrombotic complications. Although more recently, additional mechanisms of regulation of the VWF-ADAMTS13 axis have been evaluated for their role in SCD. Demagny *et al.* [11▪▪] confirmed previous reports of elevated VWF antigen levels occurring SCD patients (median 167 IU/dl) and especially so in VOC patients in whom a two-fold increase was observed. Although when evaluating ADAMTS13 activity, median activity levels were normal, with only a fraction of patients showing a partial activity deficiency. When evaluating the ratio of ADAMTS13 activity to VWF antigen levels, no change was observed under VOC. In addition, positive ADAMTS13 antibody titres were present in nearly half of the patients evaluated [11▪▪]. These results provide evidence of the need for further investigation of the mechanism responsible for VWF-ADAMTS13 dysregulation in SCD, as these studies suggest a TTP-like mechanism to be occurring potentially alongside Hgb-induced ADAMTS13 inhibition in SCD. Furthermore, Al-Awhadhi *et al.* [23▪] reported Thrombospondin 1 as an additional inhibitor of ADAMTS13 in SCD patients of Arab ethnicity. They found TSP-1 to be negatively correlated with ADAMTS13 activity in adults, while a negative correlation between TSP-1 and ADAMTS13/VWF levels in paediatric patients was observed [23▪]. Further suggesting that this mechanism is not yet elucidated and needs to be studied more broadly, as it may provide an age-dependent target of interest for the correction of VWF-ADAMTS13 dysregulation in SCD.

As the VWF – ADAMTS13 axis continued to be characterized over the last 3 years, studies have confirmed a general increase in VWF levels in steady-state and acute crisis SCD patients [11▪▪,24, 25▪,26▪,27▪].

Although there still remain gaps in our general understanding of the factors that dysregulate this pathway, particularly with respect to ADAMTS13 inhibition, as studies have recently reported additional inhibitory mechanisms. While there exists ADAMTS13-independent proteolytic pathways that increase in SCD patients to regulate VWF, such as neutrophil and endothelial-derived proteases and matrix metalloproteinase 9, their activity is not sufficient in mitigating the VWF burden in SCD [28▪▪]. Notably, studies have demonstrated that the gold standard treatment for SCD, hydroxyurea, does not prevent the dysregulation of the VWF - ADAMTS13 axis in SCD, leaving patients still susceptible to its downstream complications [29▪]. Thus demonstrating the need to directly target VWF -ADAMTS13 dysregulation in SCD.

VWF-ADAMTS13 axis dysregulation as a target for sickle cell disease therapy

Discussions of VWF's role in SCD pathophysiology have been developing since the late 1980 s. Within the last year, the magnitude of VWF's role in SCD was characterized and the potential benefits of correcting VWF-ADAMTS13 axis dysregulation have been provided. Shi *et al.* [12▪▪] reported that endothelial VWF is critical to the pathogenesis of SCD via its mediation of vaso-occlusive episodes (VOEs). In this study, two groups of Townes models for SCD were studied; one with endothelial VWF knocked-out and the other with endothelial VWF present. The results from this study demonstrated reduced anaemia occurring at baseline and following TNF-alpha-induced VOE in the VWF knockout mice. In addition, histologic examination revealed reduced inflammatory infiltrates in the liver, kidney and overall reduced organ damage in VWF knockout mice. Altogether, these results demonstrated the critical role of endothelial VWF in VOC. To specifically demonstrate the deleterious impacts of ULVWF in SCD, this group went on to evaluate the impacts exogenous ADAMTS13 administration had on the SCD-VWF knockout mice. ADAMTS13 administration prior to TNF-alpha-induced VOE significantly reduced plasma VWF levels, reduced VWF-positive thrombi in the liver and other critical organs, and a similar pattern of reduced thromboinflammation was observed upon histological examination of major organ tissues. The group also explored the potential of exogenous ADAMTS13 as an acute treatment option for VOE by administering ADAMTS13 following the initiation of VOE. These results also demonstrated a pattern of reduced pathological transformation [12▪▪]. Subsequent work conducted by Rossato *et al.* [30▪▪] provided evidence that treatment with recombinant ADAMTS13 reduced hypoxia/reoxygenation-induced lung and kidney injury in humanized SCD mouse models. Also, in evaluating the adverse

outcomes resulting from the usage of recombinant ADAMTS13, secondary bleeding events related to its use were not observed. These results are significant, as they provide a means to safely reduce the incidence of acute chest syndrome and renal failure among other thrombotic events observed in SCD [30▪▪]. In their subsequent work, they evaluated the bleeding risks associated with recombinant ADAMTS13 use and confirmed that its use did not increase the bleeding risk even at supraphysiologic levels [31▪▪]. These results have led to the initiation of a phase one clinical trial for the use of recombinant ADAMTS13 in SCD, which has recently completed participant recruitment.

