Circulating Endothelial Microparticles (CD144+) and von Willebrand Factor Antigen as Markers of Endothelial Dysfunction in β-Thalassemia Patients

Thesis

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بسماللهالرحمنالرحيم

وَأَنْزَلَاللهُعَلَيْكَالْك
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LIST OF ABBREVIATIONS

Abbrev.	Full term
AF	: Atrial fibrillation
APC	: Activated protein C
BMI	: Body mass index
CAM	: Cell adhesion molecule
CBC	: Complete blood count
CECs	: Circulating endothelial cells
CEPCs	: Circulating endothelial progenitor cells
cGMP	: Cyclic guanylate monophosphate
DDAVP	: 1-desamino-8-D-arginine vasopressin
DMT1	: Divalent metal transporter 1
EC	: Endothelial cells
ED	: Endothelial dysfunction
EDHF	: Endothelium derived hyperpolarizing factor
EMPs	: Endothelial derived microparticles
eNOS	: Endothelial NO synthase
EPCR	: Endothelial protein C receptor
ET-1	: Endothelin-1
GSTM1	: Glutathione S-transferase-M1
HMEC-1	: Human microvascular endothelial cell-1
HPLC	: High performance liquid chromatography
ICAM-1	: Intracellular cell adhesion molecule-1
IL-1K	: Interleukin-1K
IQR	: Interquartile Range
IRAK1	: Interleukin receptor-associated kinase 1
LDH	: Lactate dehydrogenase
LPS	: Lipopolysaccharide
MDCT	: Multidetector computed tomography
MMP	: Matrix metalloproteases
MPs	: Microparticles
NF	: nuclear factor

LIST OF ABBREVIATIONS *(Cont...)*

Abbrev.	Full term
NO	: Nitric oxide
PAI-1	: Plasminogen activator inhibitor
PAR-1	: Proteinase-activated receptor1
PE	: Phycoerythrin
PNH	: Paroxysmal nocturnal haemoglobinuria
PS	: Phosphatidylserine
PSGL-1	: P-selectin glycoprotein ligand 1
RBC	: Red blood cell
RTKs	: Receptor tyrosine kinases
SCD	: Sickle cell disease
SD	: Standard deviation
SPSS	: Statistical Program for Social Science
sTM	: Soluble thrombomodulin
TFPI	: Tissue factor pathway inhibitor
TF	: Tissue factor
TM	: Thrombomodulin
TNF	: Tumor necrosis factor
t-PA	: Tissue plasminogen activator
TRAIL	: Tumer Related apoptosis-inducing ligand
uPAR	: Urokinase plasminogen activator receptor
VCAM-1	: vascular cell adhesion molecule-1
VEGF	: Vascular endothelial growth factor
VEGFR-1	: Vascular endothelial growth factor receptor-1
vwFAg	: von Willebrand factor antigen
WBC	: White blood cell

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INTRODUCTION

Transfusion-related iron overload in β-thalassemia has been associated with the onset of cardiovascular complications, including cardiac dysfunction and vascular anomalies ***(Stoyanova et al., 2012).*** Endothelial function is impaired in young thalassemia patients, and this dysfunction is associated with oxidant stress ***(Kukongviriyapan et al., 2008).***

In the last 10 years, identification of endothelial derived microparticles (EMPs) has raised considerable interest as non invasive markers of vascular dysfunction ***(Sabatier et al., 2009)***. EMPs are small vesicles released from disturbed endothelial cells that have recently been reported as a marker of endothelial injury and systemic vascular remodelling ***(Horstman et al., 2004)***. EMPs are biologically active and stimulate pro-inflammatory responses in target cells. Thus, EMPs can promote a prothrombogenic and pro-inflammatory vicious circle leading to vascular dysfunction ***(Boulanger et al., 2008)***.

EMPs contain membrane, cytoplasmic, and nuclear constituents, characteristic of their precursor cells that confer to EMPs the properties of circulating multifunctional effectors, promoting inflammation of the arterial wall and thrombogenicity through cellular cross-talk ***(Boulanger et al., 2008)***. Leukocyte adhesion and migration are dependent on a range of cellular adhesion molecules (CAMs) that are up regulated in the endothelium during atherosclerosis ***(Blankenberg et al., 2003)***.

Because microparticles are fragments of endothelial cell membranes, they also express CAMs ***(Hunter MP et al., 2008)***.

EMPs can be characterized by their expression of different cell surface antigens including CD31, CD34, CD54, CD62E, CD51, CD105, CD106, CD144 and CD146 ***(Burnier et al., 2009)***.

von Willebrand factor antigen (vwF Ag) has been purposed as a biomarker of endothelial dysfunction as it is important in the aggregation of platelets and their adhesion to subendothelial cells contributing to inflammatory and atherosclerotic vascular diseases and represent a link between hemostasis and angiogenesis ***(Horvathet al., 2004; Papassotiriou and kattamis, 2012)***. Increased activated circulating endothelial cells, enhanced vWF Ag and adhesion molecules were observed in patients with β-thalassemia/hemoglobin E ***(Butthep et al., 2004).***