Adhesion Molecules Polymorphism in Peripheral Atherosclerosis

THESIS
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PRESENTED BY
Gehan Abd El-Fattah Mohammed Hegazy

M.B., B.Ch. M.Sc. Medical Biochemistry
Assistant lecturer of Medical Biochemistry
Faculty of Medicine MUST.

SUPERVISED BY

Prof. Dr. OLFAT G.SHAKER
Prof. of Medical Biochemistry
Faculty of Medicine, Cairo University

Prof. Dr. ZAKARIA EL-KHAYAT
Prof. of Medical Biochemistry Department
National Research Center

Prof. Dr. KHALED M. EL-HINDAWY
Professor of General and Vascular Surgery
Faculty of Medicine, Cairo University

Dr. AMR ZAHRA
Lecturer of Medical Biochemistry
Faculty of Medicine, Fayoum University

Faculty of Medicine
Cairo University
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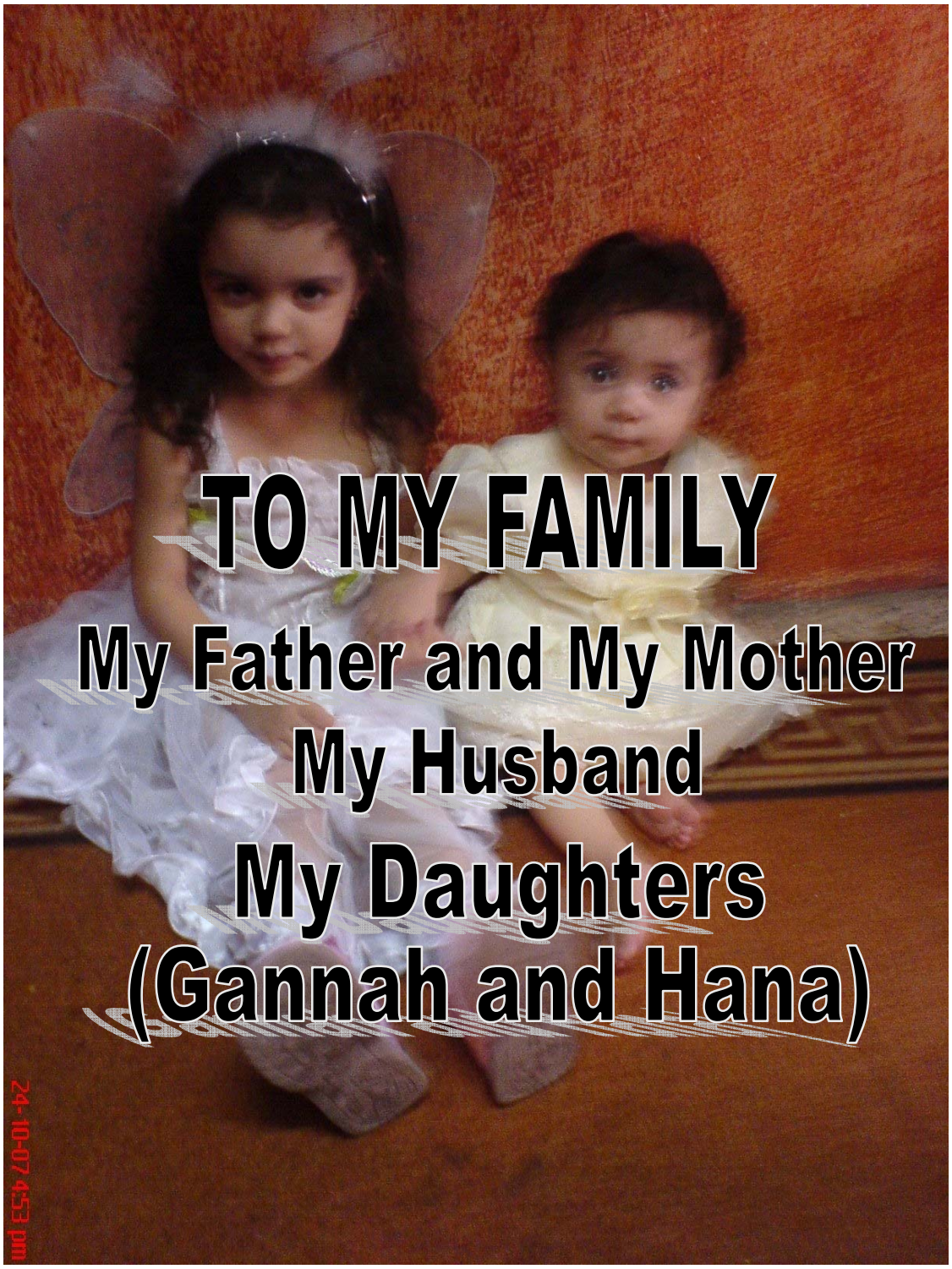
TO MY FAMILY
My Father and My Mother
My Husband
My Daughters
(Gannah and Hana)
24-10-07 4:53 pm