Thromboembolic implications of von Willebrand factor in sickle cell disease

As discussed earlier, recent studies have emphasized the implications of VWF-ADAMTS13 dysregulation in the pathophysiology of SCD, particularly through its role in mediating VOC. How and whether this dysregulation plays a role in SCD associated thromboembolic events, such as stroke and acute chest syndrome, is not yet clear.

Recent studies have proposed a central role for VWF in both VOC and thromboembolic events. Van der Land *et al.* [32] found elevated VWF levels to be correlated with SCD patients classified under the haemolysis-endothelial-dysfunction subphenotype of SCD. This subphenotype is known to be associated with higher rates of stroke and pulmonary hypertension [32]. Whether VWF elevation is a product or cause of these occurrences should be investigated. Anea *et al.* [33] reported profound platelet thrombi to exist in 30% of autopsied SCD patients whose cause of death was ACS. Upon histological examination of these thrombi, significant endothelial VWF deposition and large VWF aggregates adhered to the endothelium were observed. In addition, platelet-rich thrombi were not observed in SCD patients whose cause of death was not ACS [33]. Providing additional evidence that VWF's role in thromboembolic events in SCD should be further investigated. In examining stroke, Buerki *et al.* [34] reported VWF levels to be more elevated in SCD neonates and children with stroke compared to those without stroke, although merely correlative these results suggest the potential role of VWF in general thromboembolic phenomena in SCD. Recently, Enifeni *et al.* [35▪] evaluated the relationship between transcranial doppler velocity and VWF levels in children with SCD. Their investigation corroborated previous evidence of elevated VWF levels in SCD and interestingly found abnormal TCDs to be associated with elevated platelet counts, though a connection between VWF level and TCD results remained elusive and emphasized the need for further research to determine the implications of VWF levels on stroke risk [35▪]. These studies beget continued investigations probing VWF in thromboembolism in SCD. Thrombotic risk is high in this patient population and patients may benefit from being treated following regimens used for diseases of thrombotic origin [36].

Experts in the field have frequently described the overlap between TTP and SCD, as well as the overlap between thrombotic microangiopathies (TMAs) and SCD overall. However, pointed investigations of this overlap have been limited. Shome *et al.* [37] reported an increased frequency of TMA in Bahraini SCD patients in crisis, and this is, to our knowledge, the only study reporting the frequency of TMA in SCD patients.

The results demonstrating the impact of increased thrombotic regulation in SCD through enhanced VWF-ADAMTS13 axis control sheds light on the primary role dysregulated thrombotic pathways play in SCD pathophysiology. Further exploration of the overlap between these two disease groups is integral to advancing therapy options for patients with SCD. Notably, there may be therapeutics used to treat TMAs that could have therapeutic benefits for patients with SCD, particularly options that may prove to be viable intervention options for acute crisis. For example, Caplacizumab, a VWF platelet-binding antagonist, used in TTP, has not been tested in the context of SCD management [38▪]. ULVWF multimers are described in the literature as hyperreactive with the enhanced ability to bind platelets. Exploring the outcomes of inhibiting this interaction may reduce the occurrence of crisis events and provide another therapeutic option for patients.

Ongoing investigations have also begun to evaluate the utility of additional antithrombotic and anticoagulative agents in SCD VTE treatment and prophylaxis, but further investigation is needed to characterize the thrombotic pathways active in SCD, so agents that best target them can be identified. [39▪,40▪].

CONCLUSION

VWF and the dysregulation of the VWF – ADAMTS13 axis are largely involved in the pathogenesis of SCD and hence are ideal targets for therapeutic intervention. However, much remains to be understood about the mechanisms that drive this dysregulation, thus necessitating further investigation [26▪]. As results from ongoing clinical trials testing the efficacy of recombinant ADAMTS13 in

SCD patients become available, we anticipate additional targets of thrombosis and coagulation to be evaluated for their efficacy in SCD treatment and management. However, treating SCD more like a thrombotic condition can increase the risk of bleeding in these patients. Current results have not shown VWF-ADAMTS13 axis regulation through recombinant ADAMTS13 administration to cause acquired von Willebrand's disease. This will continue to be an important avenue to explore as additional targets are investigated. The role that general thrombotic and coagulative regulation plays in the development of SCD should be emphasized and we encourage the investigation of the efficacy of treatment regimens such as those used for TTP and other TMAs in SCD, as they may prove useful in SCD management and treatment.

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Conflicts of interest

There are no conflicts of interest.

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