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REVIEW ARTICLE

Blood groups and their relationship with plasma levels of von Willebrand Factor

Grupos sanguíneos y su relación con los niveles plasmáticos del Factor de von Willebrand

Yusselfy Márquez-Benítez[1]* orcid.org/0000-0002-7677-6329

Adriana María Lancheros-Silva[1] orcid.org/0000-0003-0639-4373

Estéfani Díaz-Chaves[2] orcid.org/0000-0002-4461-4923

1. Bacteriology and Clinical Laboratory Research Group (GRIBAC), University of Boyacá, Boyacá, Colombia
2. Bacteriology and Clinical Laboratory Program, University of Boyacá. Boyacá, Colombia

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Resumen

Introducción: El tipo de grupo sanguíneo entre otros factores, influye en los niveles plasmáticos del Factor de von Willebrand (FvW), su actividad biológica podría incidir en el desarrollo de eventos trombóticos y hemorrágicos. **Objetivo:** Describir las características y los mecanismos de reacciones postrasduccionales del grupo sanguíneo que permiten la variación en la concentración plasmática del FvW. **Materiales y métodos:** Revisión teórico descriptiva de tipo documental. Las bases de datos consultadas fueron Medline, Lilacs, ScienceDirect, Scopus, SciELO, Proquest, Ovid y Pubmed. Como criterio de selección se incluyeron artículos en idioma inglés y español a partir del año 2010 y algunos anteriores como referente histórico. **Resultados:** Se describieron los principales mecanismos e investigaciones que evidencian la influencia del tipo de grupo sanguíneo ABO en los niveles plasmáticos del FvW, así como la estructura y función de dicha proteína. **Conclusiones:** Las concentraciones plasmáticas del FvW pueden depender del tipo de grupo sanguíneo, la edad, sexo, embarazo, ciclo menstrual, variación de proteínas y factores bioquímicos e inmunológicos. Se podría tener en cuenta el tipo de grupo sanguíneo de los pacientes como un posible factor predictor a futuro de complicaciones clínicas tanto trombóticas como hemorrágicas.

Palabras clave: Factor de von Willebrand; antígenos de grupos sanguíneos; proteína ADAMTS13; trombofilia. (Fuente: DeCS, Bireme).

Abstract

Introduction: The type of blood group among other factors influences the plasma levels of von Willebrand Factor (FvW) and its biological activity could influence the development of thrombotic and hemorrhagic events. **Objective:** To describe the characteristics and mechanisms of post-translational reactions of the blood group that generate variation in the plasma concentration of FvW. **Materials and methods:** A descriptive theoretical review of documentary type. The databases consulted were Medline, Lilacs, ScienceDirect, Scopus, SciELO, Proquest, Ovid and Pubmed. As a selection criterion, articles in English and Spanish were included beginning in 2010 and some previous ones as historical reference. **Results:** The main mechanisms and investigations that show the influence of the ABO blood group type on the plasma levels of FvW, as well as the structure and function of this protein were described. **Conclusions:** FvW plasma concentrations may depend on the type of blood group, age, sex, pregnancy, menstrual cycle, protein variation and biochemical and immunological factors. The type of blood group of patients could be considered as a possible future predictor of both thrombotic and hemorrhagic clinical complications.

Key words: von Willebrand factor; blood group antigens; ADAMTS13 protein; thrombophilia. (Source: DeCS, Bireme).

***Corresponding author at:**
Yusselfy Márquez Benítez
e-mail: ymarquez@uniboyaca.edu.co

Introduction

Blood cells have different antigenic and immune properties in each individual such as the ABO system discovered by pathologist Landsteiner in 1901[1]. Two antigens (A and B) appear on the surface of erythrocytes in a large proportion of humans. These antigen types are called agglutinogens because they agglutinate erythrocytes and cause most of the blood transfusion reactions[2].

Blood types can be defined as a set of encoded antigens (A, AB, B, O) that are transmitted following a Mendelian inheritance pattern[1]. The determination of a specific type in blood banks is essential to identify the appropriate products for transfusions. People that lack A and B type antigens, i.e., people that belong to the O group, start producing antibodies against those erythrocyte antigens a few months after birth[3].

At the level of blood plasma, in addition to these blood type antigens, there are other molecules that play important biological roles such as the von Willebrand Factor (VWF). This protein is synthesized by cells in the vascular endothelium and megakaryocytes, being then stored in platelet alpha granules[2,4]. VWF has several functions, including: a) mediating platelet adhesion to vascular damage sites by binding to the Gplb/IX membrane glycoprotein complex and collagen in vascular subendothelim; b) facilitating platelet aggregation by binding to the IIb/IIIa platelet receptor glycoprotein; and c) binding to the protothrombotic factor VIII (FVIII) to prevent its degradation by activated protein C in blood[4].

The type of blood group is related to concentration levels of von Willebrand Factor in plasma. This association has drawn attention because variations in the concentration of this protein increase patient's risk of presenting thrombotic problems and, in some cases, bleeding[5,6]. In the future, this relationship could serve as a possible predictor of those events. This literature review is aimed to examine the mechanisms by which the type of blood affects plasma concentration levels of FVW, beginning with the analysis of its conformational structure, its genetic variability and functions of associated proteins.

Materials and methods

A literature review was carried out through an electronic search in *Medline, Lilacs, ScienceDirect, Scopus, SciELO, Proquest e-library* and *Pubmed* databases, using the keywords: von Willebrand Factor, blood groups, ADAMTS13, thrombophilia, and their combinations. Original research and review articles published in English and Spanish since 2010, with a few previous ones that were used as a historical reference, were included. In addition, updated electronic books were used to support essential theoretical aspects.

Results

The blood group antigen

Although the antigens present in erythrocytes are believed to be pure proteins, it is possible that those molecules are only carriers of antigenic determinants and need lipids and carbohydrates to act as complete antigens[2,7]. The genes that control the structure of a particular antigen occupy a corresponding location (locus) within a pair of homologous chromosomes[8]. Each chromosome is formed by two DNA strands that contain an assembly of genes, which encode genetic information through a specific sequence of nucleotides[9].

