Clinical Utility of Serum Chemerin as a Novel Marker of Metabolic Syndrome and Type 2 Diabetes Mellitus

Thesis

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By

Nesreen Ahmed Badawy Ahmed Mayhoub

M.B., B.Ch., Ain Shams University

Supervised by

Professor / Mona Mostafa Osman

Professor of Clinical and Chemical Pathology
Faculty of Medicine, Ain Shams University

Professor / Karim Yehia Shaheen

Professor of Clinical and Chemical Pathology
Faculty of Medicine, Ain Shams University

Doctor / Rania Salah El Din Kamle Shahin

Lecturer of Clinical and Chemical Pathology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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List of Contents

Title **Page No.**

List of Contents i
List of Abbreviations iv
List of Tables viii
List of Figures ix
Introduction and aim of the work 1
Review of Literature:
Chapter I- Diabetes Mellitus 5
A- Introduction 5
B- Definition 5
C- Epidemiology and Prevalence 5
D- Classification 6
1- Etiological Classification of Diabetes Mellitus 8
(a) Type 1 diabetes mellitus 8
(b) Type 2 diabetes mellitus 10
(i) Incidence and prevalence 10
(ii) Risk factors 10
(iii) Pathogenesis 13
(iv) Complications of type 2 DM 16
○ Acute complications 17
○ Chronic complications 19
(c) Other specific types of diabetes mellitus 21
(d) Gestational diabetes mellitus 21
2- Categories of Increased Risk for Diabetes 22
(a) Impaired glucose tolerance 23
(b) Impaired fasting glucose 23
(c) Hemoglobin A1C levels of 5.7-6.4% 24
E- Diagnosis of Diabetes Mellitus 24
1- Clinical Diagnosis 24
2- Laboratory Diagnosis 24
3- Monitoring Patient Compliance to Treatment 26
4- Diagnosis of Diabetic Complications 28
Chapter II- Metabolic Syndrome 30
A- Introduction 30

B- Definitions of the Metabolic Syndrome 31
1- Brief History 31
2- Diverging Definitions 31
C- Epidemiology and Prevalence of the Metabolic Syndrome 36
1- Prevalence Estimates According to Sex 36
2- Prevalence Estimates According to Race/Ethnicity 36
3- Prevalence Estimates According to Age 37
4- Prevalence Estimates According to Smoking and Lifestyle 38
D- Pathophysiology of the Metabolic Syndrome 38
1- Insulin Resistance and Metabolic Syndrome 40
(a) Definition of insulin resistance 40
(b) Structure of insulin receptor 41
(c) Physiology of insulin action 41
(d) Pathophysiology of insulin resistance 42
(e) Causes of insulin resistance 44
(f) Laboratory assessment and measurement of insulin resistance 45
(g) Insulin resistance in various organs and its relation with the metabolic syndrome 48
2- Obesity and Metabolic Syndrome 53
3- Hypertension and Metabolic Syndrome 54
4- Proinflammatory Molecules and Metabolic Syndrome 55
(a) C-reactive protein (CRP) 56
(b) Tumor necrosing factor-α (TNF-α) 57
(c) Resistin 57
(d) Interleukins 57
(e) Visfatin 58
(f) Adiponectin 59
5- Other Contributors to Metabolic Syndrome 59
6- Genetic Determinants of Metabolic Syndrome 59
E- Risks of the Metabolic Syndrome 60
1- Cardiovascular Disease 60
2- Type 2 Diabetes Mellitus 63
F- Associated Conditions of the Metabolic Syndrome 65
1- Nonalcoholic Fatty Liver Disease 65

