

Soluble Lectin like Oxidized LDL Receptor-1 (sLOX-1): A Recent Marker for Prediction of High Risk CAD Patients

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

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List of Abbreviations

Abbrev.	Full term
Ab	: Antibody
ACE	: Angiotensin-converting enzyme
ACS	: Acute coronary syndrome
ADMA	: asymmetric dimethyl arginine
Ag	: Antigen
AMI	: Acute myocardial infarction
Ang II	: Angiotensin II
ATP III	: Adult Treatment Panel III
AUC	: Area under the curve
BMI	: Body mass index
Ca	: Calcium
CABG	: Coronary artery bypass graft
CAD	: Coronary artery disease
cAMP	: Cyclic adenosine monophosphate
CD	: Cluster of differentiation
CE	: Cholesterol esterase
CHD	: Coronary heart disease
CK	: creatine kinase enzyme
CK-MB	: Creatine kinase MB fraction
CK-MM	: Creatine kinase MM fraction
CK-BB	: Creatine kinase BB fraction
CO	: Cholesterol oxidase
CRP	: C-reactive protein
cTn	: Cardiac troponin
CVD	: Cardiovascular diseases
DHBS	: Dichloro 2 hydroxybenzene sulphuric acid
DNA	: Deoxyribonucleic acid
ECG	: Electrocardiography

List of Abbreviations *(Cont...)*

Abbrev.	Full term
ECM	: extracellular matrix
ECs	: Endothelial cells
ELISA	: Enzyme-linked immunosorbent assay
eNOS	: Endothelial nitric oxide synthase
ERK	: Extracellular signal-regulated kinases
ESC/ACC	: European Society of Cardiology and the American College of Cardiology
ESR	: Erythrocyte sedimentation rate
ET-1	: Endothelin-1
FFA	: Free fatty acid
FN	: False negative
FP	: False positive
FRS	: Framingham risks
GK	: Glycerol kinase
GLDH	: Glutamate dehydrogenase
GO	: Glycerophosphate oxidase
H2O2	: Hydrogen peroxide
HCAECs	: Human coronary artery endothelial cells
HCL	: Hydrochloric acid
HDL-C	: High-density lipoprotein-Cholesterol
H-FABP	: Heart-fatty acid binding protein
HRP	: Horseradish peroxidase
hsCRP	: High-sensitivity CRP
ICAM-1	: Intercellular adhesion molecule-1
IFG	: Impaired fasting glucose
IFN γ	: Interferon gamma
Ig	: Immunoglobulin
IGF-1	: Insulin growth factor-1
IGFBP-4	: Insulin-like growth factor binding protein-4

List of Abbreviations *(Cont...)*

Abbrev.	Full term
IGT	: Impaired glucose tolerance
IL-6	: Interleukin-6
INR	: International normalized ratio
IQR	: Inter-quartile Range
KDa	: Kilodalton
LOX-1	: Lectin-like oxidized low-density lipoprotein receptor-1
LDL -C	: Low density lipoprotein -Cholesterol
LSD	: Least significant difference
MAPK	: Mitogen-activated protein kinase
MCP-1	: Monocyte chemoattractant protein-1
MI	: Myocardial infarction
MMPs	: Matrix metalloproteinases
MPO	: Myeloperoxidase
mRNA	: Messenger RNA
NADPH	: Nicotinamide adenine dinucleotide phosphate-oxidase
NCEP	: National cholesterol education program
NF-κB	: Nuclear factor kappa
NO	: Nitric oxide
NOS	: Nitric oxide synthase
NSTEMI	: Non ST-Segment elevated myocardial infarction
OxLDL	: Oxidized low-density lipoprotein
p	: Probability
PA	: Plasminogen activator
PAD	: Peripheral artery disease
PAI-1	: Plasminogen activator inhibitor-1
PAPP-A	: Pregnancy-associated plasma protein
PCI	: Percutaneous coronary intervention