The genes of the ABO system are located in human chromosome 9 and have three alleles (A, B and O), which vary according to nucleotide substitutions that determine the specificities of the encoded enzymes[10]. The A allele encodes for transferase A that catalyzes the binding of N-acetylgalactosamine (GalNAc) to H antigen (precursor oligosaccharide encoded in chromosome 9) to generate the A antigen. The B allele encodes for transferase B, which catalyzes the binding of D-galactose to antigen H to give rise to the B antigen. In contrast, the O allele produces an enzyme without transferase activity. As a result, blood group O cells contain large amounts of the H antigen, while the concentration of this molecule on the surface of A- and B-type blood cells is comparatively low[2,10]. Individuals who do not inherit the H gene belong to the Bombay phenotype (hh) and do not produce H antigen. Therefore, they do not express any allelic form of A, B or O on the erythrocyte membrane[2].

Von Willebrand Factor (VWF)

VWF is a multimeric glycoprotein synthesized in vascular endothelial cells and megakaryocytes that has a half-life of nearly 12-16 hours. It is encoded by a 52-exon gene (178Kb) located in the 12p13.2 region[11], which has more than 160 allelic variants[12]. 75-85% of the freely circulating VWF in plasma

comes from the endothelium, whereas the remaining 15-25% is stored in circulating platelets that develop from megakaryocytes. During the course of the synthesis of VWF, the pre-pro-VWF precursor protein is formed, which has a size of 300-350 KDa (2813 aa) containing a 22 aa signal peptide, a 741 aa propeptide and a 2,050 aa mature protein[13].

The structure of the VWF glycoprotein consists of several repeated domains arranged in the following order: D1-D2-D'-D3-A1-A2-A3-D4-C1-C2-C3-C4-C5-C6-CK[14]. D1, D2, D' and D3 domains participate in the regulation of the multimer formation process, while D' and D3 mediate binding to FVIII. Both A1 and A3 domains possess collagen binding properties. While the A1 domain of VWF is required for its interaction with Glycoprotein Ib/IX platelet receptor complex (GpIb/IX), the C2 domain is used for VWF binding to Glycoprotein IIb/IIIa platelet receptor complex (GpIIb/IIIz). Thus, each VWF monomer has domains that facilitate its physical interaction with ligands present in platelets (GpIb/IX and GpIIb/IIIa), subendothelium (collagen) and bloodstream (FVIII)[13].

VWF is originally synthesized as a precursor (pre-pro-VWF) in the endoplasmic reticulum (ER). After its cleavage and separation from the signal peptide located at the amino-terminus, pro-VWF is assembled in dimers via disulfide bonds (S-S) formed between its carboxy-terminus (CK domain). Following successive sulfation and glycosylation processes, VWF is then multimerized by S-S bonds between the amino-terminal ends of the dimers (D3 domain). After the proteolytic cleavage of the propeptide (VWFpp), both VWF and VWFpp are secreted to plasma in equimolar amounts (1:1), stored as ultra-large von Willebrand factor (ULVWF) multimers, or directly released to plasma to be degraded into smaller and less thrombotic multimers[14,15].

Von Willebrand Factor Propeptide (VWFpp)

Historically, VWF has also been known as "factor VIII-related antigen"[16]. This propetide was originally identified by Montgomery and Zimmerman in 1978 as a second von Willebrand disease (VWD) antigen that was deficient in platelets and plasma of patients[17]. VWFpp (vW AgII) is released from platelets during the blood coagulation process, revealing its presence in both platelets and plasma. The propeptide is cleaved in the ER and functions as a mediator for the formation of VWF multimers. VWF and its propeptide are released into the bloodstream in an equimolar relation. However, the molecules are removed at different rates, with circulating half-lives of approximately 12-16 h and 2-3 h for VWF and VWFpp, respectively[18].

The life cycles of VWF and VWFpp are related due to the fact that VWFpp is subjected to extensive intracellular processing events[19]. VWFpp translocates into the endoplasmic reticulum where the signal peptide is removed, the protein is folded and disulfide bonds between most of the 234 cysteine residues of VWF are formed. This factor is then post-translationally glycosylated at its 17N-linked glycosylation sites (4 in VWFpp and 13 in mature VWF)[20]. Before leaving the ER, VWF forms a carboxy-terminal dimer (C-terminal). When this protein reaches the Golgi Complex, linked glycans are added, carbohydrates are further modified and sulfation occurs. Then, C-terminal dimers form amino-terminal multimers (N-terminal) with varying molecular weight, ranging from 500 to 20,000 KDa[19-21]. Although a proteolytic cleavage by furin separates VWFpp from mature VWF, both proteins remain attached through non-covalent bonds[21]. Finally, VWF and VWFpp are stored in regulatory secretory granules, Weible-Palade bodies (WPB) in endothelial cells, and within α-granules in magakacyocytes/platelets[22].

Von Willebrand Factor Clearance

Characterization of VWFpp is achieved through capture antibodies, whose plasma levels are proportional to VWF:Ag and reflect VWF synthesis. An increase in the VWFpp/VWF:Ag ratio (>2) indicates a greater purification caused by different mechanisms[23]. Changes that occur during the purification process of WVF can affect its plasma levels but do not seem to affect its clearance. Therefore, several laboratories have used the VWFpp/VWF: Ag ratio as a measure of VWF clearance[22,23].

If VWF and FVIII establish a circulating complex, there are significant relative differences in VWF clearance, reflected as a clear increase in FVIII without affecting plasma levels of VWF[23]. In acquired von Willebrand disease (VWD), caused by an autoantibody directed against VWF, the clearance of VWF and FVIII takes place. Recently, several studies have identified variants of type 1 von Willebrand disease that is caused by accelerated clearance rather than reduced synthesis. In these

individuals, the VWFpp/VWF:Ag ratio is markedly high[24].

Modifiers of VWF plasma levels are related to its plasma reference values (50-150%), taking into consideration that low levels are associated with bleeding. This symptom, in addition to being unspecific, it is frequent in human populations, so it is necessary to distinguish healthy individuals from those with VWD[25].

