Tissue Factor Pathway Inhibitor in Patients with Coronary Heart Diseases

Thesis

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List of Abbreviations

2hrPPG.....2-hours postprandial plasma glucose.

ACS .....Acute coronary syndrome.

AMI .....Acute myocardial infarction.

Apo B.....Apolipoprotein B.

APS .....Antiphospholipid syndrome.

BMI.....Body mass index.

CHD.....Coronary heart disease.

CK-MB.....Creatinine kinase muscle-brain fraction.

CMV .....Cytomegalovirus.

CRP .....C-reactive protein.

cTnI .....Cardiac troponin which binds to actin and inhibits actin-myosin interactions.

cTnT .....Cardiac troponin which binds to tropomyosin.

DM.....Diabetes mellitus.

DNA.....Deoxyribonucleic acid.

DPT.....Diluted prothrombin time.

ECG.....Electrocardiogram.

ECs.....Endothelial cells.

EPI.....Extrinsic pathway inhibitor.

HbA1c.....Glycated haemoglobin.

Hcy.....Amino acid homocysteine.

HDL .....High-density lipoprotein.

HLE .....Human leukocyte elastase.

HMG-COA ..Hydroxy-methylglutaryl coenzyme A.

hs-CRP .....Highly sensitive C-reactive protein.

HTN .....Hypertension.

HUVECs.....Human umbilical vein endothelial cell.

ICAM-1 .....Intercellular adhesion molecule-1.

IDL.....Intermediate density lipoprotein.

IGT .....Impaired glucose tolerance.

IHD .....Ischaemic heart disease.

IL-1 .....Interleukin-1.

IL-6 .....Interleukin-6.

LACI.....Lipoprotein-associated coagulation inhibitor.

LDL .....Low density lipoprotein.

LDL .....Low density lipoprotein.

LP (a).....Lipoprotein (a).

MI .....Myocardial infarction.

mRNA.....Messenger ribonucleic acid.

NCEP.....National Cholesterol Education Program.

NSTEMI.....Non-ST elevation myocardial infarction.

PAI-1 .....Plasminogen activator inhibitor-1.

PAPS.....Primary Antiphospholipid syndrome.

PECAM1.....Platelet endothelial cell adhesion molecule.

r TFPI.....Recombinant tissue factor pathway inhibitor.

SMCs .....Smooth nuscle cells.

STEMI.....ST elevation myocardial infarction.

TF.....Tissue factor.

TFI.....Tissue factor inhibitor.

TFPI.....Tissue factor pathway inhibitor.

TGF .....Tumor growth factor.

TNF-α .....Tumor necrosis factor-α.

t-PA.....Tissue plasminogen activator.

UA.....Unstable Angina.

VCAM-1.....Vascular cell adhesion molecule-1.

VLDL.....Very low density lipoprotein.

WHO .....World Health Organization.

Introduction

Coronary heart disease is a leading cause for morbidity and mortality in many countries world wide. Despite the search for novel risk factors, established ones still play a major role. These are the dyslipidaemias, hypertension, cigarette smoking, diabetes, obesity and physical inactivity **(Lee et al., 2001).** Haemostasis plays an important role in the development of cardiac complications **(Lisowski et al., 2004).**

One of the most frequent and serious complications associated with cardiovascular disease is thrombosis, possibly arising from increased platelet activation and/or loss of the regulation of coagulation and fibrinolysis **(Ross, 2007).**

Tissue factor is the main physiological initiator of blood coagulation **(Vieira et al., 2007).** It binds and acts as an essential cofactor for active factor VII (FVIIa) **(Soejima et al., 2000).**

Tissue factor pathway inhibitor is the main physiological inhibitor of tissue factor induced coagulation, it is mainly synthesized by endothelial cells **(Bajaj et al., 2001).** It has a dual inhibitory function, it inhibits the complex factor VIIa/tissue factor and directly inhibits factor Xa by binding at or near its active site **(Li et al., 2001).**

The presence of tissue factor pathway inhibitor in atherosclerotic plaques is associated with reduced tissue factor activity and its local administration is highly effective in reducing arterial thrombosis in atherosclerotic lesions **(Badimon et al., 2003).**

Blood clotting activation has been demonstrated in patients with ischaemic heart disease **(Theroux et al., 2000)** and a key role of tissue factor expressed by monocytes in triggering thrombin generation has been documented **(Neri Serneri et al., 2001).**

Moreover; in ischaemic heart disease patients; tissue factor pathway inhibitor activity was found to be moderately higher **(Sandset et al., 2002),** particularly in hyperlipidemics.

Aim of the Work

1- To measure the plasma level of tissue factor pathway inhibitor in patients with acute myocardial infarction, unstable angina and stable angina pectoris and compare it with those found in normal healthy subjects.

2- To evaluate the role of tissue factor pathway inhibitor as a risk factor for coronary heart disease.

CORONARY HEART DISEASE

Coronary heart disease (CHD) is the leading cause of death and disability in both men and women. Its presentation varies from chronic CHD to acute coronary syndrome (ACS) that includes unstable angina and myocardial infarction **(Nguyen and McLanghlin, 2002).**

Understanding the pathophysiology that leads to CHD and identifying the risk factors are crucial steps for efforts to prevent this disease **(Wilson et al., 2002 and Pischon et al., 2007)**.

According to the Ministry of Health (MOH) and World Health Organization (WHO) Regional office report, there is an increased prevalence of coronary heart disease in Egypt which is responsible for about 47% of all deaths among Egyptians **(Ibrahim et al., 2009).**

I) PATHOGENESIS of CORONARY HEART DISEASE:

The underlying processes that lead to atheroma formation and coronary thrombosis are complex and involve multiple interrelated systems that regulate vasoactivity, adhesion molecules and their ligands, lipid metabolism, coagulation and fibrinolytic pathways **(Lane and Grant**, **2000).**