

Omentin-1 Level and Carotid Intimal Thickening in Patients with Fatty Liver Disease and Diabetes Type 2

Thesis

Submitted for partial fulfillment of MD degree in
Internal Medicine

By

Ebrahim Eid Basyouny Mohamed
M.B, B.Ch, M.Sc.

Under supervision of

Prof. Dr. Mohamed Ali Marei Makhoulf

Professor of Internal Medicine
Faculty of Medicine, Ain Shams University

Prof. Dr. Esam Farid Mohamed El Mahdy

Professor of Internal Medicine
Faculty of Medicine, Ain Shams University

Prof. Dr. Amir Helmy Samy

Professor of Internal Medicine
Faculty of Medicine, Ain Shams University

Asst. Prof. Dr. Khaled Amr Zaky

Assistant Professor of Internal Medicine
Faculty of medicine, Ain Shams University

**Faculty of Medicine
Ain Shams University
2018**



**FIRST AND FOREMOST THANKS TO ALLAH,
THE MOST MERCIFUL**

*I would like to express my deep appreciation to **Prof. Dr. Mohamed Ali Maraey Makhlouf** and **Prof. Dr. Esam Fariid Mohamed El Mahdy**, Professors of Internal Medicine, Faculty of Medicine, Ain Shams University, for their meticulous supervision, kind help, valuable support, I am deeply affected by their noble.*

*Moreover I would like to express my sincere and deepest gratitude to **Prof. Dr. Amir Helmy Samy**, Professors of Internal Medicine, Faculty of Medicine, Ain Shams University and **Asst. Prof. Dr. Khaled Amr Zaki**, Assistant Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, for their supervision, help, valuable support and guidance. I am deeply affected by their character, perfection, care and consideration.*

*Many thanks to **Prof Dr. Moustafa Rezk**, Professor of clinical pathology, Alex Univ and **Dr. Wael Abdelhamed**, specialist of Radiology, Alex Police Hospital, for their participation in the practical part of this work,*

Many thanks to my professors and colleagues in Internal Medicine department.

Many thanks to my Father and mother for their great support to complete this work,

Many thanks to my Wife for her support, help and continuo's encouragement through the whole research.

Ebrahim Eid Basyouny Mohamed

LIST OF CONTENTS

	Page
ACKNOWLEDGMENT	-
LIST OF ABBREVIATIONS.....	i
LIST OF TABLES	iii
LIST OF FIGURES	iv
I. INTRODUCTION.....	1
II. AIM OF THE WORK	4
III. REVIEW OF LITERATURE	5
Chapter I: Non Alcoholic Fatty Liver Disease	5
Chapter II: Diabetes Mellitus.....	28
Chapter III: Obesity	72
Chapter IV: Adipokines in Obesity and Diabetes	79
IV. SUBJECTS AND METHODS	90
V. RESULTS.....	98
VI. DISCUSSION	141
VII. SUMMARY	154
VIII. CONCLUSION.....	158
IX. RECOMMENDATIONS.....	160
X. REFERENCES	161
ARABIC SUMMARY.....	--

List of Abbreviations

ABI	: Ankle/brachial index
ACEI	: Angiotensin converting enzyme inhibitor
ADA	: American diabetes association
AGE	: Advanced glycation end products
AMI	: Acute myocardial infarction
ARB	: Angiotensin receptor blocker
BMI	: Body mass index
CAD	: Coronary artery disease
CLD	: Chronic liver disease
COX	: Cyclo-oxygenase enzyme
CRP	: C-reactive protein
CVD	: Cardiovascular disease
CVS	: Cerebrovascular stroke
DM	: Diabetes mellitus
DNA	: Deoxyribonucleic acid
ELF	: Enhanced liver fibrosis
ESRD	: End stage renal disease
FBG	: Fasting blood glucose
FXR	: Farnesoid X receptor
GAD	: Glutamic acid decarboxylase enzyme
GDM	: Gestational diabetes mellitus
HbA1C	: Hemoglobin A1C
HDL	: High density lipoprotein
HLA	: Human leukocyte antigen
HPL	: Human placental lactogen
HR	: Heart rate
HTN	: Hypertension
HS	: Hepatic steatosis
ICAM-1	: Intercellular cell adhesion molecule -1
IFG	: Impaired fasting glucose
IGT	: Impaired glucose tolerance
IDF	: International Diabetes Federation
IHD	: Ischemic heart disease
IL-6	: Interleukin-6

List of Abbreviations (Cont.)

IMT	: Intima media thickness
LADA	: Latent autoimmune diabetes of adults
LDL	: Low Density lipoprotein
MAPK	: Mitogen-activated protein kinase
MI	: Myocardial infarction
MMPs	: Matrix metalloproteinase
MODY	: Maturity-onset diabetes mellitus
MRE	: Magnetic resonance elastography
mRNA	: Messenger ribonucleic acid
NAFLD	: Non-alcoholic fatty liver disease
NFS	: NAFLD fibrosis score
NIDDM	: Non-insulin dependant diabetes mellitus
NO	: Nitric oxide
NPDR	: Non-progressive diabetes retinopathy
OGTT	: Oral glucose tolerance test
OSAS	: Obstructive sleep apnea syndrome
OCA	: Obeticholic acid
PAD	: Peripheral arterial disease
PCOS	: Polycystic ovary syndrome
PDR	: Progressive diabetes retinopathy
PPARS	: Peroxisome proliferator-activated receptors
TNF-α	: Tumor necrosis factor- α
TIA	: Transient ischemic attack
TZDs	: Thiazolidinedione's
UKPDS	: United Kingdom prospective diabetes study
VCAM-1	: Vascular cell adhesion molecule -1
VEGD	: Vascular endothelial growth factor
WAT	: White adipose tissue
WHO	: World health organization

List of Tables

Table	Title	Page
(1)	Classification of obesity according to BMI values for Caucasians	72
(2)	Comparison between the three studied groups according to demographic data	99
(3)	Comparison between the three studied groups according to Thyroid Function	101
(4)	Comparison between the three studied groups according to liver function	102
(5)	Comparison between the three studied groups according to Diabetes profile	104
(6)	Comparison between the three studied groups according to lipid profile	105
(7)	Comparison between the three studied groups according to renal function	110
(8)	Comparison between the three studied groups according to serum omentin	111
(9)	Comparison between the three studied groups according to IMT	112
(10)	Correlation between different parameters in total sample (n= 90)	114
(11)	Correlation between different parameters in NAFLD group (n= 30)	126
(12)	Correlation between different parameters in diabetic group (n= 30)	131

Table	Title	Page
(13)	Diagnostic performance of serum omentin level in prediction of NAFLD	137
(14)	Diagnostic performance of Carotid-IMT in prediction of NAFLD	138
(15)	Relation between BMI with serum omentin and carotid doppler in NAFLD group (n= 30)	139

List of Figures

Figure	Title	Page
(1)	Pathologic processes in NAFLD and potential therapeutic targets	22
(2)	Geographical distribution of diabetes prevalence worldwide	29
(3)	Disorders of glycemia: etiologic types and stages	37
(4)	Human omentin ELISA standard curve	97
(5)	Comparison between the three studied groups according to BMI (kg/m ²)	100
(6)	Comparison between the three studied groups according to Waist (cm)	100
(7)	Comparison between the three studied groups according to PPBS (mg/dl)	105
(8)	Comparison between the three studied groups according to HAC 1 (%)	105
(9)	Comparison between the three studied groups according to FBS (mg/dl)	106
(10)	Comparison between the three studied groups according to lipid profile	109
(11)	Comparison between the three studied groups according to serum omentin	111
(12)	Comparison between the three studied groups according to IMT	113

Figure	Title	Page
(13)	Correlation between serum omentin (ng/ml) with BMI (kg/m ²) in total sample	115
(14)	Correlation between serum omentin (ng/ml.) with waist (cm) in total sample	116
(15)	Correlation between serum omentin (ng/ml.) with PPBS in total sample	116
(16)	Correlation between serum omentin (ng/ml.) with HbA1C(%) in total sample	117
(17)	Correlation between serum omentin (ng/ml.) with LDL (mg/dl) in total sample	117
(18)	Correlation between Carotid Doppler (cm) with BMI (kg/m ²) in total sample	118
(19)	Correlation between Carotid Doppler (cm) with waist (cm) in total sample	119
(20)	Correlation between Carotid Doppler (cm) with PPBS in total sample	120
(21)	Correlation between Carotid Doppler (cm) with HbA1C (%) in total sample	120
(22)	Correlation between Carotid Doppler (cm) with LDL (mg/dl) in total sample	120
(23)	Correlation between Waist (cm) with BMI (kg/m ²) in total sample	121
(24)	Correlation between FBG (mg/dl) with BMI (kg/m ²) in total sample	122