Even though the plasma level of VWF is a product of the relationship between its production and purification, the blood group is a factor that modifies VWF concentration in plasma. Other elements that affect VWF concentration include racial and hormonal factors, VWF gene polymorphisms, pregnancy, menstrual cycle, biochemical and immunological factors[24,26]. Regarding age, people older than 40 years of age experience a permanent increase in plasma VWF[26]. While African-American women consistently have elevated levels of VWF[27]. Hormonal factors have shown discrepancies with respect to its variations during the menstrual cycles[24,26].

VWF and FVIII levels increase early in the first trimester of pregnancy and as the gestational process progresses they can continue to rise until reaching two to three times above baseline levels. However, VWF and FVIII concentrations start to decrease shortly after birth, returning to baseline levels after a few weeks[28]. Although this temporary increase is sufficient to correct partial quantitative deficiencies, it is not enough to correct qualitative or severe ones[29].

Relationship between blood group and von Willebrand Factor plasma levels

VWF plasma concentrations can vary widely among individuals. Indeed, several studies have reported the evident relationship between VWF levels and the type of ABO blood group. Particularly, they have shown that whereas 66% of changes of the factor in plasma are associated with mutations, 30% of them are related to the ABO blood group[30,31].

O-blood type individuals have been characterized as having lower concentrations of VWF, followed by A-, B- and, finally, AB-type people, who show the highest concentrations[32]. O-blood type adults have approximately 25-30% lower concentrations of VWF compared to individuals with A, B or AB blood type[33]. These physiological differences cannot be detected during the first years of life, probably due to the slow postnatal development of blood group systems[34].

Glycosylation represents 19% of the molecular weight of VWF, and the ABO determinants identified in the oligosaccharide chains attached to Asn (N) are part of this post-translational modification[35]. Thus, this process partially explains the relationship between VWF and blood groups. The ABO groups are attached to the N-linked glycans of VWF in the post-Golgi compartment of endothelial cells, with variable contributions by endothelial cells from different vascular beds[34,35].

The decline in VWF concentration in patients with type-O blood group can be associated to how this factor is subjected to N- and O-glycosylation events at the same locations where the carbohydrates of blood groups participate[36]. Different glycosylation profiles are generated depending on the blood group determinants carried by each person, affecting the stability of certain domains since they are the ones exposed to metalloprotease activity. Consequently, the glycosylation profile of VWF is a determinant factor that affects its circulating half-life[34,36]. If the VWF is present in an individual of type O-blood group, a resulting decline in glycosylation exposes this factor to enzymes such as ADAMTS-13 metalloprotease. This sustained exposure could be the cause of blood type O individuals having VWF with a short half-life and lower plasma concentrations[35-37].

A higher propetide:mature peptide ratio could also disturb VWF levels since the presence of both in large numbers would also stimulate an accelerated clearance in blood type O individuals. That is, the lower the level of VWF, the higher the VWFpp/VEF:Ag ratio[23,38,39], which suggests that the clearance contributes to maintaining a balance in circulating concentrations of the factor. In addition, this would indicate that the VWFpp/VEF:Ag ratio is higher in people with type O- blood group than in those with type A-blood group, at any given level of VWF. In this context, circulating levels of VWF can represent a steady state equilibrium between secretion and clearance events[40-42].

ADAMTS13 protein and its association with VWF levels

There is evidence showing that the ADAMTS13 encoding gene interferes with plasma levels of VWF.

This gene is located in the ninth chromosome (9q34) and shares this location with ABO blood group alleles[43]. ADAMTS13 protein is a disintegrin and metalloprotease that is responsible for the excision of ultra-large multimers of VWF identified in 1996[43-45]. In 2001, this protein was assigned the name of ADAMTS13 due to its structure and homology with other members of the family of metalloproteases[46].

Under physiological conditions, VWF is released by endothelial cells and adheres to the surface of the cell. Here, ADAMTS13 recognizes its A2 domain and excises the ultra-large multimers, which have a high affinity for platelets. The activity of this metalloprotease is dependent on the presence of calcium and zinc divalent cations[47]. VWF is then released to bloodstream in a conformation that inhibits its interaction with platelets. Some studies suggest that ABO antigens affect VWF proteolysis by ADAMTS13. In fact, ADAMTS13-mediated proteolysis of VWF appears to be faster in blood group O carriers than that observed in non-O blood carriers. Similarly, the ADAMTS13 ratio revealed that this enzyme was higher in non-O blood group subjects compared to that in the O group. A possible explanation for this difference is that the increase in plasma levels of VWF in non-O blood group individuals triggers a compensation mechanism that would induce a rise in ADAMTS13[48-50]. The basis of these sequential events is the role of ADAMST13 in the excision of VWF multimers that reach bloodstream, this way preventing a hypercoagulable state[48].

A recent study revealed a relationship of levels of FvW, ADAMTS13, and the blood type of lung cancer patients with coagulant activation in this cancer type[51]. Significantly higher levels of VFW and FVIII activity as well as an important reduction in ADAMTS13 levels were observed in distant metastatic patients compared to those without metastases and healthy controls. Similarly, plasma VWF levels and FVIII activity significantly increased in subjects with non-O blood compared to those with type O blood. Nevertheless, there was a significant decrease in ADAMTS13 levels only in the control group with non-O type blood in comparison to those with type O blood. These results indicate that the increase in VFW and the reduction in ADAMTS13 levels facilitate the invasiveness and metastasis of lung cancer[51]. The authors suggest that continuous monitoring of the levels of VWF and ADAMTS13 as well as FVIII activity in lung cancer patients in relation to different blood groups could contribute to control the incidence of thrombotic events and improve the evaluation of progression of the disease[51].

