

**NOVEL CARDIOVASCULAR RISK
MARKERS PARAOXONASE,
APOLIPOPROTEIN A-1 (Apo A-I) AND
GLUTATHIONE PEROXIDASE
GENOTYPE-1 IN CORONARY
ARTERY DISEASE**

By

WICKRAMASINGHEGE DINUSHKA

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M.Phil

2014

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PARAOXONASE, APOLIPOPROTEIN A-1 (Apo A-I) AND
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By

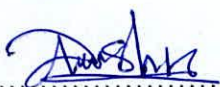
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Thesis submitted to the University of Sri Jayewardenepura for the
Degree of Master of Philosophy in Biochemistry on 18th August
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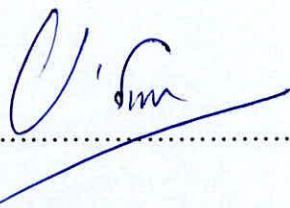
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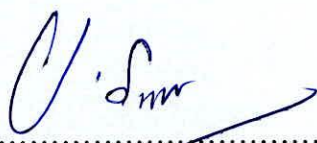
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Dedication

I dedicate this thesis to
my wife Sugandika, parents and teachers.

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ABBREVIATIONS

ABCA1	-	ATP Binding cassette A1
ABCG1	-	ATP Binding cassette G1
AMI	-	Acute Myocardial Infarction
ANOVA	-	Analysis of Variance
Apo A-1	-	Apolipoprotein A-1
Apo J	-	Apolipoprotein J
BMI	-	Body Mass Index
BP	-	Blood Pressure
CABG	-	Coronary Artery Bypass Grafting
CAD	-	Coronary Artery Disease
CRP	-	C- Reactive protein
Cys	-	Cysteine
DBP	-	Diastolic blood pressure
DM	-	Diabetes mellitus
dNTP	-	di Nucleotide Tri Phosphate
GI	-	Gastro Intestinal
Glu	-	Glucose
Gly	-	Glycine
GPX	-	Glutathione Peroxidase
GR	-	Glutathione Reductase
GSH	-	reduced glutathione

GSSG	-	Oxidized glutathione
HDL-C	-	High density lipoprotein cholesterol
HRP	-	Horse raddish peroxidases
IHD	-	Ischemic heart disease
kDa	-	kilo dalton
KO	-	Knockout mice
LDL-C	-	Low density lipoprotein cholesterol
Leu	-	Leucine
Lp (a)	-	Lipoprotein (a)
MI	-	Myocardial infarction
PAF	-	Platelet activate factor
PCR	-	polymerase chain reaction
PON	-	Paraoxonase
PTCA	-	Percutaneous trans coronary angioplasty
RCT	-	Reverse cholesterol transport
RFLP	-	Restriction fragment length polymorphism
ROS	-	Reactive oxygen species
SBP	-	Systolic blood pressure
Se	-	Selenium

SNP	-	Small Nucleotide Polymorphism
SOD	-	Superoxide dismutase
WHO	-	World Health organization

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Novel cardiovascular risk markers Paraoxonase, Apolipoprotein A-1 (Apo A- 1) and Glutathione Peroxidase genotype -1 in Coronary Artery Disease.

Wickramasinghe Dinushka Wickramasinghe

ABSTRACT

Introduction: Coronary artery disease (CAD) is one of the major causes of mortality in both developed and developing countries. Oxidative stress has been demonstrated to have a role in pathogenesis of atherosclerosis. Reactive oxygen species (ROS) formed during oxidative stress result in oxidation of proteins and lipids of the cell membrane, leading to endothelial injury and microvascular dysfunction. Thus, the present study was designed to assess the relationship between severity of CAD as assessed by coronary angiography and Glutathione Peroxidase-1 (GPX-1), Paraoxonase-1 (PON-1), Apolipoprotein A-1 (Apo A-1) and GPX-1 genetic variants.

Objectives: This study was designed to investigate the relationship between GPX-1 variant, PON-1 and apoA-1 activity in healthy individuals and patients with CAD based on coronary angiographic severity scoring systems.

Methods: A case-control study of 75 patients (58 males, 17 females) with CAD (patients were selected from those awaiting coronary angiography) and age and sex matched 75 healthy volunteers as control subjects. Fasting venous blood samples were collected from all subjects for laboratory analysis of erythrocyte total GPX, erythrocyte GPX-1, serum PON-1 activity, Apo A-1 level and GPX-1 Pro198Leu polymorphisms.

Results: Data revealed that the serum PON-1 concentration, total erythrocyte GPX and erythrocyte GPX -1 activity were significantly ($p \leq 0.05$) low in patients when compared to controls. Paraoxonase-1 activity and Apolipoprotein A-1 levels did not show significant correlations with vessel, stenosis, and extent scores. Total erythrocyte GPX

and erythrocyte GPX-1 activities showed significantly strong inverse relationship with vessel, stenosis, and extent scores. Frequency distribution of GPX-1 Pro198Leu (CT) genotype was significantly higher in patients (25.3%) when compared to controls (10.7%) (χ^2 test =1.019). Results of genotype polymorphism in GPX-1 showed that the Leu198Leu (TT) genotype was not present in our study population. Interestingly, Pro198Leu (CT) genotype showed a 2.84 fold risk for CAD [odds ratio 2.84 (95% CI 1.15 – 6.98), $p = 0.019$] in our study population. The Pro198Leu (CT) genotype carriers in subjects with age ≤ 50 years showed significantly higher (6.19 fold) risk for CAD compared to Pro198Pro (CC) genotype carriers in the same age group [odds ratio 6.19 (95% CI 1.1 – 34.3), $p = 0.037$]

Conclusion: Low serum PON-1 concentration, total erythrocyte GPX, and erythrocyte GPX -1 activity are independent risk factors for CAD. Decreased total GPX and GPX-1 activities are associated with increased severity of CAD. The Pro198Pro (CC) genotype is the most prevalent genetic variant of GPX-1 Pro198Leu polymorphism in the study population. However, Leu198Leu (TT) genotype not detected in our study population. The Pro198Leu (CT) genetic variant appeared to be the most significant predictor of CAD. Thus, this may have a future potential in early identification and management subjects with CAD.