Association between Plasma Adiponectin Levels and Unstable Coronary Syndromes

Thesis

Submitted for fulfillment of M.Sc. Degree in
Critical Care Medicine

Presented by

Ahmed Mohamed Ali El Maghraby
(M.B. B.C.H.)

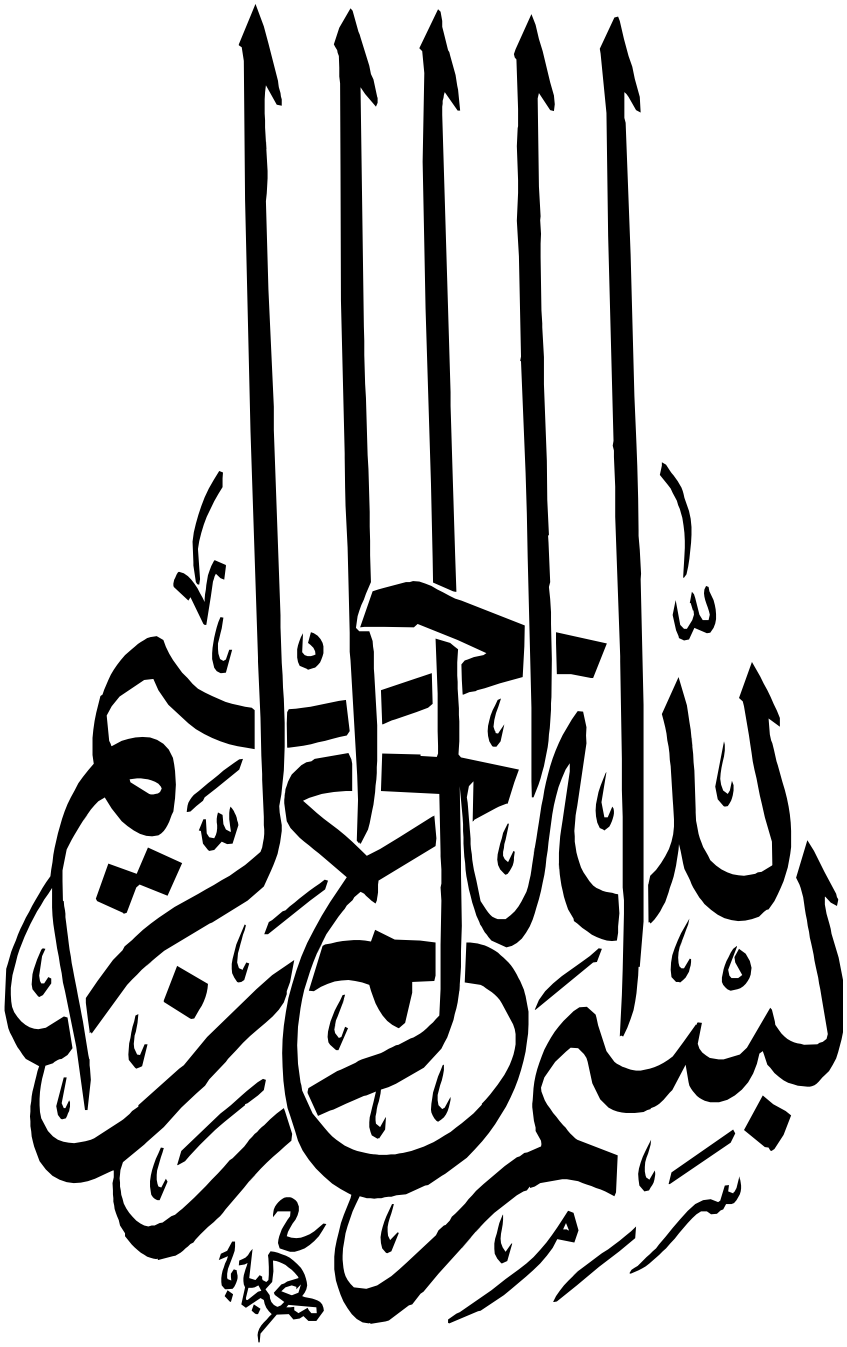
Supervised by

Prof. Dr. Ashraf Wadie Andraos
Assistant professor of critical care medicine
Faculty of Medicine
Cairo University

Prof. Dr. Mervat Mohamed El Damarawy
Professor & head of critical care dept
Theodor Bilharz Research Institute

Dr. Emad El Deen Omar
Lecturer of critical care medicine
Faculty of Medicine
Cairo University

Faculty of Medicine
Cairo University
2010


بسم الله الرحمن الرحيم

Acknowledgment

*First and foremost, I feel always deeply indebted to **ALLAH,** the Most Gracious and the Most Merciful.*

*I would like to express my sincere gratitude to **Prof. Dr. Hassan Khalid** Professor of Critical Care Medicine and Chief of Critical Care Medicine Department, Cairo University.*

*I would like to express my deepest gratitude and cardinal appreciation to Prof. Dr. **Ashraf Wadie**, Assistant Professor of critical care medicine, Faculty of medicine, Cairo University, who kindly supervised and motivated the performance of this work, for his kind guidance and constant encouragement throughout this work.*

*I am greatly honored to express my sincere appreciation to Prof. Dr. **Mervet El Damarawy**, Professor& Head of critical care dept., Theodor Bilharz Research Institute, for devoting part of her precious time to help me in the preparation of this work.*

*I am greatly honored to express my deep thankfulness to Dr. **Emad El Deen Omar**, Lecturer of Cardiology, Faculty of medicine, Cairo University, for his continuous support, help and generous advice throughout this work.*

*I would like to thank Prof. Dr. **Nihal El ASLY** Assistant Professor of clinical pathology, Theodor Bilharz Research Institute, for her great effort in fulfilling this work.*

I am very grateful to all my staff members and my colleagues in the department of Critical care, in Theodor Bilharz Research Institute and Faculty of medicine, Cairo University, for their help and support throughout the course of the work.

Finally, I am most grateful to my family for their patience and everlasting support.

Abstract

Aims and Objectives: Obesity is established risk factor for coronary artery disease and acute coronary syndrome (ACS). Association between obesity and ACS are independent of other traditional risk factors suggestive of possible contribution of other fat related mediators like adiponectin. Adiponectin is a recently discovered adipocyte-specific cytokine which, in contrast to other adipokines, has anti-inflammatory, anti-thrombotic, and anti-atherogenic properties. It is abundant in the plasma of normal subjects, but decreased in conditions such as obesity and type 2 diabetes mellitus. Furthermore in healthy individuals, low plasma adiponectin levels have been associated with increased risk of cardiovascular events. Present study evaluates the relationship between adiponectin and ACS. The association between plasma adiponectin levels and coronary lesion severity on coronary angiography (CAG) was also assessed using Gensini score.

Methods and Results: Thirty patients with acute coronary syndromes(ACS) undergoing CAG in critical care department of Cairo University from April 2009 to April 2010 were enrolled and divided into three subgroups according to presentation-patients with ST elevation myocardial infarction (STEMI) (n = 10) , with Non ST elevation myocardial infarction (NSTEMI) (n = 12) and with unstable angina(UA), in addition to nineteen apparently normal volunteers as a control group, comparable in age, gender, waist to hip ratio and BMI. After statistical analysis, patients with ACS were found to have lower adiponectin (4.55 ± 2.78 µg/ml) level than control group (9.01 ± 3.2 µg/ml) and the difference was statistically significant ($p < 0.001$). Moreover, lower levels of adiponectin were associated with more severe coronary artery lesion evaluated by Gensini score ($p < 0.0001$). Furthermore, A significant difference was reported between three subgroups regarding the severity of CAD evaluated by **Gensini score**, where more severe conditions were reported in the NSTEMI than in the STEMI than in the unstable angina group (98.67 ± 34.04, 85.9 ± 35.32 and 25.25 ± 11.94, $P < 0.0001$ respectively).

Conclusion: Present study concludes that lower adiponectin levels are independently associated with higher risk of ACS and more severe coronary lesions.

Key words: acute coronary syndrome, adiponectin, Gensini score, coronary angiography.

Table of Contents

List of Tables IV

List of Figures VII

List of Abbreviation X

Introduction 1

Aim of work 3

Chapter I 4

Acute coronary syndromes 4

Definition of myocardial infarction: 4

Pathophysiology of acute coronary syndromes: 5

Diagnosis of acute coronary syndrome: 15

Management of acute coronary syndrome: 34

Chapter II 47

Adiponectin 47

Introduction 47

What is Adiponectin? 48

Adiponectin receptors..... 50

Adiponectin as a Clinical Marker of Cardio metabolic Disease 52

Adiponectin and Surrogates of Atherosclerosis 59

Adiponectin as a molecular regulator of atherosclerosis 62

Adiponectin as a Molecular Regulator of Insulin Resistance and Diabetes 66

Adiponectin and Cardioprotection..... 67

Modifying Adiponectin Levels to Combat Cardio metabolic Disease... 68

Patients and Methods..... 70

Inclusion criteria:..... 71

Exclusion criteria: 72

Methods: 73

*Evaluation of patients:..... 73

*Adiponectin kit: 74

*Coronary angiography:..... 77

*Statistical methods:..... 79

Results 81

A-Demographic (descriptive) data of ACS & control group:..... 82

B-Relation between Gensini score, adiponectin level and significant predictors: 87

C-Relation between adiponectin level & Gensini score: 97

D-Demographic (descriptive) data between three types of ACS:..... 104

Discussion 116

Summary and conclusion 128

Recommendations 131

References 132

List of Tables

Table 1 Universal definition of myocardial infarction [10] 4

Table 2 Primary components of atherosclerotic plaque formation, initiated by endothelial dysfunction 7

Table 3 Features associated with cardiac chest pain 16

Table 4 Features of chest pain associated with a low (<3%) likelihood of ACS. 16

Table 5 Differential diagnosis of chest pain[26] 17

Table 6 Cardiac risk factors [26] 20

Table 7 Examination findings suggestive of a diagnosis other than ACS[26]. 22

Table 8 Examination findings suggesting increased risk of adverse outcome 22

Table 9 Anatomical relationships of ECG leads 24

Table 10 Causes of ST-segment elevations 25

Table 11 Molecular biomarkers for the evaluation of patients with myocardial infarction. : cTn=cardiac troponin 28

Table 12 Advantages of primary percutaneous coronary intervention over thrombolysis [57] 40

List of Tables

Table 13 comparison between both groups as regard demographic criteria*: 82

Table 14 Comparison both groups as regard gender, smoking, positive family history & hypertension: 83

Table 15 Comparison between both groups as regard laboratory outcomes*: 84

Table 16 Correlations between Gensini score and adiponectin (µg/L) versus other variables in cases (n=30): * 87

Table 17 Correlations between waist/hip ratio and other variables in cases (n=30)..... 98

Table 18 Correlations between (waist\hip) versus other variables in controls (n=19)..... 101

Table 19 Correlations between Adiponectin versus other variables in controls (n=19):..... 102

Table 20 Comparison between both male and female cases as regard demographic criteria* 103

Table 21 Comparison between the three categories of cases as regard demographic criteria*: 104

Table 22 Comparison between three categories of cases as regard laboratory data*:..... 106

Table 23 Comparison between ST elevation and Non ST elevation myocardial infarction as regard laboratory data and severity of CAD *: .. 110

List of Tables

Table 24 Comparison between unstable angina and STelevation myocardial infarction as regard laboratory data and severity of CAD*:..... 111

Table 25 Comparison between unstable angina & Non STelevation myocardial infarction as regard laboratory data and severity of CAD*: ... 113

List of Figures

Figure 1 Processes contributing to the development of ACS (Braunwald, 1989) 6

Figure 2 mechanism of atherosclerotic plaque formation (Ross, 1999) [12] 8

Figure 3 representative histology of atherosclerotic plaque. (Hellings et al., 2008) 10

Figure 4 Determinants of myocardial oxygen balance and related pathophysiologic factors that contribute to acute coronary syndrome. 11

Figure 5 Abbreviated ischemia of thrombus formation and pharmacologic agents targeting thrombosis pathways. (Selwyn, 2003) 13

Figure 6 sequence of morphologic changes in ST-segments and T-waves during acute myocardial infarction. (Morris and Brady, 2002) 25

Figure 7 Release of cardiac biomarkers in acute myocardial infarction. (Galla et al., 2006) [30] 28

Figure 8 A risk-based initial diagnostic pathways. (Eli et al., 2009)[26] 33

Figure 9 Summary of management of acute coronary syndromes (SIGN, 2007) [53] 46

Figure 10 Structure and domains of adiponectin (Fruebis et al., 2001) 49

Figure 11 Proposed structure of adiponectin receptors and their expression in various tissues. (**Yamauchi et al., 2003**) 51

Figure 12 Molecular mechanisms of adiponectin action.**(Yamauchi et al., 2003)** 60

Figure 13 Adiponectin as a molecular regulator of atherosclerosis. (Paul et al., 2006) 65

List of Figures

Figure 14 Test procedure summary [155] 75

Figure 15 Adiponectin standard curve..... 76

Figure 16 Gensini score. (European Heart Journal 2006) 78

Figure 17 Comparison between cases and controls as regard HDL levels... 85

Figure 18 Comparison between cases and controls as regard adiponectin levels 86

Figure 19 Negative correlation between adiponectin (µg/L) and BMI statistically high significant..... 88

Figure 20 Negative Correlation between adiponectin (µg/L) and waist to hip ratio is statistically significant..... 89

Figure 21 Positive Correlation between adiponectin (µg/L) and HDL level (mg/dl) is statistically significant 90

Figure 22 Negative Correlation between adiponectin (µg/L) and TG level (mg/dl) is statistically significant 91

Figure 23 Positive correlation between waist hip ratio and Gensini is statistically highly significant 93

Figure 24 Positive correlation between Gensini Score and BMI showing highly statistically significant 94

Figure 25 Negative correlation between Gensini Score and HDL level showing highly statistically significant 95

Figure 26 Positive correlation between Gensini Score and TG level showing statistically significant 96

Figure 27 Negative correlation between Gensini Score and Adiponectin level showing highly statistically significant 97

Figure 28 Positive correlation between waist hip ratio and BMI is statistically highly significant..... 99

List of Figures

Figure 29 Positive correlation between waist hip ratio and LDL is statistically highly significant..... 100

Figure 30 Comparison between the three categories as regard waist/hip .. 105

Figure 31 Comparison between the three categories as regard BMI 105

Figure 32 Comparison between the three categories as regard HDL (mg/dl) 107

Figure 33 Comparison between the three categories as regard adiponectin (µg/L) 108

Figure 34 Comparison between the three categories as regard Gensini score 109

Figure 35 Comparison between unstable angina group and STEMI group as regard adiponectin (µg/L) 112

Figure 36 Comparison between unstable angina group and STEMI group as regard Gensini score 112

Figure 37 Comparison between unstable angina group & NSTEMI group as regard HDL (mg/dl) 114

Figure 38 Comparison between unstable angina group and NSTEMI group as regard adiponectin (µg/L) 115

Figure 39 Comparison between unstable angina group and NSTEMI group as regard Gensini score 115

List of Abbreviation

ACC : American College of Cardiology

ACE : Angiotensin converting enzyme

Acrp30 : adipocyte complement related protein of 30 kDa

ACS : acute coronary syndrome

AdipoRl : adiponectin receptor

ADP : adenosine diphosphate

AHA : American Heart Association

AMI : acute myocardial infarction

AMPK : activated protein kinase

apM1 : adipose Most abundant gene transcript-1

apoE : apolipoprotein E

ASSENT : The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen

AST : Aspartate aminotransferase

bFGF : basic fibroblast growth factor

BMI : body mass index

BMI : body mass index

SS : severity score

CAD : coronary artery disease

CAD : coronary artery disease

CCT : Coronary computed tomography

CIMT : common carotid artery intima-media thickness

CK : creatine kinase

CMR : Cardiovascular magnetic resonance

COMM IT : Clopidogrel and Metoprolol in Myocardial Infarction Trial

CRP : C-reactive protein

CURE : Clopidogrel in Unstable angina to prevent recurrent ischemic Events

DIGAMI : Diabetes mellitus insulin-glucose infusion in acute myocardial infarction

DNA : Deoxyribonucleic Acids

EC : endothelial cell

ECG : Electrocardiogram

EGF : epidermal growth factor

eNOS : endothelial NO synthase

ERK : extracellular signal-related kinase

ES : extent score

ET : endothelin

FA : Fatty acid

fAd : full-length adiponectin

FBF : forearm blood flow

GBP-28 : gelatin-binding protein of 28 kDa

GH : Growth hormone

GISSI : Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico

GP : glycoprotein

GPCR : G protein- coupled receptor.

GRACE : The global registry of acute coronary events

HB-EGF : heparin-binding epidermal growth factor