Several studies have been conducted to assess the plasma levels of VWF in patients with different ABO blood types. Jaewoo Song, *et al*. determined that individuals with type O blood have lower levels of plasma VWF than those in people with A and B type blood, regardless of gender and race[52]. The overall difference in the average concentration of VWF between type O subjects and those with type B blood was 31.7%. This difference was significantly higher between individuals of African descent (AA), with 32.3% for women and 32.5% for men, than American people of European descent (AE), with 29.8% and 29.1% for women and men, respectively. For type A and type B individuals, the levels of VWF antigen were 123 ± 45% and 135 ± 46% for AO and BO types respectively, which were significantly lower than those of homozygous for A alleles (144 ± 52%,) B alleles (160 ± 53%). In addition, VWF levels were found to be significantly different between A1, A1A2 and A2 genotypes as well as for the eight gender groups per race ($p<0.0001$). This information shows how the ABO system influences VWF, FVIII and the FVIII/VWF ratio differently as well as how race and gender can modify these effects. These data also suggests that the effect of ABO in FVIII variability can be greater in subjects with low VWF basal levels[52].

A study by Norma Sousa, *et al*. describes the relationship between the type of blood group and concentration levels of VWF[53]. They showed that the ABO blood type has an important effect on the plasma concentration of VWF. They also concluded that individuals carrying an O allele (AO and BO) have significantly lower plasma levels of VWF and FVIII than those who do not have it (AA, AB and BB). Here, a total of 144 blood samples were analyzed to determine the levels of VWF, FVIII and ristocetin. As shown in Table 1, the average concentrations of these factors were lower in A2O1 subgroup than in AA, AB, and A2B subgroups and BelO1, and higher than in subgroup O1O1. The levels of the same three factors in AO1, AXO1 and Belo1 were statistically lower than those in groups AA, AB, BB and A2B. These data show that not only is there a variation in VWF levels, but subgroup participation is also influenced.

Table 1. Circulating levels of von Willebrand Factor (VWF: Ag), factor VIII (FVIII) and ristocetin cofactor (VWF: RCo) in people with different blood subgroups[53]

	VWF: Ag		FVIII		VWF: RCo	
	%	*P* value	%	*P* value	%	*P* value
A201	89	-	96	-	99	-
AA, AB, BB	120	<0.001	117	<0.001	19	<0.001
A2B	169	<0.001	112	<0.001	132	0.001
O1O1	69	0.018	75	0.048	65	0.001
A01, AX01, Bel01	75	0.001	88	0.004	76	0.001

A study by Zongkui Wang, *et al.* shows the participation of additional aspects that modify the VWF levels such as age and gender[54]. They worked with a Chinese population of 290 healthy voluntary donors, between the ages of 22 and 56 from Guanghan and Changning Plasmapheresis, belonging to geographically different regions of the Sichuan Province. The study showed that the average levels of FVIII:C and VWF (FvW:Ag, FvW:CBA and FvW:RCo) were significantly higher in subjects with non-O blood group. While ADAMTS13 decreased with age, the rest of the parameters increased. With the exception of ADAMTS13, no gender-related variations were observed in the other parameters. The level of ADAMTS was evidently higher in women than in men[54].

As seen in Table 2, even though FVIII:C, Fibrinogen, VWF:Ag, VWF:CBA and VWF:RCo showed significant and positive relationships with age, a negative association was observed for ADAMTS13 antigen. On the other hand, FVIII:C was strongly correlated with VWF:Ag, VWF:CBA and VWF: RCo. The authors suggest that the ABO blood type significantly affected plasma levels of FVIII:C and FvW (FvW:Ag, FvW:CBA and FvW:RCo), but did not modify fibrinogen and ADAMTS13.

ABO blood group, age and gender did not show any effect on the corresponding proportions, with the only exception being the VWF antigen:ADAMTS13 ratio.

At the clinical level, it has been shown that, depending on the type of blood group, the increase in VWF levels may be a predisposing factor for cardiovascular diseases and thrombotic events. Studies have shown that individuals with O blood group are protected against Acute Coronary Syndrome (ACS) due to their lower coagulation capacity. In contrast, one of the causes of ACS in individuals of the Non-O type blood group could be the increase in coagulation associated with high VWF levels[55]. Regarding atherosclerosis risk, ABO glycosyltransferases affect Cell Adhesion Molecules (CAM) that are expressed in vascular endothelial cells. CAMs play an important role in recruiting large numbers of leukocytes during inflammatory processes, leading to vasculature damage and the consequent formation of thrombi. Moreover, elevated blood levels of these proteins are associated with coronary artery disease, myocardial infarction and atherosclerosis[56-59].

The functional connection between the ABO system and VWF is also associated with bleeding. Research shows that patients with type O blood group display lower VWF levels and more frequent bleeding complications. Maike Kahr, *et al*. compared the magnitude of postpartum blood loss between mothers with type O and Non-O blood[5]. They observed that women with type O blood group experienced a significantly greater postpartum blood loss compared to women with Non-O blood (529.2 mL ± 380.4 mL and 490.5 mL ± 276.4 mL, respectively, p=0,024)[5]. Based on these results, women with type O blood group have a higher risk of postpartum bleeding and suffering aggravated hemorrhages in the presence of additional pathologies linked to obstetric bleeding[5].

A study by Mehment Akin, *et al.* related to children population[60], corroborated the effect of the type of ABO blood group on VWF levels in a population without bleeding symptoms. They concluded that children of blood group O have lower levels of the factor. It was also suggested that normal values of VWF, based on the ABO system, can affect the clinical diagnosis of VWD. An important indication of this report is that even though the approach of using ABO groups to establish a VWF:Ag concentration lower than 50 UI/dl as an indicator of the VWD is scientifically appropriate, this value could not be useful for physicians to identify people with higher bleeding risks[60].

Table 2. Relationship between age and circulating levels of factor VIII (FVIII:C), fibrinogen, von Willebrand Factor (VWF:Ag, VWF:CBA, ristocetin cofactor VWF: RCo) and Adamts 13[54]

FVIII: C		Fibrinogen		VWF: Ag		VWF: CBA		VWF: RCo		Adamts 13	
r	P	r	P	r	P	r	P	r	P	r	P
0.421	<0.0001	0.445	<0.0001	0.410	<0.001	0.401	<0.001	0.589	<0.001	0.306	<0.0006

Discussion

The purpose of this article is to analyze characteristics and mechanisms by which the type of blood group could affect the plasma concentration of VWF as well as to describe diverse studies that support such influence[34,36,48].

