Accepted Manuscript online: 2021-01-07 Article published online: 2021-02-18

Endothelial Dysfunction, Atherosclerosis, and Increase of Von Willebrand Factor and Factor VIII: A Randomized Controlled Trial in Swine

Bernhard Lämmle[1,2,3]

[1] Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[2] Center for Thrombosis and Hemostasis, University Medical Center, Mainz, Germany
[3] Haemostasis Research Unit, University College London, London, United Kingdom

Address for correspondence Bernhard Lämmle, MD, Schützenweg 3, CH 3065 Bolligen, Switzerland (e-mail: bernhard.laemmle@uni-mainz.de).

Thromb Haemost 2021;121:552.

High Von Willebrand factor (VWF) levels are associated with a prothrombotic tendency, the metabolic syndrome, atherosclerosis, and ischemic cardiovascular and cerebrovascular diseases. Factor VIII (FVIII) clotting activity (FVIII:C) correlates with VWF: antigen (VWF:Ag). Cross-sectional case–control studies in young women showed increasing VWF:Ag and decreasing ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity independently correlated with increased risk for ischemic stroke and myocardial infarction, while oral contraceptives further increased the risk.[1] A prospective study in hypertensive subjects revealed higher VWF levels in those with the metabolic syndrome at baseline but VWF was not predictive for its development over 4 years of follow-up.[2] In a large population cohort, VWF in the highest quartile and ADAMTS13 in the lowest quartile independently predicted ischemic stroke over 10 years of follow-up.[3]

Could high VWF and FVIII then cause endothelial dysfunction and atherosclerosis or vice versa in the presence of classic risk factors such as diabetes mellitus (DM) and hypercholesterolemia (HC)?

To address this question, Atiq et al performed two separate randomized controlled trials (RCTs) in swine.[4] First, they induced DM by streptozotocin and HC by high-fat diet in 18 miniswine and compared them with 16 controls over 5 months. DM/HC did not induce endothelial dysfunction or atherosclerosis and VWF:Ag remained at baseline levels. Nevertheless, FVIII:C increased significantly in DM/HC swine at 5 months as compared with controls, independently of VWF, and the ratio of FVIII:C/VWF:Ag correlated with fasting glucose and cholesterol concentrations. A second RCT followed five swine with induced DM/HC and five with HC over 15 months. Both groups developed endothelial dysfunction, atherosclerosis, and significantly higher VWF at 15 months than at 9 months. The authors conclude that VWF is a biomarker reflecting endothelial dysfunction and advanced atherosclerosis, whereas the early increase of FVIII:C, independent of VWF, is induced by DM/HC. Possible mechanisms of the FVIII:C increase such as its binding to lipids instead of VWF are discussed. Future studies should investigate the specific activity of FVIII by measuring FVIII:C/FVIII:Ag to distinguish increased concentration from activation of FVIII.

Conflict of Interest

B.L. is the chairman of the Data Safety Monitoring Committees for studies of recombinant ADAMTS13 in congenital and acquired TTP (now run by Takeda); he is on the Advisory Board of Sanofi for the development of caplacizumab for acquired TTP; he received lecture fees from Ablynx, Alexion, Siemens, Bayer, Roche, and Sanofi, outside the present work.

References

1 Andersson HM, Siegerink B, Luken BM, et al. High VWF, low ADAMTS13, and oral contraceptives increase the risk of ischemic stroke and myocardial infarction in young women. Blood 2012;119 (06):1555–1560
2 Lim HS, Lip GYH, Blann AD. Plasma von Willebrand factor and the development of the metabolic syndrome in patients with hypertension. J Clin Endocrinol Metab 2004;89(11):5377–5381
3 Sonneveld MAH, de Maat MPM, Portegies MLP, et al. Low ADAMTS13 activity is associated with an increased risk of ischemic stroke. Blood 2015;126(25):2739–2746
4 Atiq F, van de Wouw J, Sorop O, et al. Endothelial dysfunction, atherosclerosis, and increase of von Willebrand factor and Factor VIII: a randomized controlled trial in swine. Thromb Haemost 2021; 121(05):676–686

received
January 5, 2021
accepted
January 5, 2021
published online
January 14, 2021

DOI https://doi.org/10.1055/a-1347-8761.
ISSN 0340-6245.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany