Clinical Utility of Serum Lipocalin-2 in Pre-Eclampsia

Thesis

Submitted for partial fulfillment of Master Degree in Clinical and Chemical Pathology

By

Mervat Ibrahiem Mohamed
M.B., B.Ch., Ain Shams University

Under Supervision of

Prof. Dr./ Dalia Helmy Farag
Professor of Clinical and Chemical Pathology
Faculty of Medicine- Ain Shams University

Dr./ Nermine Helmy Mahmoud
Assistant Professor of Clinical and Chemical Pathology
Faculty of Medicine- Ain Shams University

Dr./ Hala Abdel Al Ahmed
Assistant Professor of Clinical and Chemical Pathology
Faculty of Medicine- Ain Shams University

Faculty of Medicine
Ain Shams University
2013

List of Abbreviations

AKI	: Acute kidney injury
ALT	: Serum alanine aminotransferase
AM	: Adrenomedullin
ASH	: American Society of Hypertension
AST	: Aspartate aminotransferase
BP	: Blood pressure
CBC	: Complete blood picture
CKD	: Chronic kidney disease
DIC	: Disseminated intravascular coagulopathy
DBP	: Diastolic Blood pressure
Enos	: Endothelial nitric oxide synthase
ELISA	: Enzyme-linked immunosorbent assay
ET-1	: Endothelin-1
FVL	: Factor V Leiden
HELLP	Hemolysis, elevated Liver function tests, low Platelets
HIV	: Human immune deficiency virus
HLA	: Human leukocyte antigen
HLA-C2	: Human leukocyte antigen class II haplotype
IDDM	: Insulin-dependent diabetes mellitus
IGF	: Insulin-like growth factor
IL-6	: Interleukin 6
IL-8	: Interleukin 8
IUGR	: Intrauterin growth retardation
IVF	: In vitro fertilization
KDR	: Kinase domain region
KIR	: Killer Ig-like receptor
LCN-2	: Lipocalin-2
LDH	: Lactate dehydrogenase
MAHA	: Microangiopathic hemolytic anemia
MMP	: Matrix metalloproteinase
MMP-9	: Matrix metalloproteinase-9
MUP	: Major urinary protein
NGAL	: Neutrophil gelatinase-associated lipocalin

List of Contents

List of Contents *(Cont...)*

List of Contents *(Cont...)*

List of Abbreviations *(Cont...)*

NO	: Nitric oxide
NTBI	: Non–transferrin-bound iron
PAI-1	: Plasminogen activator inhibitor 1
PAPP-A	: Pregnancy associated plasma protein A
PE	: Pre-eclampsia
PDGF	: Platelet derived growth factor
PGE2	: Prostaglandin
PlGF	: Placental growth factor
PTH	: Parathyroide hormone
PP-13	: Placental protein-13
RBP	: Retinol binding protein
ROS	: Reactive oxygen species
SBP	: Systolic Blood pressure
sEng	: Soluble endoglin
sFlt-1	: Soluble fms-like tyrosine kinase-1
SLE	: Systemic lupus erythematosus
SOGC	: Society of Obstetricians and Gynaecologists of Canada
TGF-β	: Transforming growth factor beta
TGF-β1	: Transforming growth factor beta1
TGF-β3	: Transforming growth factor beta 3
TNF-α	: Tumor necrosing factor alfa
tPA	: Tissue plasminogen activator
uPA	: Urokinase
VEGF	: Vascular endothelial growth factor
VEGFR-1	: Vascular endothelial growth factor receptor-1

List of Tables

List of Tables *(Cont...)*

List of Figures

بِسْمِ اللّهِ الرّحمَنِ الرّحيمِ

(...رَبِّ أَوزِعنِي أَن أَشكُرَ نِعمَتَكَ الّتِي أَنْعَمْتَ عَلَيَّ و عَلى والِدَيَّ

و أَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ و أَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

صدق الله العظيم

النمل.. اية رقم 19

Acknowledgement

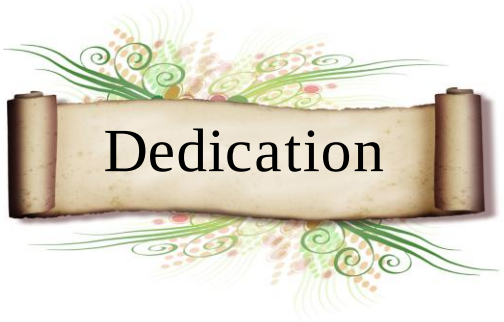
First of all, all gratitude is due to ***Allah*** *for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

Really I can hardly find the words to express my gratitude to ***Prof. Dr. Dalia Helmy Farag,*** *Professor of Clinical and Chemical Pathology, faculty of medicine, Ain Shams University, for her supervision, continuous help, encouragement throughout this work and great effort she has done in the meticulous revision of the whole work. It is a great honor to work under her guidance and supervision.*

I am also grateful to ***Dr. Nermine Helmy Mahmoud,*** *Ass. professor of Clinical and Chemical Pathology, faculty of medicine, Ain Shams University for her guidance, continuous assistance and sincere supervision of this work.*

I would like also to express my sincere appreciation and gratitude to ***Dr. Hala Abdel Al Ahmed****, Assistant Professor of Clinical and Chemical Pathology, faculty of medicine, Ain Shams University, for her continuous directions and support throughout the whole work.*

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.



I would like to dedicate this Thesis to my Mother, Father and ***my husband;*** *to them I will never find adequate words to express my gratitude.*

Introduction

Pre-eclampsia (PE) is a medical condition in which new onset hypertension arises in pregnancy after 20 weeks of gestation and is characterized by significant proteinuria ***(Sibai et al., 2003)***. It occurs in up to 5%–8% of pregnancies, and is considered the leading cause of maternal and fetal morbidity and mortality ***(Sankaralingam et al., 2006 and Duley, 2009).***

The mechanisms involved in the etiology of this disorder have not been yet clearly identified ***(Arikan et al., 2010)***. Placental ischemia secondary to an initial defective placentation and generalized endothelial cell damage and dysfunction have been proposed to be the pathogenic mechanisms underlying PE ***(Turner, 2010).*** Furthermore, recent studies suggest that adipokines may play an important role in the pathogenesis of PE through their role in low-grade systemic inflammation, atherosclerosis, and insulin resistance. Therefore, it is reasonable to suppose that adipokines may directly or indirectly influence the function of placental endothelial cells ***(Arikan et al., 2010).***

Lipocalin-2 (Lcn-2), a novel adipokine, also known as neutrophil gelatinase associated lipocalin (NGAL), is a 25 kDa secretory adipokine belonging to the highly heterogeneous family of lipocalins ***(Flo et al., 2004 and Devireddy et al., 2005).*** It is present mainly in specific granules of human neutrophils in addition to its expression in other tissues, including adipose tissue, macrophages, liver, kidneys, and

lungs. Moreover it has been implicated in diverse actions, such as innate immunity and apoptosis ***(Wang et al., 2007).***

Many studies demonstrated the over-expression of Lcn-2 in epithelia damaged by inflammation or neoplasia leading to increased angiogenesis and tumor cell proliferation ***(D'anna et al., 2008).*** Moreover, over production of LCN2 was rapidly induced in renal failure, and was well correlated with residual renal function ***(Nickolas et al., 2008).*** Recently, few studies started to highlight the role of LCN2 in hypertension ***(D'anna et al., 2010).***

Aim of the Work

The aim of the present work is to study the clinical utility of serum lipocalin-2 (LCN-2) in pre-eclampsia and its relation to the disease severity.