2- Polycystic Ovarian Syndrome 66
3- Obstructive Sleep Apnea 66
4- Hypogonadism and Menopause 67
5- Lipodystrophy 67
6- Microvascular Disease 68
G- Management of the Metabolic Syndrome 68
Chapter III- Chemerin 71
A- Introduction 71
B- Structure 71
C- Distribution 72
D- Activation 73
E- Receptors 74
F- Mode of Action 76
G- Physiological Role of Chemerin 78
H- Pathophysiological Role of Chemerin 80
1- Role in Chemotaxis and Inflammation 80
2- Role in Diabetes 81
3- Role in Obesity and Metabolic syndrome 83
4- Role in Blood Pressure Regulation 84
5- Role in Atherosclerosis 85
6- Role in Psoriasis 86
7- Role as a Biomarker in Tumors 86
I- Methods of Assay of Chemerin 87
1- Enzyme Linked Immunosorbent Assay 87
2- Reverse Transcriptase Polymerase Chain Reaction 89
3- Immunohistochemistry 92
4- Western Blot Technique 94
Subjects and Methods 98
Results 116
Discussion 127
Summary and Conclusion 139
Recommendations 142
References 143
Arabic Summary .....___

List of Abbreviations

ADA..... American Diabetes Association
ADLS..... Atopic dermatitis lesional skin
AHA-NHLBI .. American Heart Association and the National Heart Lung and Blood Institute
Apo A1 ..... Apolipoprotein A1
Apo B..... Apolipoprotein B
AS ..... Aortic stenosis
AT1-R..... Angiotensin 1 receptor
AUC..... Area under curve
BMI ..... Body mass index
CABG……...Coronary artery bypass graft
CAD-risk..... Coronary arterial disease risk
c-AMP ..... Cyclic adenosine monophosphate
CCNB2 ..... Cyclin B2
CCRL2 ..... Chemokine (C-C motif) receptor like 2
cDNA ..... Complementary DNA
CE..... Cholesterol esterase
CETP..... Cholesteryl ester transfer protein
CHD..... Coronary heart disease
ChemR23 ..... Chemerin receptor 23
CI..... Confidence interval
CMKLR1 ..... Chemokine-like receptor-1
CRP ..... C-reactive protein
CV..... Coefficient of variation
CVD..... Cardiovascular disease
DBP ..... Diastolic blood pressure
DCs ..... Dendritic cells
DKA..... Diabetic ketoacidosis
DM..... Diabetes mellitus
dNTPs..... Deoxynucleotides
EGIR ..... European Group for the Study of Insulin Resistance
ELISA ..... Enzyme linked immunosorbant assay

ERK 1/2..... Extacellular signal regulated kinase 1 and 2
FBG ..... Fasting blood glucose
FBS……..Fasting blood sugar
FBI..... Fasting blood insulin
FFAs ..... Free fatty acids
FITC ..... Fluorescein isothiocyanate
FN ..... False negative
FP..... False positive
FPG ..... Fasting plasma glucose
GAD65..... 65-kD isoform of glutamic acid decarboxylase
GCT..... Glucose challenge test
GDM..... Gestational diabetes mellitus
GLUT4 ..... Glucose transporter 4
GPR1 ..... G protein coupled receptor 1
HbA1C ..... Hemoglobin A1C (Glycated hemoglobin)
HDL-C..... High density lipoprotein cholesterol
HHS..... Hyperglycemic hyperosmolar state
HMW..... High molecular weight
HOMA-IR..... Homeostatic model assessment of insulin resistance
HS ..... Highly significant
HSL ..... Hormone-sensitive lipase
HSPs ..... Heat shock proteins
HTR2B ..... Hydroxytryptamine receptor 2B
IA-2A, IA-2βA Insulinoma-associated antigens
IAAs..... Insulin auto-antibodies
ICAs..... Islet cell cytoplasmic auto-antibodies
IDDM ..... Insulin dependent diabetes mellitus
IDF..... International Diabetes Foundation
IFG ..... Impaired fasting glucose
IGT ..... Impaired glucose tolerance
IL-1β..... Interleukin-1β
IL-6..... Interleukin-6
IL-10..... Interleukin-10
IL13RA2 ..... Interleukin-13 receptor alpha2

