von Willebrand Factor As a marker of Endothelial Dysfunction in Acute Coronay Syndrome

Thesis

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Summary and Conclusion

Under physiological conditions, the vascular endothelium produces many substances that contribute importantly to hemostasis, fibrinolysis, and regulation of vessel tone and permeability. One such substance is glycoprotein von Willebrand factor (vWf), which is almost exclusively produced by the endothelium, and thus is a marker of endothelial activation or dysfunction. vWf mediates platelet adhesion to the vascular wall, platelet aggregation and serves as a plasma carrier for factor VIII, stabilizing it in the circulation**.** Since almost all acute coronary syndromes (ACSs) result from thrombus formation in preexisting atherosclerosis, and given the key role of vWf in arterial thrombus formation, this biomarker attracted considerable interest as a predictor of cardiovascular disease (CVD)**.**

Previously published studies suggest that there is a weak association between vWf plasma levels and risk of coronary heart disease (CHD) in general population, but its predictive value significantly rises in patients with preexisting vascular disease, diabetics, and the elderly**.** It was noticed that vWf rises during the course of ACSs, and it is thought that vWf is not only a marker, but also a mediator in the pathogenesis of myocardial infarction (MI). Although a number of studies pointed out the prognostic value of vWf, there is still a long way to go before plasma vWf levels can be used as a predictor of cardiovascular disease in clinical practice.

In this regards, our study aimed to evaluate the role of vWF as marker for prognosis in association with other inflammatory marker such as hs-CRP in patients with acute coronary syndrome.

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List of Abbreviations

ACS	Acute Coronary Syndrome
ADMTS13	A Disintegrin and Metallo- protinase with ThromoboSpondin type 1 repeats-13
AMI	Acute Myocardial Infarction
APP	Acute Phase Protein
APR	Acute Phase Reaction
APTT	Activated Partial Thromboplastine Time
AUC	Area Under Curve
CAD	Coronary Artery Disease
CK	Creatine Kinase
CK MB	Creatine Kinase MB fraction
CRP	C- Reactive Protein
CtnI	Cardiac Tropnin I
ECG	ElectroCardioGram
ED	Emergency Department
ELISA	Enzyme Linked ImmunSorbant Assay
FⅤⅢ	Factor ⅤⅢ
GPIb	GlycoProtein Ib
HDL-C	High Density Lipoprotein – Cholesterol
hs CRP	High sensitivity C-Reactive Protein
ICAM	IntraCellular Adhesion Molecules
IL-6	InterLeukin – 6
LD	Lactate Dehydroogenase
MeTS	Metabolic Syndrome
NADH	Reduced β-nicotinamide adenine dinucleotide
Ox-LDL	Oxidized –LDL
PCI	Percutaneous Coronary Intervention
PDGF	Platelet Derived Growth Factor
PFA100	Platelet Function Analyser 100
POCT	Point Of Care Testing
ROS	Reactive Oxygen Sepecies

List of Abbreviations (Cont.)

STEMI	ST Elevation Myocardial Infarction
SBT	Skin Bleeding Test
TFPI	Tissue Factor Plasminogen Inhibitor
TF	Tissue Factor
TGF	Transforming Growth Factor
TM	Thrombomodulin
TNF	Tumor Necrosis Factor
t-PA	Tissue Plasminogen Activator
TIMI	Thrombolysis In Myocardial Infarction
UA	Unstable Angina
VCAM	Vascular Cell Adhesion Molecules
vWD	von Willebrand Disease
Vwf	von Willebrand Factor
vWF: Rco	Ristocetin cofactor activity assay
vWF:Ag	Antigen of von Willebrand Factor
vWF:CB	von Willebrand Factor Collagen Binding
vWF:PB	vWF Platelet-Binding
VSMCs	Vascular Smooth Muscle Cells

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Introduction

It has been known that alterations in blood flow vascular wall, and blood components, the so-called **Virchow's triad,** may progressively lead to thrombus formation. Recently, a more understanding of the complex interactions among the vascular endothelium, platelet adhesion, activation, aggregation, and clotting factor activation are involved in this process ***(Alexander et al., 2008).***

Under physiological conditions, the vascular endothelium produces many substances that contribute importantly to hemostasis, fibrinolysis, and regulation of vessel tone and permeability. One such substance is the multimeric glycoprotein von Willebrand factor (vWF), which is produced almost exclusively by endothelial cells ***(Hollestella et al., 2001).***

Plasma levels of vWF are raised in different states of endothelial damage and have therefore been proposed as useful markers of endothelial dysfunction**,** Along this line, blockade of nitric oxide enhances the stimulated release of vWF in humans**.** Furthermore, vWF plays a crucial role in platelet adhesion and aggregation under high shear condition ***(Pernerstorfer et al., 2000)***.

