Resistin and its Relation to Inflammation and Insulin Resistance in Morbidly Obese

Thesis

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BY

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ADSF	Adipocyte-secreted factor
AgRP	Agouti-related protein
Akt	A family of sereine proteases
AMPK	AMP-activated protein kinase
apoB	apolipoprotein B
AT	Adipose tissue
ATF-2	Activating transcriptional factor 2
ATP	adenosine triphosphate
BMI	Body mass index
CCR5	C-C chemokine receptor type 5
CKK	Cholecystokinin
CRP	C reactive protein
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
DCs	Dendertic cells
EDHF	Endothelium-derived hyperpolarizing factor
eNOS	Endothelial Nitric oxide synthase
ER	Endoplasmic reticulum
ET-1	Endothelin-1
FBG	Fasting blood glucose
FFAs	free fatty acids
FIZZ3	Found in inflammatory zone 3
FOXO1	Forkhead box protein O1
FoxP3	Forkhead box protein 3
G-6-Pase	Glucose-6-phosphatase
GH	Growth hormone
GIP	Gastric inhibitory peptide
GLP-1	Glucagon like peptide-1

GLUT4	Glucose transporter
HDL	High density lipoprotein
HGF	Hepatocyte growth factor
HIF-1	Hypoxia-inducible factor-1
HOMA-IR	Homeostatic model assesment of insulin resistance
ICAM-1	Intracellular adhesion molecule-1
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IFN-γ	Interferon-γ
IGT	Impaired glucose tolerance
IKK	Kinase inhibitor of NF-Kb
IL-12	Interleukin 12
IL-15R α	Interleukin 15 receptor alpha
IL-1RA	Interleukin 1 receptor antagonist
IL-6	Interleukin 6
IR	Insulin resistance
IRF1	Interferon regulatory factor 1
IRS-1	Insulin receptor substrate-1
JNK	c-Jun NH2-terminal kinase
KATP	ATP- sensitive potassium channels
KDa	Kilo-Dalton
LDL	Low density lipoprotein
LIF	Leukemia inhibitor factor
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemo-attractant protein-1
MIF	Macrophage migration inhibitory factor
MMP	Matrix metalloproteas

MS	Metabolic syndrome
NCEP	National Cholesterol Education Program
NEFAS	Non-esterified fatty acids
NF-κβ	Nuclear factor kappa beta
NHLBI	National Heart, Lung, and Blood Institute
NK cells	Natural killer cells
NO	Nitric oxide
NPY	Neuropeptide Y
ob /ob	Mouse lacks the functional form of leptin
Ob gene	Obese gene
OHS	Obesity hypoventilation syndrome
OSA	Ostructive sleep apnea
PAI-1	Plasminogen activator inhibitor type 1
PBMC	Peripheral blood mononuclear cells
PEPCK	phosphoenolypyruvate carboxykinase
PI3K	Phosphatidylinositol triphosphate kinase
PKC-θ	Protein kinase C-θ
POMC	Pro-opiomelanocortin
PPARγ	Peroxisome proliferator activated receptor gamma
PTEN	Phosphatase and Tensin Homolog Deleted on Chromosome Ten
PTX3	Pentraxin 3
PYY	Peptide YY
RELMs	Resistin like molecules
RETN	gene coding for resistin
ROS	Reactive oxygen species
SIRS	Systematic inflammatory response syndrome
SNPs	Single-nucleotide polymorphisms
SOCS-3	Suppressor of cytokine signaling-3

T2DM	Type 2 diabetes mellitus
TG	Triglycerids
TGF-β	Transforming growth factor-beta
TNF-α	Tumour necrosis factor alpha
TRAF-3	TNF-receptor-associated factor-3
TZDS	Thiazolidinedions
VCAM-1	Vascular wall adhesion molecule-1
VEGF	Vascular endothelial growth factor
VLDL	Very low density lipoproteins
WC	waist circumference
WHR	waist-to-hip ratio
α-MSH	α-melanocyte stimulating hormone

INTRODUCTION

Most attention in recent years has been devoted to the concept that obesity elicits a chronic low-grade systemic inflammatory response that results from a combination of increased insulin resistance and an increased production of inflammatory mediators by the expanding pool of adipocytes **(Rensen et al., 2009).**

Several research studies in different population indicate that inflammation may be the link between obesity and insulin resistance **(Doumatey et al., 2010)**.

Obesity is a common risk factor for dyslipidemia, insulin resistance, type 2 diabetes, hypertension and atherosclerosis, a cluster of metabolic abnormalities included in metabolic syndrome **(Grunfy et al., 2004).**

Numerous evidences suggest that fat tissue is viewed as an active endocrine organ with high metabolic activity **(Kershaw et al., 2004).** Adipocytes produce and release several bioactive substances that act as true hormones responsible for the regulation of energy intake and expenditure **(Mora et al., 2002).** The dysregulation in the production of these hormones, called adipocytokines, can contribute to the proinflammatory environment

associated with obesity **(Vendrell et al., 2004)**.

Following the observation that serum concentration of the number of inflammatory markers including CRP, TNF-a, and interleukin 6 are elevated in over weight and obese individuals, obesity is now viewed as a low grade inflammatory disease **(Fantuzzi, 2005).**

Taken these data inconsideration one could argue for a role of the adipose tissue as a new member of the innate immune system **(Anderson et al., 2007).**

Among the proteins synthesized and released from adipose tissue (adiponectin, angiotensin, estradiol, IL-6, leptin and TNF-a) resistin is an adipocyte secreted hormone belonging to a cysteine – rich protein family. It is expressed in white adipose tissues in rodents and has also been found in several other tissues in human**.** Insulin, glucose, many cytokines and anti-diabetic thiazolidinedione are regulators of resistin gene expression. Resistin was firstly proposed to be involved in insulin resistance and type 2 diabetes mellitus. Recently, it was found to be relevant to inflammation and inflammation related diseases like atherosclerosis and arthritis **(Shanshan and Yingying, 2006).**

It was found that resistin might link obesity with insulin resistance and diabetes in mice models. However, subsequent studies in rodent models have produced disparate findings on the role of resistin in obesity and insulin resistance **(Le Lay et al., 2001).**

In humans, while the expression of resistin in human adipocytes is very low compared with that seen in rodents and does not differ between normal, insulin-resistant or type 2 diabetic individuals, a more recent study using a large size of case suggests that the plasma resistin levels are increased in type 2 diabetes **(Engert et al., 2002).** Genetic case-control studies have demonstrated that genetic variations in the resistin gene are associated with insulin resistance and obesity **(Rajala et al., 2003)**.

More recently; it has been shown that resistin acts on the liver and antagonizes insulin signaling; thereby increasing gluconeogenesis and hepatic glucose output **(Cho et al., 2004).**

Therefore determination of the plasma resistin levels may be important for understanding onsets of metabolic diseases such as type 2 diabetes that is considered as a complication of obesity.

AIM OF THE WORK

The aim of the present study is to determine serum concentrations of resistin in morbidly obese patients in comparison to normal weight controls. It is also designed to assess the possible relation of resistin to the high sensitivity CRP as an inflammatory marker and to insulin resistance in morbidly obese.