The results of the research presented in this study corroborate that plasma levels of VWF are lower in patients with blood type O than in those with type Non-O (A, B, AB), due to the faster metalloprotease-mediated proteolysis of VWF in the former group. Other studies have shown that the rate of proteolysis is different from the metalloprotease concentration. Surprisingly, higher concentrations of ADAMTS13 metalloprotease have been reported in patients with Non-O blood type[48-50], which could be due to a form of regulation since these patients have higher levels of VWF. These conflicting results show the need to conduct further studies aimed at supporting the findings described during the review of this paper.

A decrease in plasma levels of VWF in group-O patients could be established as a risk factor in hemorrhagic complications or in situations with a tendency for bleeding since these levels could affect the coagulation process. In this context, several studies have shown the greater tendency to bleed in type O patients, especially during gyneco-obstetric events or secondary surgical procedures[5]. Therefore, we suggest to carry out further studies in patients with scheduled surgical procedures to determine the possible risk of suffering critical hemorrhagic events and generate protocols based on the history of these patients.

Another concern is the thrombotic events related to non-O patients, who have a higher VWF concentration[61] in comparison to that of O-group individuals. In addition, the activation of certain inflammatory proteins, previously mentioned, exacerbate those thrombotic events that can lead to cardiovascular disease and death.

Different laboratories have focused on the mechanisms that trigger variability in plasma levels of VWF according to the type of blood group and the clinical risks of thrombotic and hemorrhagic events that these variations generate. Thus, we suggest to determine in future studies the ranges of concentration of von Willebrand Factor according to blood groups, which could be used by clinicians as a reference to predict these pathologies.

Given that the type blood group affects plasma levels of VWF, health care workers should identify these antigens in their patients and use them as a predicting factor of clinical complications in both thrombotic and hemorrhagic events. This characterization is important given the biological role that this factor plays in coagulation processes. Consequently, we suggest that future studies should be aimed at establishing physiological associations between plasma levels of VWF and the appearance of thrombotic and coronary events in patients with diseases that have a higher risk of generating thrombotic situations, such as cancer and autoimmune disorders.

Conclusions

Plasma levels of VWF are regulated by its own glycosylation status, which, in turn, depends on the type of blood group. The basis of this regulatory relationship is the exposure level of the VWF to the metalloproteases that are responsible for adjusting VWF plasma concentrations. As shown by some reports, VWF proteolysis is faster in blood type O subjects than in Non-O individuals. This proteolysis triggers a quicker degradation of VWF multimers, leading to lower plasma concentrations.

The concentration of VWF in plasma varies significantly in healthy individuals and the ABO blood group is its main genetic modulator. This variation has been related to the dynamics with which the ABO blood group affects the synthesis, secretion and catabolism of VWF through a functional effect of the ABO locus.

Several reports have presented evidence corroborating that VWF changes under other conditions. For instance, its VWF levels are elevated in people over 40 years of age (6-10% higher). Likewise, women have higher concentrations of VWF than men, and these levels can rise even higher in pregnant women (two to three times above basal values). However, these hormone-mediated changes tend to normalize a few weeks after child birth.

Research focused on the clinical implications of the physiological association between VWF levels and blood group is necessary, especially in at risk populations such as pregnant women, older adults and patients with pre-existing chronic diseases with higher risks to generate thrombotic and hemorrhagic events.

Conflict of interests: The authors state that they do not have conflicts of interests.