ABSTRACT

Numerous reports document the role of vascular adhesion molecules in the development and progression of atherosclerosis. E-selectin plays a role in the early stages of vascular disease by facilitating the attachment of leukocytes to the endothelium. Polymorphism in the E-selectin gene leading to a replacement of serine by arginine at position 128 has been associated with premature coronary artery disease. Intercellular adhesion molecule-1 (ICAM-1) plays a crucial role in lymphocyte migration and activation, and is considered important in the pathogenesis of atherosclerosis. The aim of the present study was to evaluate the association between gene polymorphism of E-selectin & ICAM-1 and peripheral arterial occlusive disease (PAOD) in Egyptian. We investigated 2 mutations, namely S128R in E-selectin and K469E in ICAM-1 in 52 patients with PAOD and 30 control subjects using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis in an Egyptian population. Patients were classified into 31 diabetic and 21 non diabetic subjects.

The distribution of E-selectin genotypes in patients affected by PAOD was 84.6% AA genotype and 15.4% AC genotype. The distribution of E-selectin genotypes in control subjects was 96.7% AA and 3.3% AC. The AC genotype was significantly more common in patients than controls. Additionally, the distribution of ICAM-1 genotypes in patients affected by PAOD was 30.8% EE, 48% EK, and 21.2% KK. The distribution of ICAM-1 genotypes in control subjects was 13.3% EE, 33.4% EK and 53.3% KK. The EE genotype was significantly more common in patients than controls. It is interesting in this study those patients having AC genotype, also having EE genotype.

Conclusions- Our data support the hypothesis that inflammatory mechanisms are important in the pathophysiology of vascular diseases with an atherosclerotic basis. E-selectin gene S128R polymorphism and ICAM1 gene K469E polymorphism were associated with increased risk in PAOD. The E allele may serve as a genetic risk factor for PAOD.

Early detection of these gene polymorphism helps in early prophylaxes against PAOD.

Key Words: PAOD (Peripheral Arterial Occlusive disease), ICAM-1, E-selectin, RFLP.

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ABI	Ankle – Brachial Index
ACE	Angiotensin Converting Enzyme
AP-1	Activator Protein 1
APC	Adenomatous Polyposis Coli
A561C	Adinine/Cytosine 561
ALT (IU/l)	Alanine Transaminase
AT1	Angiotensin II Type 1
ARE	Antioxidant Response Elements
Arg	Argnine
AST	Asprtate Transaminase
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
CAMs	Cell Adhesion Molecules
CD	Celiac Disease
cDNA	Complemtary Deoxyriboneucleic Acid
CHD	Coronary Heart Disease
CLA	Cutaneous Lymphocyte Antigen
C. pneumonia	Chlamydia Pneumonia
CR	Consensus Repeat
CRBP-1	Cellular Retinol Binding Protein-1
CRC	Colorectal Cancer
CRP	C-Reactive Protein
CS	Cigarette Smoking
CSF	Colony-Stimulating Factor
CT	Computed Tomography
CTA	Computed Tomographic Angiography
CVD	Cardiovascular Disease
CVS	Cerebrovascular Stroke
DM	Diabetes Mellitus
Dgl	Desmoglein Isoforms
Dsc	Desmocollin Isoforms
EC	Endothelial Cells
ECG	Electrocardiogram
ECM	Extracellular Matrix
EDTA	Ethylene Diamine Tetraacetic Acid
EGF	Epidermal Growth Factor
ELAM	Endothelial Leukocyte Adhesion Molecule
eNOS	Endothelial NO Synthase

ESL	E-Selectin Ligand
ESR	Erythrocyte Sedimentation Rate
ET-1	Endothelin-1
FBS	Fasting Blood Sugar.
FGF	Fibroblast Growth Factor
GAP	GTPase Activation Protein
GEF	Guanine Exchange Factor
GDP	Guanisine Diphosphate
GMP	Guanosine Mono Phosphate
GSK-3 β	Glycoprotein Synthase Kinase-3 β
HA	Hyaluronate
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HSP	Heat Shock Protein
HTN	Hypertension
HUVEC	Human Umbilical Vein Endothelial Cells
IBD	Inflammatory Bowel Disease
IC	Intermittent Claudication
ICAM-1	Intercellular Adhesion Molecule-1
IDDM	Insulin Dependent Diabetes Mellitus
IHD	Ischemic Heart Disease
IL	Interleukin
I/R	Ischemia/Reperfusion.
IRS	Insulin Resistance Study
ITIMs	Immunoreceptor Tyrosine Inhibition Motifs
KB	Kilobases
LDL	Low Density Lipoprotein
LECAM	Lymphocyte Endothelial CAM
LFA	Lymphocyte Function Associated Antigen
Lp	Lipoprotein
LPS	Lipopolysaccharide
MAP	Mitogen Activated Protein
MAdCAM	Mucosal Addressin CAM
MCP-1	Monocyte Chemoattractant Protein-1
MI	Myocardial Infarction
MIDAS	Metal Ion Dependent Adhesion Site
MIF	Macrophage Migration Inhibitory Factor
MIP-2	Macrophage Inflammatory Protein-2
MMP	Matrix Metalloproteinase
MRA	Magnetic Resonance Angiography
mRNA	Messenger Ribonucleic Acid

