

The Clinical Significance of Serum Chemerin in Type 2 Diabetic Patients with Renal Dysfunction

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

(... رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ
الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ
وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ وَأَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

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List of Abbreviations

ADA	: American Diabetes Association
AGEs	: advanced glycosylation ends
AHA/NHLBI	: American Heart Association and National Heart Lung and Blood Institute
ATP-III	: Adult Treatment Panel III
AUC	: Area under curve
BMI	: Body mass index
BTP	: β -Trace Protein
CCNB2	: Cyclin B2
CCRL2	: Chemokine receptor like 2
CKD	: Chronic kidney disease
CTGF	: Connective tissue growth factor
DCs	: Dendritic cells
DKA	: Diabetic ketoacidosis
DM	: Diabetes mellitus
EGIR	: European Group for the Study of Insulin Resistance
ELISA	: Enzyme-linked immuno sorbent assay
EMME	: Mediterranean and Middle East Region
ERK	: Extracellular signal–regulated kinase
ESRD	: End stage renal disease
FITC	: Fluorescein isothiocyanate
FN	: False Negative
GAD65	: Glutamic acid decarboxylase
GBM	: Glomerular basement membrane
GDM	: Gestational Diabetes Mellitus
GFR	: Glomerular filtration rate
GHB	: Glycated hemoglobin
GLDH	: Glutamate dehydrogenase
HbA_{1c}	: Hemoglobin A1c
HDL-C	: High-density lipoprotein-cholesterol
HHS	: Hyperglycemic hyperosmolar state
HOMA-IR	: Homeostasis model assessment of insulin resistance
HPLC	: High-performance liquid chromatography
HRP	: Horseradish peroxidase

List of Abbreviations (*Cont...*)

HTR2B	: Hydroxytryptamine receptor 2B
IAAs	: Insulin autoantibodies
ICAs	: Islet cell cytoplasmic antibodies
IDDM	: Insulin dependent diabetes mellitus
IDF	: International Diabetes Federation
IFG	: Impaired fasting glucose
IGT	: Impaired glucose tolerance
IL13RA2	: Interleukin-13 receptor alpha2
IL-6	: Interleukin 6
IQR	: Median Interquartile range
IR	: Insulin resistance
LA	: Lactic acidosis
L-FABP	: Liver-type fatty acid binding protein
MDRD	: Modification of Diet in Renal Disease formula
MENA	: Middle East and Northern Africa
MS	: Metabolic syndrome
NCEP	: National Cholesterol Education Program
NCP	: nitrocellulose paper
NIDDM	: Non insulin dependent diabetes mellitus
NKDEP	: National Kidney Disease Education Program
OGTT	: Oral glucose tolerance test
PCR	: Polymerase chain reaction
PEG	: Polyethylene Glycol
PKC	: Protein kinase C
RARRES2	: Retinoic acid receptor responder 2
RBP4	: Retinol-binding protein 4
RIA	: Radio immunoassay
RID	: Radial immunodiffusion
RT-PCR	: Reverse Transcriptase Polymerase Chain Reaction
SD	: Standard Deviation
SDS-PAGE	: Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SMBG	: Self monitoring of blood glucose
SRID	: Single radial immunodiffusion
SSC	: Skin squamous cell carcinoma
TGFβ1	: Transforming growth factor-β1
TP	: True positive

List of Abbreviations (*Cont...*)

tPA	: Tissue plasminogen activator
UAE	: Urinary albumin excretion
U-LFABP	: Urinary L-FABP
WC	: Waist circumference
WHO	: World Health Organization
YLL	: Years of life lost
α 1-M	: α 1-microglobulin

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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*).

In 2003, the international diabetes federation (IDF) estimated that almost 200 million people around the world had diabetes, by 2025 this figure is expected to rise to 333 million. Egypt was considered one of the world's top 10 in terms of the highest number of diabetic patients in 2003 (3.9 million) and highest projected number of people with diabetes in 2025 (7.8 million) (*IDF, 2003*).

Diabetic nephropathy is a serious microvascular complication of diabetes mellitus. The decrease in renal function of diabetic nephropathy is characterized by glomerular dysfunction, which is closely related to elevated urinary albumin excretion. Diabetic nephropathy has been categorized into two stages, microalbuminuria ($30 < \text{urinary albumin excretion} < 300 \text{ mg/24h}$) and macroalbuminuria ($\text{urinary albumin excretion} > 300 \text{ mg/24h}$) (*Wenchao and Ping, 2010*). In addition, it is recommended that glomerular filtration rate be routinely estimated for appropriate screening of nephropathy,

because some patients present a decreased glomerular filtration rate while urine albumin values are in the normal range (*Themis et al., 2009*).

Adipose tissue represents an active endocrine organ that release 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, 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, a recently discovered adipocytokine, has been associated with autocrine/paracrine signaling for adipocyte differentiation and maturation. In addition, it can regulate glucose uptake and stimulate lipolysis via phosphorylation of some intermediates in human adipocytes which are involved in mediating lipolysis and insulin signaling pathway (*Goralski et al., 2007*).

Several studies suggested that it could induce insulin resistance in skeletal muscle cells. Thereby, it is thought to be elevated in adipose tissue of type 2 diabetic patients. Furthermore, chemerin levels have been reported to be associated with components of the metabolic syndrome, including elevated levels of body mass index (BMI), plasma triglycerides and blood pressure (*Bozaoglu et al., 2007 and Sell et al., 2009*).

Recently, serum chemerin levels were found to be significantly higher in patients on chronic hemodialysis compared with controls, suggesting that determinants of renal function are independently related to circulating chemerin levels. Therefore, serum chemerin concentration might be altered in patients with diabetic nephropathy (*Pfau et al., 2010*).