IL-18..... Interleukin-18
INF-γ ..... Interferon-γ
IR..... Insulin resistance
IRS-1 ..... Insulin receptor substrate-1
LA..... Lactic acidosis
LDL-C..... Low density lipoprotein cholesterol
LPL..... Lipoprotein lipase
LS..... Lesional skin
LV..... Liver tissue
MCP-1..... Monocyte chemotactic protein 1
MEIA..... Micro-particle enzyme immunoassay
MMPs..... Matrix metalloproteinases
MS ..... Metabolic syndrome
NAFLD..... Nonalcoholic fatty liver disease
NASH ..... Nonalcoholic steatohepatitis
NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III
NCP ..... Nitrocellulose paper
ND..... Not detected
NIDDM ..... Non insulin dependent diabetes mellitus
NLS..... Non-lesional skin
NPV ..... Negative predictive value
NS ..... Non significant
OGTT..... Oral glucose tolerance test
OSA ..... Obstructive sleep apnea
Ox-LDL..... Oxidized low density lipoprotein
PCOS..... Polycystic ovarian syndrome
PCR ..... Polymerase chain reaction
PPBG..... Post-prandial blood glucose
PPV..... Positive predictive value
QC ..... Quality control
QUICKI ..... Quantitative insulin sensitivity check index
RARRES2..... Retinoic acid receptor responder 2
ROC..... Receiver operator characteristics

RT-PCR ..... Reverse Transcriptase Polymerase Chain Reaction
RV..... Reaction vessel
S ..... Significant
SBP ..... Systolic blood pressure
SD ..... Standard deviation
SDS-PAGE..... Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SLC16A..... Solute linked carrier 16A
SM ..... Skeletal muscle
SPSS ..... Statistical package for social sciences
SSC ..... Skin squamous cell carcinoma
TC..... Total cholesterol
TG..... Triglycerides
Th-1 ..... T helper 1
TIG2 ..... Tazarotene induced gene 2
TN..... True negative
TNF-α..... Tumour necrosis factor-α
TP ..... True positive
Type 1 DM..... Type 1 diabetes mellitus
Type 2 DM..... Type 2 diabetes mellitus
VLDL ..... Very low density lipoprotein
WA..... White adipose tissue
WC..... Waist circumference
WHO ..... World Health Organization

List of Tables

Table No.	Table Title	Page No.
1	Etiological classification of diabetes mellitus	7
2	Classification of diabetic complications	16
3	The ADA recommendation for diabetes diagnosis and other high risk categories	25
4	Diagnosis of GDM	26
5	Definitions of the metabolic syndrome	35
6	Ethnicity-specific values for waist circumference	37
7	Baseline characteristics of included subjects	116
8	Statistical difference between study groups concerning clinical parameters using Mann-Whitney's U-test	119
9	Statistical difference between study groups concerning laboratory parameters using Mann-Whitney's U-test	120
10	Statistical difference between study groups concerning clinical parameters using Kurskal Wallis test	121
11	Statistical difference between study groups concerning laboratory parameters using Kurskal Wallis test	122
12	Correlation analysis between serum chemerin level and other variables using Spearman's rank correlation coefficient in all patients' groups	124
13	Univariate analysis of measured parameters as predictors of metabolic syndrome	125

List of Figures

Figure No.	Figure Title	Page No.
1	The pathophysiology of the metabolic syndrome	39
2	Mechanism of insulin resistance	43
3	The pathophysiology of the metabolic syndrome and insulin resistance	50
4	Proinflammatory molecules and the metabolic syndrome	56
5	Pathophysiology of atherosclerosis in the metabolic syndrome	63
6	Structure of G-protein coupled receptor	74
7	The regulation of chemerin actions by active, pro-inflammatory chemerin and inhibitory chemerin-derived peptides	77
8	The role of chemerin and CMKLR1 in adipose tissue biology	78
9	Principle of sandwich Enzyme Linked Immunosorbant Assay	88
10	Polymerase chain reaction	91
11	Chemerin expression in healthy and diseased skin	93
12	Western blot method	96
13	Detection of chemerin in tissues using western blot technique	97
14	Chemerin ELISA standard curve	110
15	Box-Plot Chart showing difference between study groups concerning serum chemerin level	123
16	ROC curve for serum chemerin as a predictor of metabolic syndrome showing its best cutoff point	126

