Serum Adiponectin And Resistin Levels in Association With Bronchial Asthma In Adults

Thesis

Submitted for partial fulfillment of M.D. Degree in Internal Medicine

By

Radwa Hassan Abou El Fotoh M.B., B.Ch., (Ain Shams university) *Under supervision of*

Professor Dr/ Salwa Seddik Hosny

Professor of Internal Medicine, Endocrinology and Metabolism. Faculty of Medicine-Ain Shams University.

Professor Dr/ Mohamed Nazmy Farres

Professor of Internal Medicine, Allergy and Clinical Immunology. Faculty of Medicine-Ain Shams University.

Dr/ Nermine Abd Elnour Melek

Assistant Professor of Internal Medicine, Allergy and Clinical Immunology.

Faculty of Medicine-Ain Shams University.

Dr/ Amira Ramadan El Mahdi

Lecturer of Internal Medicine, Allergy and Clinical Immunology. Faculty of Medicine-Ain Shams University.

Dr/ Sylvia Talaat Kamal

Lecturer of Internal Medicine, Allergy and Clinical Immunology. Faculty of Medicine-Ain Shams University.

Faculty of Medicine Ain Shams University 2019

Acknowledgement

First, the foremost word to be written is "thanks my Lord for your help to finish this work".

Second, from among the numerous great people whose involvement in this study was invaluable, I would like to distinguish the following individuals:

My best thanks are for *Prof. Dr. Salwa Seddik Hosny*, *Profosser of Internal Medicine*, *Ain Shams University*, for her valuable help and advice. Her knowledge and experience were helpful to me.

My sincere gratitude is due to *Prof. Dr. Mohammed Nazmy farres, Profosser of Internal Medicine, Ain Shams University*, for his supervision, expert guidance, valuable help and advice throughout. His wide knowledge and experience were very helpful to me.

I feel also extremely grateful to *Prof. Dr Nermine Abd Elnour Melek*, *Assistant Professor of Internal Medicine*, *Ain Shams University*, for her supervision, everlasting support and encouragement throughout this study.

I am indebted to *Dr. Amira Ramadan El Mahdi*, *Lecturer of Internal Medicine*, *Ain Shams University*, for her kind treatment, generosity and extraordinary effort in supervising and instructing me.

I feel thankful to *Dr. Sylvia Talaat Kamal*, *Lecturer of Internal Medicine*, *Ain Shams University*, for her continuous monitoring and great efforts to complete this thesis.

List of Figures

No. of	Title of Figure	Page
Figure		No.
Figure (1)	Worldwide prevalence of clinical asthma	7
Figure (2)	Asthma pathophysiology	9
Figure (3)	Obese asthma phenotypes	40
Figure (4)	Relationship between obesity and asthma	47
Figure (5)	ACT according to American lung society	65
Figure (6)	Serum adiponectin in both asthmatics and non-	84
	asthmatics	
Figure (7)	Serum resistin in asthmatic and non-asthmatic	85
	group	
Figure (8)	Comparison between serum adiponectin in atopic	86
	and non-atopic group	
Figure (9)	Comparison between serum resistin levels among	87
	the atopic and non-atopic groups	
Figure (10)	Comparison between obese asthmatic and non-	88
	obese asthmatic as regard serum Adiponectin	
Figure (11)	Comparison between obese asthmatic and non-	89
	obese asthmatic as regard serum Resistin	
Figure (12)	ROC curve for Serum adiponectin differentiation	95
	between asthmatics and non-asthmatics.	
Figure (13)	ROC curve for Serum adiponectin differentiation	96
	between asthmatics and non-asthmatics.	

List of Tables

Table No.	Title of table	Page No.
Table (1)	Classification of asthma severity	15
Table (1)	Classification of asthma control	16
		43
Table (3)	Comparison between obese asthma phenotypes	
Table (4)	American Thoracic Society Grades for Severity of a Pulmonary Function Test Abnormality	72
Table (5)	Demographic and clinical characteristics of the	77
(1)	whole study groups	
Table (6)	Laboratory characteristics of the whole study	78
	group	
Table (7)	Clinical characteristics of the Asthmatic group	79
Table (8)	Comparison between atopic and non-atopic	80
	group as regard clinical and demographic data	
Table (9)	Comparison between Atopic and Non-atopic	81
	group as regard laboratory data	
Table (10)	Comparison between Obese asthmatics (OA)	82
	and non-obese asthmatics (NOA) as regard	
	demographic and clinical data	
Table (11)	Comparison between obese and non-obese	83
	asthmatics as regard laboratory data	
Table (12)	Serum adiponectin and resistin in asthmatic and	84
	control group	
Table (13)	Comparison between serum adiponectin and	85
	resistin in Atopic vs non-atopic groups.	
Table (14)	Comparison between obese and non-obese	87
	asthmatics as regard adiponectin and resistin	
	levels	
Table (15)	Comparison between serum adiponectin	90
	according to other different study parameters	
Table (16)	Comparison between serum resistin levels	91
	according to the different study parameters	

Table (17)	Correlation between serum adiponectin and	92
	other study parameters	
Table (18)	Correlation between serum resistin and other	93
	study parameters	
Table (19)	Correlation between serum resistin/ Adiponectin	94
	ratio and other study parameters	
Table (20)	Serum adiponectin level Accuracy	95
Table (21)	Serum Resistin level Accuracy	96

List of Abbreviations

ABG	Arterial Blood Gases
ACQ	Asthma Control Questionnaire
ACRP30	Adipocyte Complement Related Protein
ACT	Asthma Control Test
ACT	Asthma Control Test
AdipoR	Adiponectin receptor
ADP	Adiponectin
AHR	Airway Hyperresponsiveness
AIT	Allergen Immunotherapy
AMPK	Adenosine MonoPhosphate-activated Protein Kinases
APM1	Aminopeptidase M1
ATS	American Thoracic Society
AUC	Area Under the Curve
BFP	Body fat percentage
BMI	Body mass index
CAP-1	Adenylyl cyclase associated protein 1
CBC	Complete Blood Count
CD	Cluster of Differentiation
CDC-42	Cell division control protein 42
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease

CRP	C reactive protein
CVD	Cardio-Vascular Disease
CXR	Chest X-Ray
DCs	Dendritic cells
DNA	Deoxyribonucleic acid
EBC	Exhaled Breath Condensate
ELISA	Enzyme Linked Immunosorbent Assay
eNoses	Sensor based electronic noses
EOA	Early onset allergic obese asthma
ESR	Erythrocyte sedimentation rate
FEF25- 75%	Forced Expiratory Flow Rate at 25 to 75%
FENO	Fractional Exhaled Nitric Oxide concentration
FEV1	Forced expiratory volume 1
FRC	Functional Residual Capacity
FVC	Forced vital capacity
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GWAS	Gene wide associated studies
HbA1C	hemoglobin A1c
HMW	High Molecular Weight form
HRCT	High-Resolution Computed Tomography
ICS	Inhaled corticosteroids
IFN	Interferon
IgE	Immunoglobulin E

IL	Interleukin
ILCs	Innate Lymphoid Cells
IQR	Inter Quartile Range
LABA	Long Acting Beta Agonist
LAMA	Long-Acting Anti-Muscarinics
LMW	Low Molecular Weight forms
LONA	Late Onset Non-Allergic asthma
LPS	Lipopolysaccharide
LTRA	Leukotriene Receptor Antagonists
MEKK1	Mitogen-activated protein kinase kinase 1
MMW	Middle Molecular Weight form
mRNA	Messanger Ribonucleic Acid
NF-ĸB	Nuclear Factor Kappa B
NOA	Non-Obese Asthmatic patients
NPV	Negative Predictive Value.
OA	Obese Asthmatic
OCS	Oral Corticosteroids
OD	Optical Density
p38 MAPK	Mammalian p38 mitogen-activated protein kinases
PBMCs	Peripheral Blood Mononuclear Cells
PC	Personal computer
PC20	Provocative concentration causing a 20 % fall in forced expiratory volume 1

PEF	Peak expiratory flow
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test
PKA	Protein Kinase A
PPARα	Peroxisome proliferator-activated receptor
PPV	Positive Predictive Value
RA ratio	Resistin Adiponectin Ratio
RCP	Royal College of Physicians
RELM	Resistin-Like Molecules
ROC	Receiver Operating Characteristic
RSV	Respiratory syncytial virus
SABA	Short agonist beta agonist
SARP	Severe Asthma Research Program
SD	Standard Deviation
SDF1	Stromal cell-Derived Factor 1
SH3	Src Homology 3
sIgE	Specific Immunoglobulin E
SNPs	Single nucleotide polymorphisms
SP-A	Surfactant Protein A
SPSS	Statistical package for Social Science
SPT	Skin Prick Test
Th2	T Helper 2
TLC	Total Leucocytic Count

TLR	Toll-Like Receptor
TNF- α	Tumor Necrosis Factor α
TSLP	Thymic stromal lymphopoietin
USA	United States of America
W/H ratio	Waist/ Hip ratio
YLD	Years of Life lived with Disability
YLL	Years of life lost
ABG	Arterial Blood Gases

List of Contents

INTRODUCTION AND AIM OF THE WORK	
REVIEW OF LITERATURE	5
CHAPTER I (BRONCHIAL ASTHMA)	5
Introduction	5
Definition	5
Epidemiology	6
Pathophysiology of Asthma	8
Mortality and Morbidity	12
Asthma phenotypes	13
Asthma Severity	
Asthma Control	
Risk factors	
Diagnosis of Asthma	
Asthma Management	31
CHAPTER II (OBESITY AND ASTHMA)	37
Introduction	37
Mechanisms by which obesity cause asthma	38
Treatment challenges in obesity	49
CHAPTER III (ADIPONECTIN AND RESISTIN)	51
Introduction	51
Adiponectin	51
Resistin	57
Resistin/ Adiponectin ratio	62
SUBJECTS AND METHODS	63
RESULTS	77
DISCUSSION	97
CONCLUSION AND RECOMMENDATIONS	106
SUMMARY	109
REFERENCES	110

Serum Adiponectin And Resistin Levels in Association With Bronchial Asthma In Adults

The association between obesity and bronchial asthma has been demonstrated by many studies, either observational or interventional studies in both children and adults. However, the mechanism behind this association is still unknown (**Ziora et al, 2013**).

Potential mechanisms have been suggested including obesity-related changes in lung volumes, systemic inflammation, and adipocyte-derived factors, such as the pro-inflammatory and anti-inflammatory factors, which include leptin, adiponectin, and resistin (Fantuzzi, 2005) (Shore and Fredberg, 2005).

Adiponectin (Yamauchi et al, 2010) and resistin hormones are considered significant root factors for the regulation of energy, glucose, and lipid homeostasis as well as insulin signaling pathway (Galic et al, 2010).

Adiponectin is an adipocyte-secreted anti-inflammatory polypeptide hormone (244 amino acids) (Yamauchi et al, 2010). Resistin, (polypeptide; 108 amino acids) getting its name from its ability to resist insulin, is a pro-inflammatory adipokine discovered first in mice (Steppan et al, 2001).

In contrast with adiponectin, resistin has low circulating levels (Galic et al, 2010).

A significant inverse correlation between serum adiponectin and resistin levels has been reported in the literatures (Wasim et al, 2006) (Lewandowski et al, 2005).

Those with highest increases of adiponectin displayed a trend towards a decline in resistin levels (Lewandowski et al, 2005)

Serum adiponectin was reduced during pulmonary allergic reactions, and adiponectin treatment attenuated allergic airway inflammation and airway hyperresponsiveness in mice (Lillioja and Wilton 2009).

Some studies reported that resistin, may be involved in the pathogenesis and severity of bronchial asthma either in children or in adults (**Ziora et al, 2013**). However, other studies in children showed that resistin reduces the risk for asthma (**Kim et al, 2008**) or has no influence on the disease (**Arshi et al 2010**).

Hence, the rationale intended behind this study is to further assess serum level of adiponectin and resistin among bronchial asthma patients in more details.

Aim of the study:

To determine serum levels of adiponectin and resistin in adult asthmatics in relation to obesity, asthma severity and atopic status.

Subjects and methods:

This study will be conducted on 96 subjects; 64 with bronchial asthma (selected from the allergy and chest out patients' clinics at Ain shams University hospitals) and 32 healthy individuals as control group (age and sex matched).

<u>Inclusion criteria for the asthmatic group (cases) will be the</u> following:

- a) Subjects between 18 and 65 years of age who were diagnosed as asthmatics (as defined by **GINA 2018**) attending allergy and chest outpatient clinics at Ain Shams university hospitals.
- b) Subjects on inhaled corticosteroids or other controller medications were allowed in the study.

Exclusion criteria for the asthmatic group:

- a) Current use of statins, systemic steroids (last dose > 6 months ago).
- b) Pregnant females or those taking combined oral contraceptives.
- c) Any serious concurrent disease process such as, but not limited to diabetes, coronary artery disease, or vasculitis, that would have effects on levels of systemic inflammation.
- d) Alcoholics.
- e) Patients unable to communicate adequately.

All patients will be subjected to the following:

- 1. Full detailed clinical history and physical examination with special emphasis on bronchial asthma, atopy, any other comorbidities, and details of concomitant drugs; oral contraceptives, steroids, statins, ... etc.
- 2. Asthma Control Test (ACT).
- 3. Body mass index (height and weight were measured in light clothing without shoes to calculate BMI in kilogram per

- square meter), waist / hip ratio and calculation of body fat percentage.
- 4. Skin prick test using a panel of common allergens, together with negative (saline) and positive (histamine) controls.
- 5. Serum total IgE.
- 6. Absolute Eosinophil count.
- 7. Pulmonary function tests.
- 8. Serum adiponectin level by ELISA.
- 9. Serum resistin level by ELISA.

REFERENCES

- 1. **Arshi M, Cardinal J, Hill RJ, Davies PS, Wainwright C.** Asthma and insulin resistance in children. Respirology. 2010;15: 779–784.
- 2. **Fantuzzi G.** Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005;115: 911–9.
- Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an Endocrine organ. Mol Cell Endocrinol. 2010;316: 129-139.
- Global Initiative for Asthma (GINA), 2018. Global Strategy for Asthma Management and Prevention. Available from http://www.ginasthma.org.
- 5. **Kim KW, Shin YH, Lee KE, Kim ES, Sohn MH, Kim KE.** Relationship between adipokines and manifestations of childhood asthma. Pediatr Allergy Immunol. 2008;19: 535–540.
- 6. **LaRochelle J, Freiler J, Dice J, Hagan L.** Plasma resistin levels in asthmatics as a marker of disease state. Journal of Asthma. 2007;44(7): 509–513.