References

1. Cossio-Andia E, Solis S, Jhunior A, Castellon-Bautista N, Davalos-Pacheco M, Jarro-Mena RL. Tipificación del grupo sanguíneo ABO y el factor Rh en la población de Totora-Cochabamba gestión 2012. Rev Cient Cienc Med. 2013;16(1):25-27.
2. Guyton AC, Hall JE. Tratado de Fisiología Médica. 12ª ed. Madrid: Elsevier; 2011.
3. Cruz-Bermúdez HF, Moreno-Collazo JE, Forero SE. Caracterización de donantes voluntarios de sangre por grupo sanguíneo ABO y Rh que asistieron a un banco de sangre de la ciudad de Tunja-Colombia. Arch Med [Internet]. 2012 [citado 2017 Sep 06]; 2(2):185-189. Disponible en: http://revistasum.umanizales.edu.co/ojs/index.php/archivosmedicina/article/view/7
4. Lenting P, Casari C, Christophe O, Denis C. von Willebrand factor: the old, the new and the unknown. J Thromb Haemost [Internet]. 2012 [citado 2017 Sep 06];10(12):2428-37. Disponible en: https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.12008
5. Kahr MK, Franke D, Brun R, Wisser J, Zimmermann R, Haslinger C. Blood group O: A novel risk factor for increased postpartum blood loss?. Haemophilia [Internet]. 2018 May [citado 2017 Oct 10];1-6. Disponible en: https://onlinelibrary.wiley.com/doi/abs/10.1111/hae.13537
6. Hussein E, Teruya J. Evaluating the impact of the ABO blood group on the clinical outcome of thrombotic thrombocytopenic purpura associated with severe ADAMTS13 deficiency. Vox Sang [Internet]. 2017 Jul [citado 2017 Oct 11];112(5):434-442. Disponible en: https://onlinelibrary.wiley.com/doi/abs/10.1111/vox.12511
7. Bejerano-Pérez N, García-Bejerano D, Pimentel-Figueroa CA. Discrepancias en el agrupamiento del sistema de grupos sanguíneos ABO. Rev Ciencias Médicas [Internet]. 2016 Feb [citado 2018 Abr 08];20(1). Disponible en: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1561-31942016000100026&lng=es.6)
8. Chang-Monteagudo A, Bencomo-Hernández AA, Morera-Barrios LM, Ustáriz-García C, de la Guardia-Peña O. Evolución de la nomenclatura de los factores del sistema de antígenos leucocitarios humanos. Rev Cubana Hematol Inmunol Hemoter [Internet]. 2014 Ene - Mar [citado 2017 Oct 16];30(1):11-20. Disponible en: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0864-02892014000100003
9. Bueno ML. Cromosomas, vehículos en la organización y transmisión de los caracteres. Acta Biol Colomb [Internet]. 2011 [citado 2017 Oct 16];16(3):43-60. Disponible en: http://www.redalyc.org/articulo.oa?id=319027888003
10. Matta-Camacho NE. Sistema inmune y genética: un abordaje diferente a la diversidad de anticuerpos. Acta Biol Colomb [Internet]. 2011 Sep [citado 2018 Abr 08];16(3):177-188. Disponible en: https://revistas.unal.edu.co/index.php/actabiol/article/view/19284/27967
11. Smith NL, Chen MH, Dehghan A, Strachan DP, Basu S, Soranzo N, et al. Control Consortium, Novel associations of multiple genetic loci with plasma levels of factor VII, factor VIII, and von Willebrand factor: the CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) consortium. Circulation [Internet]. 2010 [citado 2017 Nov 03];121(12):1382-1392. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2861278/
12. Terraube V, O'donnell J, Jenkins PV. Factor VIII and von Willebrand factor interaction: biological, clinical and therapeutic importance. Haemophilia [Internet]. 2010 [citado 2017 Nov 03];16(1):3-13. Disponible en: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2516.2009.02005.x
13. Lillicrap D. von Willebrand disease: advances in pathogenetic understanding, diagnosis, and therapy. Blood [Internet]. 2013 [citado 2017 Nov 04];122(23):3735-40. Disponible en: http://www.bloodjournal.org/content/early/2013/09/24/blood-2013-06-498303.short?sso-checked=true
14. Lenting PJ, Christophe OD, Denis CV. Von Willebrand factor biosynthesis, secretion, and clearance: connecting the far ends. Blood [Internet]. 2015 [citado 2017 Nov 09];125(13):2019-2028. Disponible en: http://www.bloodjournal.org/content/early/2015/02/23/blood-2014-06-528406
15. Batlle J, Pérez-Rodríguez A, Corrales I, López-Fernández M, Rodríguez-Trillo Á, Lourés E, et al. Molecular and clinical profile of von Willebrand disease in Spain (PCM-EVW-ES): Proposal for a new diagnostic paradigm. Thromb Haemost [Internet]. 2016 [citado 2017 Nov 14];115(1):40-50. Disponible en: https://www.thieme-connect.com/products/ejournals/abstract/10.1160/TH15-04-0282
16. Haberichter DL. von Willebrand factor propeptide: biology and clinical utility. Blood [Internet]. 2015 [citado 2017 Nov 16];126:1753-1761. Disponible en: http://www.bloodjournal.org/content/early/2015/07/27/blood-2015-04-512731.1
17. Eikenboom J, Federici AB, Dirven RJ, Castaman G, Rodeghiero F, Budde U, et al. VWF propeptide and ratios between VWF, VWF propeptide, and FVIII in the characterization of type 1 von Willebrand disease. Blood [Internet]. 2013 [citado 2017 Nov 18];121(12):2336-9. Disponible en:

http://www.bloodjournal.org/content/early/2013/01/24/blood-2012-09-455089.short?sso-checked=true
18. De Jong A, Eikenboom J. Developments in the diagnostic procedures for von Willebrand disease. J Thromb Haemost [Internet]. 2016 [citado 2018 Abril 7];14:449-460. Disponible en: https://www.ncbi.nlm.nih.gov/pubmed/2671418116)
19. Veyradier A, Boisseau P, Fressinaud E, Caron C, Ternisien C, Giraud M, et al. A laboratory phenotype/genotype correlation of 1167 French patients from 670 families with von Willebrand disease: a new epidemiologic picture. Medicine [Internet]. 2016 [citado 2017 Nov 18];95(11):e3038. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4839904/
20. Canis K, McKinnon TA, Nowak A, Haslam SM, Panico M, Morris HR, et al. Mapping the N-glycome of human von Willebrand factor. Biochem J [Internet]. 2012 [citado 2017 Nov 18];447(2):217-28. Disponible en: http://www.biochemj.org/content/447/2/217
21. Casonato, A, Daidone, V, Padrini R. Assessment of von Willebrand factor propeptide improves the diagnosis of von Willebrand disease. Semin Thromb Hemost [Internet]. 2011 [citado 2017 Nov 20];37(05):456-463. Disponible en: https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0031-1281029
22. Madabhushi SR, Shang C, Dayananda KM, Rittenhouse-Olson K, Murphy M, Ryan TE, et al. Von Willebrand factor (VWF) propeptide binding to VWF D′ D3 domain attenuates platelet activation and adhesion. Blood [Internet]. 2012 [citado 2017 Nov 28];119(20):4769-4778. Disponible en: http://www.bloodjournal.org/content/early/2012/03/27/blood-2011-10-387548
23. Woods AI, Blanco AN, Kempfer AC, Paiva J, Bermejo EI, Sánchez Luceros A, et al. Factor de von Willebrand y Enfermedad de von Willebrand: nuevos enfoques diagnósticos. Acta Bioquím Clín Latinoam [Internet]. 2016 [citado 2017 Dic 02];50(2):273-89. Disponible en: http://www.scielo.org.ar/pdf/abcl/v50n2/v50n2a12.pdf
24. Casari C, Lenting P, Wohner N, Christophe O, Denis C. Clearance of von Willebrand factor. J Thromb Haemost [Internet]. 2013 [citado 2017 Dic 02];11(s1):202-11. Disponible en: https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.12226
25. De Wee EM, Sanders YV, Mauser-Bunschoten EP, van der Bom JG, Degenaar-Dujardin ME, Eikenboom J, et al. Determinants of bleeding phenotype in adult patients with moderate or severe von Willebrand disease. Thromb Haemost [Internet]. 2012 [citado 2017 Dic 03];108(4):683. Disponible en: https://insights.ovid.com/thrombosis-haemostasis/jthrh/2011/07/002/determinants-bleeding-phenotype-patients-moderate/618/00149457
26. Davies JA, Hathaway LS, Collins PW, Bowen DJ. Von Willebrand factor: demographics of plasma protein level in a large blood donor cohort from South Wales in the United Kingdom. Haemophilia [Internet]. 2012 [citado 2017 Dic 09];18(3):e60-e87. Disponible en: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2516.2012.02782.x
27. Miller C, Haff E, Platt S, Rawlins P, Drews C, Dilley A, et al. Measurement of von Willebrand factor activity: relative effects of ABO blood type and race. J Thromb Haemost [Internet]. 2003 [citado 2017 Dic 09];1(10):2191-7. Disponible en: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1538-7836.2003.00367.x
28. Laffan MA, Lester W, O'Donnell JS, Will A, Tait RC, Goodeve A, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. Br J Haematol [Internet]. 2014 [citado 2018 Abril 8];167:453-465. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4283483/
29. Woods AI, Sánchez-Luceros A, Meschengieser SS, Kempfer AC, Blanco AN, Lazzari MA, ed. Diagnosis and management of von Willebrand disease in a single institution of Argentina. Semin Thromb Hemost [Internet]. 2011 [citado 2017 Dic 10];37(5):568-75. Disponible en: https://www.researchgate.net/profile/Adriana_Woods/publication/51816373_Diagnosis_and_Management_of_von_Willebrand_Disease_in_a_Single_Institution_of_Argentina/links/5a4d21c5a6fdcc3e99d158d2/Diagnosis-and-Management-of-von-Willebrand-Disease-in-a-Single-Institution-of-Argentina.pdf
30. Padilla-Romo MGZ, Jaloma-Cruz AR. Algoritmo diagnóstico para la enfermedad de von Willebrand (EVW) en población mexicana. Gac Méd Méx [Internet]. 2015 [citado 2018 Ene 13];151(6):828-33. Disponible en: https://www.anmm.org.mx/GMM/2015/n3/GMM_151_2015_3_399-402.pdf
31. Favaloro EJ. Diagnosis and classification of von Willebrand disease: a review of the differential utility of various functional von Willebrand factor assays. Blood Coagul Fibrinolysis [Internet]. 2011 [citado 2018 Ene 28];22(7):553-64. Disponible en: https://journals.lww.com/bloodcoagulation/Fulltext/2011/10000/Diagnosis_and_classification_of_von_Willebrand.1.aspx
32. Hernández-Zamora E, Zavala-Hernández C, Quintana-González S, Reyes-Maldonado E. Enfermedad de von Willebrand, biología molecular y diagnóstico. Cirugía y Cirujanos [Internet]. 2015 [citado 2018 Feb 03];83(3):255-64. Disponible en: https://www.sciencedirect.com/science/article/pii/S0009741115000687
33. Kano T, Kondo K, Hamako J, Matsushita F, Sakai K, Matsui T. Effects of plasma glycosyltransferase on the ABO(H) blood group antigens of human von Willebrand factor. Int J Hematol [Internet]. 2018 Apr [citado 2018 Feb 18];108(2):139-144. Disponible en: https://link.springer.com/article/10.1007/s12185-018-2452-0
34. Franchini M, Makris M. Non-O blood group: an important genetic risk factor for venous thromboembolism. Blood Transfus [Internet]. 2013 [citado 2018 Ene 17];11:164-5. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3626462/pdf/blt-11-164.pdf
35. Brehm MA. Von Willebrand factor processing. Hamostaseologie. 2016 Nov 21;37(1):59-72.
36. Solecka BA, Weise C, Laffan MA, Kannicht C. Site-specific analysis of von Willebrand factor O- glycosylation. J Thromb Haemost [Internet]. 2016 Abr 1 [citado 2018 Ene 15];14(4):733-46. Disponible en: http://onlinelibrary.wiley.com/doi/10.1111/jth.13260/full

