Clinical Utility of Serum Adipocyte Fatty Acid Binding Protein (A-FABP) in Type 2 Diabetes Mellitus Patients Complicated with Metabolic Syndrome

Thesis

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By

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Safiya El-Fiky

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List of Abbreviations

Abb.	Full term
1,5AG	*1, 5 anhydroglucitol*
ABCA1	*α-adenosine triphosphate -binding cassette A1*
AC-PKA	*Adenyl cyclase protein kinase A*
ADA	*American Diabetes Association*
A-FABP	*Adipocyte fatty acid binding protein*
AP1	*Adaptor protein 1*
ATP	*Adenosine Triphosphate*
ATP-III	*Adult Treatment Panel III*
AUC	*Area under the curve*
bFGF	*Basic fibroblast growth factor*
BMI	*Body mass index*
CE	*Cholesterol Esterase*
CRP	*C- reactive protein*
CVD	*Coronary vascular diseases*
DKA	*Diabetes Ketoacidosis*
DM	*Diabetes mellitus*
DM2	*Type 2 DM*
ELISA	*Enzyme-linked immunosorbent assay*
eNOS	*Endothelial nitric oxide synthase*
ER	*Endoplasmic Reticulum*
ESI	*Electrospray ionization*
EVs	*Extracellular vesicles*
FA	*Fructosamine*
FFAs	*Free fatty acids*
G-6-P	*Glucose-6-phosphate*
GA	*Glycated albumin*

List of Abbreviations (Cont...)

Abb.	Full term
GAD	*Glutamic acid decarboxylase*
GC-PKG	*Guanylyl cyclase - protein kinase G*
GDM	*Gestational diabetes mellitus*
GLUT4	*Glucose transporter 4*
GPLD1	*Glycosylphosphatidylinositol-specific phospholipase D1*
HbA1c	*Glycated hemoglobin*
HDL-C	*High-density lipoprotein-cholesterol*
HF	*Heart failure*
HHS	*Hyperglycemic hyperosmolar state*
HLA	*Human leucocytes antigen*
HOMA-IR	*Homeostasis model assessment of insulin resistance*
HPLC	*High-performance liquid chromatography (*
HRP	*Horseradish Peroxidase*
HSL	*Hormone sensitive lipase*
IDF	*International Diabetes Federation*
IEF	*Isoelectric focusing*
IFG	*Impaired fasting glucose*
IGF	*Insulin-like growth factor*
IGT	*Impaired glucose tolerance*
IKK	*Inhibitor kappa kinase*
IL-18	*Interleukin18*
IL-6	*Interleukin 6*
IR	*Insulin resistance*
IRS	*Insulin receptor substrate*

List of Abbreviations (Cont...)

Abb.	Full term
LDL-C	*Low density lipoprotein - cholesterol*
L-GPC	*L-alpha glycerylphosphorylcholine*
LXR-α	*Liver X receptor-α*
MALDI	*Matrix-assisted laser desorption*
MAP	*Mitogen-activated protein*
MASP	*MBL associated serine protease*
MBL	*Mannose Binding Lectin*
MetS	*Metabolic syndrome*
miRNA	*microRNA*
MODY	*Maturity-onset diabetes of the young*
MS	*Mass spectrometry*
MS/MS	*Tandem mass spectrometry*
MW	*Molecular weights*
NAD	*Nicotinamide adenine dinucleotide*
NCEP	*National Cholesterol Education Program*
NF-Kβ	*Nuclear factor-κB*
NPR-A	*Natriuretic peptide receptor-A (*
NPY	*Neuropeptide Y*
OD	*Optical Density*
OGTT	*Oral glucose tolerance test*
PAD	*Peripheral arterial disease*
PAI-1	*Plasminogen Activator Inhibitor-1*
PCOS	*Polycystic ovary syndrome*
PI3K	*Phosphatidylinositol-3'-kinase*
PPAR-γ	*Peroxisome proliferator-activated receptor gama*

List of Abbreviations (Cont...)