List of Abbreviations *(Cont...)*

Abbrev.	Full term
PCR	: Polymerase chain reaction
PPBG	: postprandial blood glucose
PKC	: Protein kinase C
PLGF	: Placental like growth factor
PNV	: Predictive value for a negative test
PPAR γ	: Peroxisome proliferator-activated receptor gamma
PPV	: Predictive value for a positive test
PRR	: Pattern-recognition receptors
RAS	: Rennin angiotensin system
RBCs	: Red blood cells
ROC	: Receiver-operating characteristic
ROS	: Reactive oxygen species
r_s	: Spearman's rank correlation
RT-PCR	: Reverse transcriptase polymerase chain reaction
SAA	: Serum amyloid A
sCD40L	: Soluble cluster of differentiation 40 ligand
SD	: Standard deviation
sLOX-1	: Soluble Lectin-like oxidized low-density lipoprotein receptor-1
SMCs	: Smooth muscle cells
SR	: Scavenger receptors
SS	: Syntax Score
STEMI	: ST-Segment elevated myocardial infarction
T2DM	: Type 2 diabetes mellitus
TC	: Total cholesterol
TG	: Triglycerides
TGF-h	: Transforming growth factor-h
Th	: T helper
TIMPs	: Tissue inhibitor of metalloproteinases

List of Abbreviations *(Cont...)*

Abbrev.	Full term
TLRs	: Toll-like receptors
TMB	: Trimethyl phosphate
TN	: true negative
TNF-αR1	: Tumor necrosis factor-alpha receptor-1
TNF-α	: Tumor necrosis factor-alpha
TP	: True positive
UA	: Unstable angina
UV	: Ultraviolet
VCAM-1	: Vascular-cell adhesion molecule-1
VEGF	: Vascular endothelial growth factor
VLDL	: Very low density lipoprotein
VSMCs	: Vascular smooth muscle cells
WHO	: World Health Organization
2hrs PP BG	: 2hours postprandial blood glucose
4-AAP	: 4-aminoantipyrine

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INTRODUCTION

Coronary artery disease (CAD) is a complex disease characterized by reduced or absent blood flow in one or more of the arteries that encircle and supply the heart. The disease may be focal or diffuse (*Shaw et al., 2012*). In fact, due to the progressive nature of CAD, some patients may develop advanced and complex disease that is no longer amenable to conventional surgical or percutaneous intervention (*Ngaage et al., 2008*).

It is expected that CAD will be the leading cause of death in developing countries by the year 2020. In Egypt, mortality secondary to CAD is rapidly rising. According to World Health Organization (WHO) statistics, the age-standardized mortality rates from CAD are one of the highest worldwide. One possible explanation is the high prevalence rate of CAD risk factors; Hypertension, dyslipidemia and obesity which are common among Egyptians (*Ibrahim et al., 2012*).

In almost all cases of CAD, the development of fibro-fatty atheromatous plaques within the walls of the coronary artery asymptotically begins at a young age and it is often many years later that clinical manifestations occur. In approximately 50 % of women and 40% of men the first presentation of CAD is new exertional (stable) angina, which, whilst associated with a 10% risk of death or myocardial infarction during the following year has, thereafter, a good prognosis. Conversely, in 45% men and 35% women the initial

presentation is either rapidly-worsening unpredictable (unstable) angina or Acute Coronary Syndrome (ACS) (**Poole-Wilson et al., 2007**).

Rupture of vulnerable plaques with subsequent thrombus formation has been implicated as the most common pathogenic mechanism responsible for the development of ACS. Although an invasive procedure, angiography is nowadays the gold standard for identification of high risk plaques which presents as angiography complex lesions “the angiographic hallmark of plaque vulnerability”. Angiographically complex lesions correlate with pathologic plaque rupture and thrombus and have been shown to provide prognostic information. Therefore, it is important to develop a noninvasive blood biomarker to provide incremental predictive value for accurate prognostication of angiographically complex lesions in patients with CAD when added to other traditional risk factors (**Niccoli et al., 2010**).

The lectin-like oxidized low density lipoprotein receptor (LOX-1), a type II membrane glycoprotein and scavenger receptor, was identified as an oxidized low density lipoprotein (ox-LDL) receptor mainly expressed by endothelial cells but also expressed by macrophages and vascular smooth muscle cells. Lectin-like oxidized low-density lipoprotein receptor-1 is involved in multiple phases of vascular dysfunction, including endothelial dysfunction, atherogenesis, initiation of plaque rupture, and restenosis (**Balin et al., 2012**). Like many cell-surface receptors with a single transmembrane domain, LOX-1

can be proteolytically cleaved at its membrane proximal extracellular domain and released as a soluble form (sLOX-1). The level of circulating sLOX-1 may reflect the expression of LOX-1, and is increasingly viewed as a biomarker for CAD (*Lubrano et al., 2009*).

Researches have hinted to the level of circulating sLOX-1 that is significantly higher in patients with ACS than in patients with stable CAD. Moreover, they observed a striking association between increments in sLOX-1 levels and number of complex vascular lesions (*Zhao et al., 2011*).