37. McGrath RT, van den Biggelaar M, Byrne B, O'Sullivan JM, Rawley O, O'Kennedy R, et al. Altered glycosylation of platelet-derived von Willebrand factor confers resistance to ADAMTS13 proteolysis. Blood [Internet]. 2013 Dic 12 [citado 2018 Ene 17];122(25):4107-10. Disponible en: http://www.bloodjournal.org/content/122/25/4107.long
38. Mckinnon TAJ, Goode EC, Birdsey GM, Nowak AA, Chan ACK, Lane DA, et al. Specific N-linked glycosylation sites modulate synthesis and secretion of von Willebrand factor. Blood [Internet]. 2011 [citado 2017 Dec 17];116(4):640-8. Disponible en: http://www.bloodjournal.org/content/bloodjournal/116/4/640.full.pdf
39. Lynch CJ, Lane DA. N-linked glycan stabilization of the VWF A2 domain. Blood [Internet]. 2016 Mar 31 [citado 2018 Ene 17];127(13):1711-8. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4817312/
40. Eikenboom J, Federici AB, Dirven RJ, Castaman G, Rodeghiero F, Budde U, et al. VWF propeptide and ratios between VWF, VWF propeptide, and FVIII in the characterization of type 1 von Willebrand disease. Blood [Internet]. 2013 Mar 21 [citado 2018 Ene 20];121(12):2336-9. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4191434/
41. Sanders Y V, Groeneveld D, Meijer K, Fijnvandraat K, Cnossen MH, Van Der Bom JG, et al. von Willebrand factor propeptide and the phenotypic classification of von Willebrand disease. Blood [Internet]. 2015 [citado 2018 Ene 17];125(19):3006-13. Disponible en: http://www.bloodjournal.org/content/bloodjournal/125/19/3006.full.pdf
42. Ozel AB, McGee B, Siemieniak D, Jacobi PM, Haberichter SL, Brody LC, et al. Genome-wide studies of von Willebrand factor propeptide identify loci contributing to variation in propeptide levels and von Willebrand factor clearance. J Thromb Haemost [Internet]. 2016 Sep [citado 2018 Ene 20];14(9):1888-98. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5035595/
43. Muia J, Zhu J, Gupta G, Haberichter SL, Friedman KD, Feys HB, et al. Allosteric activation of ADAMTS13 by von Willebrand factor. Proc Natl Acad Sci U S A [Internet]. 2014 Dic 30 [citado 2018 Feb 17];111(52):18584-9. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4284596/?report=reader
44. South K, Luken BM, Crawley JTB, Phillips R, Thomas M, Collins RF, et al. Conformational activation of ADAMTS13. Proc Natl Acad Sci U S A [Internet]. 2014 Dic 30 [citado 2018 Feb 17];111(52):18578-83. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4284544/?report=reader
45. Al-Awadhi AM, Al-Sharrah SK, Jadaon MM, Al-Sayegh F. Investigating the influence of age, gender and ABO blood group on ADAMTS-13 antigen and activity levels in healthy Arabs. Blood Transfus [Internet]. 2014 Jan [Citado 2018 Feb 10];12(1):138-40. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3926720/
46. Giebeler N, Zigrino P. A Disintegrin and Metalloprotease (ADAM): Historical Overview of Their Functions. Toxins (Basel) [Internet]. 2016 [citado 2018 Marzo 10];8(122). Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4848645/pdf/toxins-08-00122.pdf
47. South K, Lane DA. ADAMTS-13 and von Willebrand factor: a dynamic duo. J Thromb Haemost [Internet]. 2018 enero 1 [Citado 2018 Feb 10];16(1):6-18. Disponible en: http://onlinelibrary.wiley.com/doi/10.1111/jth.13898/full
48. Habe K, Wada H, Higashiyama A, Akeda T, Tsuda K, Mori R, et al. The Plasma Levels of ADAMTS-13, von Willebrand Factor, VWFpp, and Fibrin-Related Markers in Patients With Systemic Sclerosis Having Thrombosis. Clin Appl Thromb Hemost. 2018;24(6):920-27. doi: 10.1177/1076029617736382
49. Jacobi PM, Gill JC, Flood VH, Jakab DA, Friedman KD, Haberichter SL. Intersection of mechanisms of type 2A EVW through defects in VWF multimerization, secretion, ADAMTS-13 susceptibility, and regulated storage. Blood [Internet]. 2012 May 10 [citado 2018 Feb 17];119(19):4543-53. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3362367/
50. Nowak AA, McKinnon TAJ, Hughes JM, Chion ACK, Laffan MA. The O-linked glycans of human von Willebrand factor modulate its interaction with ADAMTS-13. J Thromb Haemost [Internet]. 2014 Ene 1 [citado 2018 Feb 17];12(1):54-61. Disponible en: http://onlinelibrary.wiley.com/doi/10.1111/jth.12451/full
51. Liu X, Chen X, Yang J, Guo R. Association of ABO blood groups with von Willebrand factor, factor VIII and ADAMTS-13 in patients with lung cancer. Oncol Lette [Internet]. 2017 [citado 2018 Mar 1];14(3):3787-3794. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5587991/
52. Song J, Chen F, Campos M, Bolgiano D, Houck K, Chambless LE, et al. Quantitative Influence of ABO Blood Groups on Factor VIII and Its Ratio to von Willebrand Factor, Novel Observations from an ARIC Study of 11,673 Subjects. PLoS One [Internet]. 2015 [citado 2018 Mar 12];10(8):e0132626. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4526567/
53. Sousa NC, Anicchino-Bizzacchi JM, Locatelli MF, Castro V, Barjas-Castro ML. The relationship between ABO groups and subgroups, factor VIII and von Willebrand factor. Haematologica [Internet]. 2007 [citado 2018 Abr 02];92(2):236-9. Disponible en: http://www.haematologica.org/content/92/2/236.short
54. Wang Z, Dou M, Du X, Ma L, Sun P, Cao H, et al. Influences of ABO blood group, age and gender on plasma coagulation factor VIII, fibrinogen, von Willebrand factor and ADAMTS13 levels in a Chinese population. PeerJ [Internet]. 2017 [citado 2018 Abr 03];5:e3156. Disponible en: https://peerj.com/articles/3156/?utm_source=TrendMD&utm_campaign=PeerJ_TrendMD_1&utm_medium=TrendMD
55. Johansson Å, Alfredsson J, Eriksson N, Wallentin L, Siegbahn A. Genome-Wide Association Study Identifies That the ABO Blood Group System Influences Interleukin-10 Levels and the Risk of Clinical Events in Patients with Acute Coronary Syndrome. PLoS One [Internet]. 2015 [citado 2018 Mar 9];10(11):e0142518. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4658192/
56. Larson NB, Bell EJ, Decker PA, Pike M, Wassel CL, Tsai MY, et al. ABO blood group associations with markers of endothelial dysfunction in the Multi-Ethnic Study of Atherosclerosis.

Atherosclerosis [Internet]. 2016 Ago [citado 2018 Mar 15];251:422-9. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4983247/

57. Nagy EE, Varga-Fekete T, Puskas A, Kelemen P, Brassai Z, Szekeres-Csiki K, et al. High circulating osteoprotegerin levels are associated with non-zero blood groups. BMC Cardiovasc Disord [Internet]. 2016 [Citado 2018 Mar 15];16(1):106. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4937555/
58. Pike MM, Larson NB, Wassel CL, Cohoon KP, Tsai MY, Pankow JS, et al. ABO blood group is associated with peripheral arterial disease in African Americans: The Multi-Ethnic Study of Atherosclerosis (MESA). Thromb Res [Internet]. 2017 May [citado 2018 Mar 16];153:1-6. Disponible en: https://www.sciencedirect.com/science/article/pii/S0049384817300531
59. Albánez S, Ogiwara K, Michels A, Hopman W, Grabell J, James P, et al. Aging and ABO blood type influence von Willebrand factor and factor VIII levels through interrelated mechanisms. J Thromb Haemost [Internet]. 2016 May [citado 2018 Mar 16];14(5):953-63. Disponible en: https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.13294
60. Akin M, Balkan C, Karapinar DY, Kavakli K. The influence of the ABO blood type on the distribution of von Willebrand factor in healthy children with no bleeding symptoms. Clin Appl Thromb Hemost [Internet]. 2011 Sep [citado 2018 Jul 26];18(3):316-9. Disponible en: https://doi.org/10.1177/1076029611422364
61. Shahidi M. Thrombosis and von Willebrand Factor. Adv Exp Med Biol. 2017;906:285-306