

Association between Insulin Resistance and Gastro-esophageal Reflux Disease

Thesis

Submitted for the partial fulfillment of Master degree
in Internal Medicine

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2014**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

(...رَبِّ أَوْزَعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ
الَّتِي أَنْعَمْتَ عَلَيَّ وَ عَلَى وَالِدَيَّ
وَأَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ وَ أَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

صدق الله العظيم

النمل.. آية رقم 19



Acknowledgements

First, and foremost, my deepest gratitude and thanks should be offered to "**ALLAH**", the most kind and most merciful, for giving me the strength to complete this work.

I would like to express my sincere gratitude to **Prof. Dr./ Wafaa Kamal Eldin Mohamed**, Professor of Internal Medicine, Gastroenterology & Hepatology, Faculty of Medicine, Ain Shams University, for her continuous support and guidance for me to present this work. It really has been an honor to work under her generous supervision.

I acknowledge with much gratitude to **Prof. Dr./ Amal Shawki Bakir**, Professor of Internal Medicine, Gastroenterology & Hepatology, Faculty of Medicine, Ain Shams University, for her great supervision and unlimited help to provide all facilities to accomplish this work.

I acknowledge with much gratitude to **Doctor/ Eslam Safwat Mohamed**, Lecturer of Internal Medicine, Gastroenterology & Hepatology, Faculty of Medicine, Ain Shams University, for his encouragement and help during this work.

Last but not least, thanks to **my Parents** and **my Family** for helping me to finish this work.

 **Mohamed Mahmoud Mohamed Said**

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List of Abbreviations

ACE	: Angiotensin converting enzyme
ACh	: Acetylcholine
AHA	: American Heart Association
AMPK	: AMP-activated protein kinase
ARBs	: Angiotensin receptor blockers
ATP	: Adenosine triphosphate
baPWV	: Brachial-ankle pulse wave velocity
BMI	: Body mass index
BP	: Blood pressure
CGIT	: Combined glucose-insulin test
CGMS	: Continuous glucose monitoring system
CGRP	: Calcitonin gene-related peptide
CHD	: Coronary heart disease
COPD	: Chronic obstructive pulmonary disease
cRDQ	: Core Reflux Disease Questionnaire
CRP	: C-reactive protein
DBP	: Diastoli blood pressure
DGER	: Duodenogastrosophageal reflux
DMN	: Dorsal motor nucleus
EE	: Erosive esophagitis
EGD	: Esophagogastroduodenoscopy
ERD	: Erosive reflux disease
ENOS	: Endothelial nitric oxide synthase
ER	: Endoplasmic Reticulum
FAs	: Fatty acids
FBI	: Fasting blood suger
FBS	: Fasting blood insulin
FDA	: Food and Drug Administration
FSIVGTT	: Frequently sampled IV glucose tolerance tests
GEJ	: Gastroesophageal junction
GERD	: Gastroesophageal reflux disease
GLP-1	: Glucagon-like peptide-1

List of Abbreviations (Cont...)

GPR120	: G-protein coupled receptor 120
H.Pylori	: Helicobacter pylori
H2RAs	: Histamine 2 receptor antagonists
HDL	: High density lipoprotein
HGD	: High-grade dysplasia
HOMA	: Homeostatic model assessment
HPA	: Hypothalamus pituitary axis
IDF	: International Diabetes Federation
IHS	: International Health Services
IL-1	: Interleukin-1
IM	: Intestinal Metaplasia
IR	: Insulin resistance
IRAS	: Insulin Resistance Atherosclerosis Study
IRS	: Insulin receptor substrate
ISI	: Insulin sensitivity index
IST	: Insulin sensitivity test
LA	: Los Angeles
LDL	: Low density lipoprotein
LES	: Lower esophageal sphincter
LGD	: Low-grade dysplasia
MODY	: Maturity Onset diabetes of the Young
MS	: Metabolic syndrome
NAFLD	: Nonalcoholic fatty liver disease
NCEPATP	: National Cholesterol Education Programme Adult Treatment Panel
NERD	: Nonerosive disease
NO	: Nitric oxide
NTS	: Nucleus tractus solitarius
OGTT	: Oral glucose tolerance test
OSA	: Obstructive sleep apnea
PAI-1	: Plasminogen activator inhibitor-1
PCOS	: Poly Cystic Ovarian Syndrome
PPID	: Pituitary pars intermedia dysfunction

List of Abbreviations *(Cont...)*

PPIs	: Proton pump inhibitors
PTH	: Parathyroid hormone
QOL	: Quality of life
SBP	: Systolic blood pressure
SCJ	: Squamocolumnar junction
SD	: Standard deviation
SHBG	: Sex-hormone binding globulin
SP	: Substance P
SPSS	: Statistical Program for Social Science
T2DM	: Type 2 diabetes
TG	: Triglycerides
TC	: Total cholesterol
TLESRs	: Transient lower esophageal sphincter relaxations
TNF	: Tumor necrosis factor
UA	: Uric acid
UES	: Upper esophageal sphincter
US	: United State
VIP	: Vasoactive intestinal peptide
WHO	: World Health Organization
11β-HSD1	: 11 β -Hydroxysteroid Dehydrogenase Type 1



Introduction

Gastroesophageal reflux disease (GERD) is defined as an abnormal reflux of gastric contents into the esophagus at least once a week, leading to symptoms such as heartburn and/or acid regurgitation, and/or esophageal mucosal damage, which may also provoke long-term complications, such as Barrett's esophagus (*Lerardi et al., 2010*).

Metabolic syndrome, which includes interrelated risk factors for cardiovascular disease and diabetes, is a common disorder that threatens public health in many countries (*Alberti et al., 2009*). Recent studies have identified that insulin resistance (IR), a principal component of metabolic syndrome, as well as related metabolic abnormalities, plays a role in carcinogenesis (*Chen et al., 2008*).

In addition, the various metabolic syndrome components increase the risk of several non cardiovascular diseases, such as non-alcoholic fatty liver disease, polycystic ovary syndrome, obstructive sleep apnoea (*Eckel et al., 2005*), and GERD (*Chung et al., 2008*). GERD is known not only to affect the quality of patients' lives but may also increase the risk of oesophageal adenocarcinoma (*Lee et al., 2009*).

Unfortunately, GERD is becoming increasingly prevalent in Asia, where it is currently estimated to affect more than 10% of the population (*Goh, 2011*). Identification of risk factors for