MS	Multiple Sclerosis
MVEC	Microvascularendothelial Cells
NIHD	Non Ischemic Heart Disease
NF-kB	Nuclear Factor kB
NO	Nitric Oxide
ox-LDL	Oxidized LDL
PAD	Peripheral Arterial Disease
PAOD	Peripheral Arterial Occlusive Disease
PCR	Polymerase Chain Reaction
PADGEM	Platelet Activation-Dependent Granule External Membrane Protein
PDGF	Platelet-Derived Growth Factor
PECAM	Platelet–Endothelial Cell Adhesion Molecule
PKC	Protein Kinase C
PSC	Primary Sclerosing Colangitis
PSGL	P-Selectin Glycoprotein Ligand
PTA	Percutaneous Transluminal Angioplasty
RA	Rheumatoid Arthritis
RAD	Renal Artery Disease
RAS	Renin-Angiotensin System
RF	Rheumatoid Factor
ROS	Reactive Oxygen Species
RPTP	Receptor Protein Tyrosine Phosphatases
RR	Relapsing Remitting
SBP	Segmental Blood Pressure
sCAD	Spontaneous Cervical Artery Dissection
SH2	Src Homology 2
SMCs :	Smooth Muscle Cells
SNP	Single Nucleotide Polymorphism
SP-MS	Secondary Progressive
SSEA	Sialyl Stage-Specific Embryonic Antigen
sTNFR	Soluble TNFR
TBE	Tris-Borate EDETA
TF II D	Transcription Factor II D
TGF-β,	Transforming Growth Factor-Beta
TM	Transmembrane
TNF-α	Tumor Necrosis Factor -α
TNFR	Tumor Necrosis Factor Receptor
UT	Untranslated
VCAM-1	Vascular Adhesion Molecule-1
VLA	Very Late Antigen
WHO	World Health Organization

INTRODUCTION

Peripheral arterial disease (PAD) is associated with high mortality rates (e.g. 30%, 50% and 70%, at 5, 10 and 15 years, respectively due to a high incidence of cerebrovascular and cardiovascular events. This may be explained, at least in part, by the ongoing endothelial and enhanced coagulation activation that occurs in PAD patients compared with normal individuals. Irrespective of the cause underlying the increased incidence of cerebrovascular and cardiovascular events, PAD patients are more likely to have a fatal or non-fatal myocardial infarction (MI) or stroke that of ever requiring a major amputation. In addition, the presence of PAD in patients with stable angina conveys a 6.3-fold increased risk for sudden death ***(Paraskevas et al., 2007)***.

Cellular adhesion molecules are markers of inflammation that are hypothesized to play a major role in the initiation of atherosclerotic lesions. The cell adhesion molecules are important for binding of leukocytes to the endothelial cells and in the infiltration of inflammatory cells into tissues. Various inflammatory mediators such as TNF-α, IL-1β and bacterial lipopolysaccharide (LPS), increase the expression of cell adhesion molecules (CAMs) including ICAM-1, VCAM-1 and E-selectin on endothelial cells ***(Kumar et al., 2007)***.

Thus, upon inflammatory stimulation, the endothelial barrier function is rapidly lost and preformed P-selectin is translocated to the luminal surface of endothelial cells, followed by expression and release of E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion molecule-1 (VCAM-1), substances that regulate attachment and

transendothelial migration of leukocytes. Both macrophages and endothelial cells produce ICAM-1 in response to inflammatory cytokines ***(Bartzeliotou et al., 2007)***.

During inflammation, E-selectin, which is usually absent in normal tissues, is expressed on the endothelium. After activation by cytokines, adhesion molecules are shed from the surface of endothelial cells and leucocytes and their circulating levels in plasma can be measured, serving as markers of endothelial activation and vascular inflammation ***(Afshar-Kharghan and Thiagarajan, 2006)***.

The inflammatory reaction that accompanies development and progression of atherosclerosis is orchestrated by several molecules, belonging to different families of inflammatory mediators, such as cytokines, chemokines, adhesion molecules, and proteolytic enzyme. Importantly, plasma levels and/or functional activity of these inflammation determinants may be strongly influenced by functional single nucleotide polymorphisms of the corresponding genes, with important clinical implications ***(Flex et al., 2007)***.

As all these inflammatory mediators display complex interactions during atherogenesis, genetic studies aimed to investigate individual susceptibility to cardiovascular diseases (CVDs) should not be limited to the evaluation of polymorphisms of single inflammatory genes, but should consider several genetic variants together, in order to account for the pleiotropic and interdependent effects of candidate genes ***(Flex et al., 2004)***.

Aim of the Work

The aim of the present study is to evaluate the association between gene polymorphisms of ICAM-1 & E-selectin and atherosclerotic peripheral diseases.