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REVIEW

Von Willebrand factor deficiency and atherosclerosis

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ABSTRACT

Von Willebrand factor (VWF) is a large multimeric glycoprotein that plays a major role in haemostasis, illustrated by the bleeding tendency in von Willebrand disease (VWD), the most common hereditary bleeding disorder caused by VWF deficiency or dysfunction. Elevated VWF levels are strongly associated with an increased risk of ischemic cardiovascular events. Whether this relation is causal, or whether increased VWF levels reflect disturbances of endothelial function remains to be elucidated. One possibility is that VWF participates in the process of atherogenesis. The aim of the current review is to determine whether VWF deficiency provides protection against the development of atherosclerosis in humans and animals. Results from animal studies suggest that, at arterial branch point predilection sites, VWF deficiency or blockage has a protective effect against atherosclerosis. Based on the available evidence, this potential protective effect of VWF deficiency can most likely be tracked to the VWF–platelet interaction. Sites involved in this interaction could prove attractive targets in future treatment and prevention of cardiovascular disease, an option that is already being explored in humans. An unequivocal protective effect of VWD on atherosclerosis has not been demonstrated in humans. However the interpretation of these results is hampered by several methodological weaknesses. In conclusion, VWF is probably a significant player in the multifaceted interaction between the haemostatic system and the atherosclerotic process which deserves further study.

1. Introduction

Von Willebrand factor (VWF) is a large multimeric glycoprotein (GP), which is secreted by platelet α-granules and endothelial Weibel–Palade bodies. VWF plays a major role in haemostasis and dysfunction or deficiency of VWF leads to a bleeding disorder known as von Willebrand disease (VWD). Acting as a carrier protein, VWF protects circulatory factor VIII from inactivation and clearance. Moreover, VWF enables platelet plug formation at sites of vascular injury. Here, VWF promotes platelet adhesion by binding to the GPIb–IX–V receptor complex (GPIb) on the platelet surface and to collagen in the subendothelial matrix. After the initial platelet arrest due to the GPIb–VWF interaction, which is further stabilized and accelerated by VWF–collagen binding, intracellular signaling occurs and platelets become activated. In addition, VWF promotes platelet-platelet interaction, thereby supporting platelet aggregation. This process occurs most effectively under circumstances of high shear, when VWF undergoes a transformation as its large multimers unfold and markedly increases its platelet-binding capacity.[1]

Elevated VWF levels appear to be strongly associated with major cardiac events.[2,3] Stroke risk also increases with increasing VWF levels.[4] In addition, the five-year risk ratio for the development of peripheral artery disease (PAD) significantly increases with higher median baseline VWF levels.[5] Whether this association between higher VWF levels and cardiovascular diseases (CVD) is indicative of a causal relationship or, rather, merely reflects VWF's entity as marker of endothelial damage and hypercoagulability, remains to be elucidated.[6,7] One possibility is that VWF participates in the process of atherogenesis. There are, indeed, experimental data that VWF might be involved in atherogenesis. In vitro, the amount of VWF on the endothelial cell (EC) surface is increased by low-density lipoproteins (LDL) and among the large number of VWF secretion agonists there are numerous factors involved in atherogenesis.[6,8] Furthermore, smooth muscle cells (SMCs) are the major constituent of atherosclerotic plaques and VWF stimulates mouse aortic SMC proliferation in vitro in a direct dose-dependent way.[9] In vivo, cholesterol- and injury-induced plaque formation is associated with a marked increase in VWF expression at plaque predilection sites in rodents.[10,11] In primates, large numbers of WPBs are found in ECs at sites of early atherosclerotic lesions.[12] In humans, ECs in advanced atherosclerotic plaques contain hyperplastic Weibel-Palade bodies.[13] Finally, atherosclerosis is an inflammatory disease, VWF levels increase during inflammation and VWF facilitates neutrophil extravasation in mice at sites of inflammation by destabilization of the endothelial barrier through platelet recruitment via their GPIb receptor.[14,15]

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These findings suggest that VWF contributes to the pathogenesis of atherosclerosis. The hypothesis, that the extent of atherosclerosis is reduced in patients with VWD, logically follows. In the current review, studies on atherosclerosis in VWF deficient animals and humans are summarized to determine whether VWF deficiency protects against the development of atherosclerosis. An answer to this question could expand our knowlegde about the role of VWF in atherogenesis and might have future diagnostic or therapeutic consequences.

2. Search strategy

A comprehensive literature search was performed using the Medline database, to identify studies, published until July 2011, on atherosclerosis in patients with all hereditary forms of VWD and in VWF deficient animal models. The following search terms and synonyms of these search terms were used to identify potentially relevant studies: von Willebrand factor, von Willebrand disease, von Willebrand factor deficiency, von Willebrand factor antibody, atherosclerosis, atherogenesis, intima media thickness, ankle arm index, plaque and stenosis. Results were screened on title and abstract. Relevant studies in English were included. Reviews, in vitro studies and studies concerning arterial thrombosis models without induction of atherosclerosis were excluded. References of the selected papers were checked for related articles that did not appear in the initial search. The literature search, review of the data and data extraction were performed by two authors independently. A total of 32 relevant studies were included in the current review comprising 27 animal and 5 human studies (Tables 1–3).