Figure	Title	Page
(25)	Correlation between LDL (mg/dl) with BMI (kg/m ²) in total sample	122
(26)	Correlation between TG (mg/dl) with BMI (kg/m ²) in total sample.	123
(27)	Correlation between FBS (mg/dl) with waist (cm) in total sample	124
(28)	Correlation between LDL (mg/dl) with waist (cm) in total sample	125
(29)	Correlation between TG (mg/dl) with waist (cm) in total sample	125
(30)	Correlation between Serum omentin (ng/ml.) with FBS (mg/dl) in NAFLD group	127
(31)	Correlation between Carotid Doppler with BMI (kg/m ²) in NAFLD group	128
(32)	Correlation between Carotid Doppler with Waist circumference (cm) in NAFLD group	128
(33)	Correlation between Carotid Doppler with PPBS in NAFLD group	129
(34)	Correlation between Carotid Doppler with FBS (mg/dl) in NAFLD group	129
(35)	Correlation between Carotid Doppler with HDL (mg/dl) in NAFLD group	131
(36)	Correlation between Carotid Doppler with BMI (kg/m ²) in diabetic group	132

Figure	Title	Page
(37)	Correlation between Carotid Doppler with Waist circumference (cm) in diabetic group	133
(38)	Correlation between Carotid Doppler with PPBS in diabetic group	133
(39)	Correlation between Carotid Doppler with HA1C (%) in diabetic group	134
(40)	Correlation between Carotid Doppler with FBS (mg/dl) in diabetic group	134
(41)	Correlation between Carotid Doppler with LDL (mg/dl) in diabetic group	135
(42)	Correlation between Carotid Doppler with TG (mg/dl) in diabetic group	135
(43)	Correlation between Carotid Doppler with TC (mg/dl) in diabetic group	136
(44)	ROC curve for serum omentin to predict NAFLD vs normal	137
(45)	ROC curve for Carotid doppler to predict NAFLD vs normal	138
(46)	Relation between BMI with serum Omentin in NAFLD group	140
(47)	Relation between BMI with Carotid doppler in NAFLD group	140

Abstract

Introduction: Adipokines are the fat-derived hormones released from adipose tissue. Many are associated with insulin resistance, obesity and metabolic syndrome. Adipokines can be both pro-inflammation and anti-inflammation factors

Aim of the Work: The primary aim of this work is to detect the level of Omentin-1 marker and carotid intimal media thickness in patients with fatty liver disease and type 2 diabetes

Subjects: This study included 90 patients recruited from the department of Internal Medicine of Alex Police Hospital and the outpatient clinic

RESULTS: The study was performed on 90 subjects divided into 3 groups, 30 of them were diabetics type 2, 30 have NAFLD and 30 were healthy subjects as control group

Discussion: Epidemiological studies have showed a significant rise in the prevalence of diabetes particularly type 2 diabetes worldwide resulting in an increased burden on individuals and health care system. In 2012, an estimated 347 million people have type 2 diabetes

Summary: Non-alcoholic fatty liver disease (NAFLD) is a well-established hepatic manifestation of the metabolic syndrome and is one of the most common causes of chronic liver disease

Conclusion: Omentin-1 level is significantly lower in subjects with diabetes and NAFLD in comparison with control group

Recommendations: Further studies with larger samples are needed to consolidate the relation between omentin-1 and carotid IMT in NAFLD and Diabetic patients

Key Word: Ankle/brachial index, Chronic liver disease, Enhanced liver fibrosis

Introduction

Adipokines are the fat-derived hormones released from adipose tissue. Many are associated with insulin resistance, obesity and metabolic syndrome. Adipokines can be both pro-inflammation and anti-inflammation factors (**Maury and Brichard, 2010**).

Omentin-1 is adipokine that is primarily secreted by stromal vascular cells in visceral adipose tissue, and is expressed to a lesser extent in the heart, lung, and placenta (**Tan et al., 2010**).

Omentin-1 is a beneficial adipokine that enhances insulin-stimulated glucose uptake and triggers Akt signaling, which mediates downstream effects such as glucose metabolism (**Auguet et al., 2011**).

Along these lines, dysregulation of omentin-1 secretion is thought to play a role in the pathophysiology of insulin resistance, inflammation, endothelial dysfunction, and cardiovascular disease (**Pan et al., 2010**).

In clinical studies, circulating omentin-1 concentrations have been shown to be decreased in patients with obesity, impaired glucose regulation, polycystic ovary syndrome, type 1 diabetes, and type 2 diabetes (**Choi et al., 2011**).

Given these clinical associations, omentin-1 has garnered attention as a possible contributor to the pathogenesis of the metabolic syndrome (**Yan et al., 2011**).

Plasma omentin-1 levels inversely correlate with body mass index (BMI), fat mass, and fasting plasma insulin, and positively