Finally, vWF supports the third component of Virchow's triad, clotting factor activation, by acting as a carrier protein and stabilizer for factor VIII ***(Alexander et al., 2008)***.

Almost all **A**cute **C**oronary **S**yndromes (**ACS**) result from thrombus formation in preexisting coronary atherosclerosis. As a result of plaque rupture and exposure of prothrombotic subendothelial matrix, local thrombus formation occurs, which subsequently leads to coronary artery occlusion and **A**cute **M**yocardial **I**nfarction (**AMI**).

The presence of vWF has been shown to play a pivotal role in platelet aggregation at sites of high shear, eg, at the sites of lesions in the coronary arteries ***(Fredrickson et al., 1998).***

Accordingly, vWF may be a marker of cardiovascular risk, and its plasma level with other inflammatory markers such as high sensitivity **C -R**eactive **P**rotein (hs-**CRP**) may increase in patients with ACS. In addition vWF may play a role in thrombogenesis. therapies that specifically inhibit vWF are of particular interest as potential new antiplatelet drug ***(Alexander et al., 2008)***.

C- Reactive **P**rotein **(CRP)** is a trace protein in the circulation of healthy subjects, concentration can increase 100-fold or more in response to injury, infection, or inflammation. Moderately increased plasma CRP concentrations are found in smokers and under conditions of atherosclerosis, psychological stress, diabetes, and obesity, and in the elderly ***(Cao et al., 2003).***

Increased biomarkers of inflammation, including hs-CRP, have been associated with increased stroke risk and further coronary events as well as an increased rate of atherosclerosis progression in the carotid and coronary vessels. The variation in hs-CRP can be affected by genetic factors, diet, exercise, and smoking cessation ***(Ridker et al., 2008).***

CRP is associated with endothelial cell dysfunction and progression of atherosclerosis, possibly by decreasing nitric oxide synthesis ***(Libby et al., 2003)***. This suggests that high **CRP** plasma concentrations and the extent of its deposition in the atherosclerotic plaque are associated with plaque vulnerability and the occurrence of acute thrombotic events ***(Pepys et al., 2003).***

Aim of The Work

This work aims to assessment of vWF in Acute Coronary Syndromes and measurement of hs-CRP level in ACS and its correlation to vWF level.

A-Endothelial cell Physiology:

The inner lining (intima) of all blood vessels consists of a monolayer of flattened, orthogonal cells referred to as the endothelium, positioned on the internal elastic lamina. The vascular endothelium is not just a cell lining, but plays an active role via various mediators in the equilibrium of haemostasis and fibrinolysis ***(Pusztaszeri et al., 2005)*.**

Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function, control of volume and electrolyte content of the intravascular and extravascular spaces. Endothelial dysfunction can result from and/or contribute to several disease processes, as occurs in septic shock, hypertension, hypercholesterolaemia, diabetes as well from environmental factors, such as from smoking tobacco products and exposure to air pollution ***(Dean field et al., 2005).***

B-Antithrombotic function of endothelium:

Endothelium produces many substances **(*Table 1*)** with autocrine and paracrine activity ***(Vermas et al., 2002)***. Factors which are regulated by the endothelium and take active part in hemostasis and thrombosis are shown in (***Table 2***). One of the most important function of endothelial cells is the prevention of non-physiological activation of blood coagulation resulting in thrombosis. This activity is mediated by the negative charge of the endothelium provided by surface expression of heparan sulfate proteoglycans and the secretion of prostacyclin, nitric oxide (NO), tissue factor pathway inhibitor (TFPI) and tissue plasminogen activator (t-PA). Endothelial expression of thrombomodulin (TM), which binds to thrombin and activates anticoagulant protein C, plays a very important antithrombotic role. Endothelial damage triggers thrombus formation due to decreased antithrombotic potential, expression of tissue factor