INTRODUCTION

Type 2 diabetes mellitus is a group of disorders characterized by hyperglycemia and associated with microvascular (i.e. retinal, renal, neuropathic) and macrovascular (i.e. coronary, peripheral vascular) complications. Hyperglycemia results from lack of endogenous insulin or resistance to the actions of insulin in muscle, fat and the liver. In addition to an inadequate response by the pancreatic beta cell ***(Wolfs et al., 2009).***

Type 2 diabetes accounts for 90 to 95% of the incidence of diabetes. It is predicted that by the year 2025, 324 million people will be diabetic. The explosive increase in number of people diagnosed with diabetes makes this disease a real health threat in the 21st century. Understanding the etiology and finding a way to prevent type 2 diabetes is an urgent challenge for the health care of our society ***(Cheng, 2005).*** .

The metabolic syndrome is a cluster of coronary heart disease (CHD) risk factors including high blood pressure, dyslipidemia, hyperglycemia and central obesity that are associated with decreased ability of insulin to stimulate glucose disposal on peripheral target tissues, referred to as insulin resistance ***(Reaven, 2004).***

Insulin resistance is determined by impaired sensitivity of insulin to its main target organs, i.e. adipose tissue, liver, and muscle. Obesity, particularly central obesity, is the prominent risk

factor for insulin resistance and results in type 2 diabetes and metabolic syndrome. More evidence has emerged that obesity is associated with inflammation that is causally involved in the development of insulin resistance ***(Zeyda et al., 2009).***

Adipose tissue represents an active endocrine organ that releases a large number of bioactive mediators (adipokines) that signal to organs of metabolic importance including brain, liver, skeletal muscle, and the immune system thereby modulating hemostasis, blood pressure, lipid and glucose metabolism, inflammation and atherosclerosis. These adipokines include adiponectin, leptin, omentin, resistin, retinol binding protein 4, tumor necrosis factor-α, interleukin-6, vaspin, visfatin and chemerin ***(Rabe et al., 2008).***

Chemerin, also known as tazarotene induced gene 2 (TIG2) and retinoic acid receptor responder 2(RARRES2), is an adipokine that has been reported to modulate immune system function through its binding to the chemerin receptor ***(Roh et al., 2007).***

Chemerin is secreted as an 18kDa inactive pro-protein and undergoes extracellular serine protease cleavage of the C-terminal portion of the protein to generate the 16kDa active chemerin which is present in plasma and serum ***(Stejskal et al., 2008).*** It is secreted by the mature adipocytes and expressed abundantly in adipose tissue in vivo. Furthermore, chemerin and its receptor/ChemR23 are expressed in mature adipocytes, suggesting

its function in autocrine/paracrine fashion ***(Takahashi et al., 2008).***

It has been reported that chemerin serves as a chemoattractant for cells of the immune system such as macrophages and immature dendritic cells that express the cognate receptor chemokine-like receptor-1 (CMKLR1). Also chemerin acts as a positive regulator of adipocyte differentiation ***(Goralski et al., 2009).***

Recent studies have shown that obesity induces inflammation in adipose tissue and since chemerin is a proinflammatory cytokine that recruits and activates immune cells, it may link obesity and inflammation. Therefore, a possible relation of chemerin to inflammatory proteins in obesity and type 2 diabetes is demonstrated ***(Weigert et al., 2009).***

It has been demonstrated that chemerin is strongly associated with markers of inflammation and components of metabolic syndrome ***(Lehrke et al., 2009).***

Furthermore, chemerin is also related to insulin level, body fat deposition and lipid metabolism suggesting that it may play a role in the pathophysiology of obesity and metabolic syndrome ***(Wang et al., 2009).***