The Association Between E-selectin Gene Polymorphism and Atherosclerosis in End-Stage Renal Disease

Thesis

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ABSTRACT

Atherosclerosis is the main cause of death and cardiovascular (CV) complications in end-stage renal disease (ESRD). A possible explanation is that decreased renal function may be associated with other non-traditional risk factors, and genetic factors. This study involved 40 end stage renal disease patients and 30 age- and sex- matched healthy control subjects. All were subjected to Full history taking, full clinical examination, kidney functions & genotyping of the "Leu 554 Phe" polymorphism in the E-selectin gene, Doppler examination of the carotid artery (for the patient group only).

The CT (heterozygous) genotype is the more prevalent genotype in our small studied groups and the presence of the T allele might not carry the risk of atherosclerosis in ESRD patients.

Key words: Chronic kidney disease,
Atherosclerosis,
E-selectin.

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LIST OF ABREVIATIONS

AA : Arachidonic acid

ABPM : Ambulatory blood pressure monitoring

ACE : Angiotensin converting enzyme

ADMA : Asymmetric dimethylarginine

ANCA : Anti-neutrophil cytoplasmic antibody

ANOVA : Analysis of variance

AOPP : Advanced oxidation protein products

B.P. : Blood pressure

BTP : Beta-Trace Protein

BUN : Blood urea nitrogen

CAD : Coronary artery disease

Ca × P : Calcium-phosphorus product

[Ca^{2+}] : Intracellular calcium

cAMP : Cyclic adenosine monophosphate

CBC : Complete blood count

CHF : Congestive heart failure

CHO : Carbohydrates

cIMT : Carotid artery intima-media thickness

CKD : Chronic kidney disease

cPLA2 : Cytosolic phopholipase A2

Creat. : Creatinine

CRF : Chronic renal failure

CRP : C-reactive protein

CT : Computed tomography

CVD : Cardiovascular disease

CysC : Cystatin C

CytP450 : Cytochromes P450

DAG : 1,2-diacylglycerol

DBP : Diastolic blood pressure

DM : Diabetes mellitus

DNA : Deoxyribonucleic acid

DTPA: ^{99}mTc-labeled diethylenetriamine pentaacetic acid

EDTA : Ethylenediamine Tetra-Acetic Acid

EGF : Epidermal growth factor

eGFR : Estimated GFR

ELAM1 : Endothelial leukocyte adhesion molecule 1

ERK : Extracellular signal-regulated kinase

ESL-1 : E-selectin ligand-1

ESRD : End-stage renal disease

FBS : Fasting blood sugar

FMD : Flow-mediated dilatation

GAPs : GTPase activating proteins

GFR : Glomerular filtration rate

GlyCAM-1: Glycosylation-dependent cell adhesion molecule-1

GRFs : Guanine nucleotide regulatory factors

GSH : Reduced glutathione

GSH-PX : Glutathione peroxidase

GSSG : Oxidized glutathione

GTP : Guanosine triphosphate

Hb : Hemoglobin concentration.