3. Atherosclerosis in VWF deficient animals

3.1. Aortic atherosclerosis in VWF deficient pigs

In the 1970s, Fuster et al. incidentally observed that homozygous VWF deficient (VWF−/−) pigs barely suffered from aortic atherosclerosis whereas control (VWF+/+) pigs exhibited significant atherosclerosis.[16] This finding instigated a rush of studies on atherosclerosis in VWF−/− pigs (Table 1). The initial observation could have been confounded because the control pigs, obtained from a slaughterhouse, carried significantly higher body weights compared to the VWF−/− pigs.[16] Therefore, subsequent studies implemented diet control.

The same authors performed a successive study, in which 3-month-old pigs were fed a high cholesterol diet for up to 6 months. Aortic atherosclerosis developed in all control pigs while less than half of the VWF−/− pigs developed only discrete atherosclerotic plaques.[16] This pronounced difference in the presence and extent of aortic atherosclerosis between VWF−/− and VWF+/+ pigs suggested that an absolute deficiency of VWF has a protective effect on the development of atherosclerosis.

Spontaneous aortic atherosclerosis, allowed to develop during a 4-year controlled low cholesterol diet was also less pronounced in VWF−/− pigs, most strikingly so in the distal aorta.[17] Heterozygous VWF+/− pigs receiving an atherogenic diet, were not resistant to aortic atherosclerosis. A dose-dependent effect could therefore not be demonstrated.[18]

To examine whether the aortas of the VWF−/− pigs were less responsive to atherosclerosis, VWF+/+ segments of the distal aorta were cross-transplanted into VWF−/− pigs and vice versa.[17]

Table 1
Animal studies on atherosclerosis and VWF deficiency.

Author	Animal type	Animal number VWF phenotype	High cholesterol diet	Site	Injury induced	FU	Protection against atherosclerosis by VWF deficiency
Fuster[16]	Pig	11−/−, 11+/+	No	Aorta	No	–	Yes
– original cohort	Pig	7−/−, 11+/+	Yes	Aorta	No	6 mo	Yes
– subsequent cohort							
Fuster[17]	Pig	5−/−, 5+/+	No	Aorta	No	4 yr	Yes
		4−/−, 4+/+	Yes	Aorta	Cross Tx	6 mo	Yes
Fuster[18]	Pig	5−/−, 5+/−, 9+/+	Yes	Aorta	No	6 mo	Yes
Griggs[19a]	Pig	7−/−, 8+/−, 6+/+	Yes	Aorta	No	4 mo	Yes, distal aorta
				Coronary artery	Yes		No
Griggs[20a]	Pig	14−/−, 13+/−, 11+/+	Yes	Coronary artery	Yes	4 mo	No; protection from MI, No
		7−/−, 7+/−, 5+/+	Yes	Aorta	Yes CO exposure		No
				Coronary and aorta			
Fuster[22]	Pig	5−/−, 5+/+	No	Coronary artery	No	4 yr	No, but barely atherosclerosis observed
		5−/−, 9+/+	Yes		No	6 mo	
Griggs[25]	Pig	5−/−, 5+/+	No	Coronary artery	Yes	–	No; retarded platelet activation
Griggs[24]	Pig	8−/−, 8+/+	Yes	Coronary artery	Yes	1–16 w	No; less platelet reactivity
Griggs[27]	Pig	10−/−, 12+/+	No	Coronary artery	Yes	–	No; no difference SMC response
Griggs[23]	Pig	6−/−, 8+/+	Yes	Coronary artery	Yes	24 w	No; protection form MI
				Carotid			No[d]
Griggs[26]	Pig	9−/−, 9+/+	Yes	Coronary artery	Yes	1 w	No; affected by chol
Griggs[21]	Pig	12−/−, 9+/+	Yes	Aorta	No	16–26 w	No[c]; affected by apoBpm No;
		14−/−, 13+/+[b]		Coronary artery			affected by apoBpm
Griggs[28]	Pig	2−/−, 3+/−, 3+/+	No	Femoral and carotid arteries	Yes shear stress	–	No; no influence on neointimal formation
Methia[32]	LDLR−/− mice	38−/−, 34+/+	Yes	Aorta	No	8–37 w	Yes; at branch points
Qin[9]	C57BL/6J mice	0−/−, 108+/− and +/+ mice in 3 groups: RIIIS/J, RIIIS/J + DDAVP, controls	No	Carotid artery	Yes	8 w	Yes; dose response effect on SMC proliferation

FU indicates the follow up time (in studies with implantation of a high cholesterol diet from start of diet until sacrifice); w, weeks; mo, months; yr, years; MI, myocardial infarction; VWF, von Willebrand factor; VWF−/−, homozygous VWF deficiency; VWF+/−, heterozygous VWF deficiency; VWF +/+, normal VWF; SMC, smooth muscle cell; LDLR-, lacking the LDL receptor; Tx, transplantation; CO, carbon monoxide; chol, cholesterol; chol, cholesterol; apoBpm, apolipoprotein B polymorphisms.

[a] Pigs from same cohort.

[b] Overlaps with Refs. 12, 31 and 42.

[c] The extent of aortic atherosclerosis tended to be lower compared to VWF+/+ pigs but not significant.

[d] Increased carotid IMT was detected in only one VWF +/+ pig.