Abb.	Full term
RAAS	*Renin angiotensin- aldosterone system*
ROC	*Receiver operating characteristic*
ROS	*Reactive oxygen species*
SD	*Stander deviation*
SDS	*Sodium dodecyl sulfate*
SDS-PAGE	*Sodium dodecyl sulfate -polyacrylamide gel electrophoresis*
TG	*Triglyceride*
TGF-β	*Transforming growth factor beta*
Th1	*T-helper 1*
Th2	*T-helper 2*
THBS1	*Thrombospondin 1*
TLR4	*Toll Like Receptor 4*
TMB	*3, 3', 5, 5'-Tetramethylbenzidine*
TNF- α	*Tumor necrosis factor-α*
VEGF-A	*Vascular endothelial growth factor-A*
VEGFR2	*Vascular endothelial growth factor receptor-2*
VLDL-C	*Very low density lipoprotein- cholesterol*
WC	*Waist circumference.*
WHO	*World Health Organization*
α -KB	*α -Keto butyrate*
α-HB	*Alpha-hydroxybutyrate*

Abstract

Objective: The adipocyte fatty acid-binding (A-FABP) has been described as a biomarker for adiposity and obesity-related disease. The aim of this study was to assess the association between fasting serum A-FABP level and the development of metabolic syndrome (MetS) among type 2 DM patients.

Methods: Fasting blood samples were obtained from 60 type 2 diabetic patients for assessment of serum A-FABP level (30 subjects without MetS and 30 subjects with MetS) compared to 30 healthy control subjects recruited from Endocrinology Department, Ain Shams University Hospitals. A-FABP protein was assayed using ELISA technique, MetS component (waist circumference, fasting serum glucose, triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and blood pressure), as well as homeostasis model assessment of insulin resistance (HOMA-IR) and highly sensitive C-reactive protein (hsCRP) were assayed for all subjects.

Results: Diabetic persons who had MetS had significantly higher serum A-FABP levels than either without MetS or healthy controls [Median (25-75 percentiles): 10.5(8.25-14.25); 3.4(0.20-6.00) and 1.5(0.78-2.63) respectively; $P<0.01$). However (HOMA-IR) and hsCRP did not show significant difference between diabetic patients with MetS versus diabetic patients without MetS ($P>0.05$).

Conclusions: Our results indicate that serum A-FABP level is an early marker for the development of MetS in type 2 DM patients, thus its assessment could be beneficial in diagnosis of MetS.

Keywords: A-FABP, Type 2 DM, Metabolic Syndrome, HSCRP, HOMA-IR

INTRODUCTION

Type 2 diabetes mellitus (Type 2 DM) is the most common form of diabetes mellitus and accounts for over 90% of all cases. It was formerly referred to as non-insulin-dependent diabetes mellitus. Type 2 diabetes mellitus is adult onset, is characterized by insulin resistance, and may also be accompanied by beta cell dysfunction causing insulin deficiency ***(Dasgupta and Wahed, 2013).*** Type 2 diabetes is significantly linked to obesity, a sedentary lifestyle, and aging. Genetic predisposition has also been established. The mechanism of type 2 diabetes involves increasing cellular resistance to insulin which results in a compensatory hypersecretion of insulin from the pancreatic beta cells that ultimately leads to a failure in insulin production ***(Dasgupta and Wahed, 2013).***

Metabolic syndrome (MetS) is a cluster of least three of the five following medical conditions. (1)Abdominal central obesity waist circumference ≥ 102 cm (male), ≥ 88 cm (female). (2) Dyslipedemia: TG ≥ 150 mg/dL. (3) Dyslipidemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female). (4) Blood pressure ≥ 130/85 mmHg (or treated for hypertension). (5) Fasting plasma glucose ≥ 110 mg/dL ***(Kaur, 2014).***

Adipocyte fatty acid binding protein (A-FABP) is one of the most abundant proteins in mature adipocytes. It is known for the ability to bind fatty acids and related compounds

throughout various cellular compartments including peroxisomes, mitochondria, endoplasmic reticulum, lipid droplets and nucleus ***(Fantuzzi, 2015).***

A-FABP has been shown to affect insulin sensitivity, lipid metabolism and lipolysis in animal studies. Furthermore, studies also found that A-FABP is a key mediator for the obesity-related cardiovascular disease ***(Xu and Vanhoutte, 2012).***

Recent evidence demonstrates circulating A-FABP level to be an independent predictor of the development of metabolic syndrome after adjustment for the effects of adiposity and the possible pharmacological utility ***(Furuhashi et al., 2015).***