HbA1c : Glycated hemoglobin

HD : Hemodialysis

HDL : High-density lipoprotein

HIV : Human immunodeficiency virus

HOCl : Hydrochlorus acid

HOMA : Homeostasis model assessment method

HTN : Hypertension

ICAM : Intercellular adhesion molecules

IgA : Immunoglobulin A

IL : Interleukin

IL-1 : Interleukin -1

IL-6 : Interleukin -6

IL-8 : Interleukin- 8

IMT : Intima-media thickness

IP3 : Inositol 1,4,5-trisphosphate

IV contrast-enhanced CT: Intravenous contrast-enhanced Computed tomography

Kg. : Kilogram

L : Ligand

LDL : Low-density lipoprotein

Leu : Leucine aminoacid

Leu554Phe : Leucine to phenylalanine at codon 554

Lp(a) : Lipoprotein(a**)**

L-PGDS : Lipocalin-type urinary prostaglandin D synthase

LPS : Lipopolysaccharide

LT : Leukotrienes

LTCSA : Left side cross-sectional area

LTIMT : Left side intema-media thickness

LX : Lipoxins

MAdCAM-1 : Mucosal addressin cell adhesion molecule-1

MAP : Mitogen-activated protein

MAP kinase : Mitogen-activated protein kinases

MDRD formula : Modification of Diet in Renal Disease formula

MPO : Myeloperoxidase

MRI : Magnetic resonant imaging

NaCl : Sodium Chloride

NADPH: Nicotinamideadenine dinucleotide phosphate

NaOH : sodium hydroxide

NF-AT : Nuclear factor of activated T cells

NO : Nitricoxide

NOS : Nitric oxide synthase

NT-pro-BNP : N-terminal pro-brain natriuretic peptide

OPG : Osteoprotegerin

OPN : Osteopontin

oxLDL : Oxidized LDL

PA : Phosphatidic acid

PC : Phosphatidyl choline

PCR : Polymerase chain reaction.

Phe : Phenylalanine aminoacid

PIP2 : Phosphatidyl inositol 4,5-bisphosphate

PKC : Protein kinase C

PLC : Phospholipase C

PLD : Phospholipase D

PSGL-1 : P-selectin glycolipid-1

PTH : Parathyroid hormone

PTKs : Protein tyrosine kinases

PTX3 : Pentraxin-3

R : Receptor

RFLP : Restriction fragment length polymorphism.

RRT : Renal replacement therapy

RT: Right side

RTCSA: Right side cross-sectional area

RTIMT: Right side intema-media thickness

SBP : Systolic blood pressure

SCRs : Short consensus repeats

SDS : Sodium Dodecyl Sulphate

SELE gene : Selectin-E gene

SELL gene : Selectin-L gene

SELP gene : Selectin-P gene

Sgp200 : Sulfated glycoprotein

sLe^a : Sialyl Lewis^a

sLe^x : Sialyl Lewis^x

SNP : Single nucleotide polymorphism

SOD : SuperOxide Dismutase

S128A : Serine to arginine at codon 128

T3 : Tri-iodothyronine.

TCL : Total cholesterol

TG : Triglycerides

TGF-β : Transforming growth factor-beta

tHcys : Homocystine

TNF-α : Tumor necrosis factor- α

U-alb : Urinary albumin excretion

UV : Ultra violet.

VCAM : Vascular cell adhesion molecule

VLDL : Very low density lipoprotein

WBC : White blood cell count

(y) : years

INTRODUCTION & AIM OF WORK

Atherosclerosis is the main cause of death and cardiovascular (CV) complications in end-stage renal disease (ESRD) ***(Testa et al., 2006)***. The dialysis population is an interesting natural model of atherosclerosis because uremia is a strong amplifier of arterial damage **(*Zoccali, 2002)***. This could partially be explained by the traditional risk factors, i.e. hypertension, smoking, diabetes and dyslipidemia ***(Foley et al., 1998)***. Besides, attention has been focused on disease- specific factors like hyperparathyroidism, hypoalbuminemia and anemia and on emerging factors like hyperhomocysteinemia and inflammation. Moreover, genetic factors are of relevance in atherosclerosis. Association studies between genetic factors and indicators of arterial damage are therefore important in order to understand the unique severity of CV disease in ESRD ***(Balakrishnan et al., 2005)***.

Soluble adhesion molecules may play an important role in the genesis of CVD by affecting thrombosis, leukocyte infiltration, smooth-muscle proliferation, and cell migration. Moreover, adhesion molecules are elevated among patients with atherosclerosis, and in patients with coronary heart disease. ***(Stenvinkel et al.,2000)***

E-selectin is a key adhesion molecule which plays a fundamental role in endothelial progenitor cell-dependent reparative mechanisms in experimental ischaemia and it serves to anchor leucocytes to the endothelium in inflammatory processes ***(Malatino et al., 2007)***. In ESRD, the Leu554Phe polymorphism of E-selectin gene is associated with the