VISFATIN IN TYPE II DIABETES MELLITUS

Thesis

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Abstract

Type II Diabetes Mellitus is considered as one of the major metabolic diseases of twenty first century. Characterized by alteration in the carbohydrate, fat, protein metabolism. Obesity can affect beta cell directly through influence of free fatty acid (lipotoxicity), or remotely through group of cytokines secreted by adipose tissue (adipokines). Visfatin (pre B cell colony enhancing factor) is a novel adipokine that appears to be produced by visceral adipose tissue and has insulin mimetic actions. Both its tissue expression and secreted plasma levels increase in parallel with obesity.

Key Words:

Type II Diabetes Mellitus – Obesity- Visfatin

Abbreviations

ACE	**Angiotensin converting enzyme**
AER	**Albumin excretion rate**
AGE	**Advanced glycation end product**
ASP	**Adipsin and acylation stimulating protein**
AT1	**Angiotensin receptors type I**
BMI	**Body mass index**
CAD	**Coronary artery disease**
CCK-B	**Cholecystokinin-B**
DKA	**Diabetic ketoacidosis**
DSPN	**Distal symmetrical polyneuropathy**
ECM	**Extracellular matrix**
ESRD	**End stage renal disease**
FFA	**Free fatty acid**
FPG	**Fasting plasma glucose**
GAD	**Glutamic acid decarboxylase**
GAPDH	**Glyceraldehyde 3-phosphate dehydrogenase**
GDM	**Gestational diabetes mellitus**
GH	**Growth hormone**
GLUT-2	**Glucose transporter-2**
HbA1c	**Hemoglobin A1c**
HDL	**High density lipoprotein**
HIF	**Hypoxia-inducible factor**
HLA	**Human leucocytic antigen**

HNF	Hepatic nuclear factor
$HOMA_{IR}$	Homeostasis model assessment of insulin resistance
HPA	Hypothalamic-pituitary-adrenal
11ßHSD1	11ß-Hydroxysteroid dehydrogenase type 1
ICA	Islet-cell antibodies
ICAM1	Intercellular adhesion molecule-1
IDDM	Insulin-dependant diabetes mellitus
IGF	Insulin like growth factor
IL-1	Interleukin-1
IPF	Insulin promoter factor
IRS-1	Insulin receptor substrat-1
LADA	latent autoimmune diabetes in adults
LDL	Low density lipoprotein
MAPK-1	Mitogen-activated protein kinase-1
MCP	Macrophages and monocyte chemoattractant protein
MODY	Maturity-onset diabetes of the young
NAFLD	Non-alcoholic fatty liver disease
NEFAs	Non-esterified fatty acids
NIDDM	Non insulin-dependant diabetes mellitus
NPDR	Nonproliferative diabetic retinopathy
OGTT	Oral glucose tolerance test
PAI-1	Plasminogen activator inhibitor-1
PARP-1	Poly ADP-ribose polymerase-1
PBEF	Pre B cell colony enhancing factor
PCI	Percutaneous coronary intervention

PDR	Proliferative diabetic retinopathy
PI-3	Phosphatidylinositol-3
PKC	Protein kinase C
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PRRs	Pattern recognition receptors
RAS	Renin angiotensin system
ROS	Reactive oxygen species
SOCS-3	Suppressor of cytokine signalling-3
TCF7-L2	Transcription factor 7-like 2 gene
TNF-α	Tumor necrosis factor-α
TRH	Thyrotrophin releasing hormone
TSH	Thyroid stimulating hormone
VCAM1	Vascular cell-adhesion molecule-1
VEGF	Vascular endothelial growth factor
WAT	White adipose tissue
WHO	World Health Organization

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INTRODUCTION

Type II Diabetes Mellitus is considered as one of the major metabolic diseases of twenty first century. Characterized by alteration in the carbohydrate, fat, protein metabolism. From the pathophysiologic point of view type II Diabetes mellitus was thought to result from two seemingly distinct pathologic processes peripheral insulin resistance and beta cell failure, both have been strongly linked to visceral fat accumulation and obesity ***(Chen MP et al 2006).***

Obesity can affect beta cell directly through influence of free fatty acid (lipotoxicity), or remotely through group of cytokines secreted by adipose tissue (adipokines) as leptin, omentin, resistin, visfatin and others, so adipose tissue is considered as an active endocrinal organ capable of synthesizing and secreting hormones (adipokines)
(Fantuzzi, G 2005).

Visfatin (pre B cell colony enhancing factor) is a novel adipokine that appears to be produced by visceral adipose tissue and has insulin mimetic actions. Both its tissue expression and secreted plasma levels increase in parallel with obesity. Although visfatin is preferentially produced in visceral adipose tissue it can be found in skeletal muscle, liver, bone marrow, and lymphocyte. Visfatin expression is regulated by cytokines that promote insulin resistance ***(Fukuhara A et al 2005).***

So, this study aimed to investigate the relation between visfatin and type 2 diabetes and whether obesity have a role at increasing hormonal level of visfatin in the blood of type 2 diabetic patients.

AIM OF THE WORK

To study the relation of plasma visfatin to type 2 diabetes mellitus and visceral liposity.

DIABETES MELLITUS

Diabetes Mellitus is a syndrome of disordered metabolism with inappropriate hyperglycemia due to either an absolute deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both ***(American Diabetes Association 2008).*** Traditionally, diabetes was classified according to the age of onset of symptoms into juvenile-onset versus adult-onset. In 1979, another classification divided diabetes into two main types according to insulin requirement into insulin-dependent and non insulin-dependent ***(WHO Expert Committee 1980).*** In 1997 an international committee of diabetologists recommended several changes in the classification of diabetes include:

1. The term insulin-dependant and non insulin-dependant diabetes mellitus and their acronyms IDDM and NIDDM were eliminated because they are based on pharmacologic rather than etiologic considerations.
2. The terms type 1 and type 2 diabetes are retained, with Arabic rather than roman numerals ***(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997).***

Etiologic Classification of Diabetes Mellitus *(American Diabetes Association 2008).*

Type 1 diabetes (B cell destruction, usually leading to absolute insulin deficiency). A. Immune-mediated B. Idiopathic **II. Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance). **III. Other specific types** A. Genetic defects of B cell function 1. Chromosome 12, HNF-1α (MODY 3) 2. Chromosome 7, glucokinase (MODY 2) 3. Chromosome 20, HNF-4α (MODY 1) 4. Chromosome 13, IPF-1 (MODY 4) 5. Chromosome 17, HNF-1β (MODY 5) 6. Chromosome 2, Neuro D1 (MODY 6) 7. Mitochondrial DNA 8. Others B. Genetic defects in insulin action 1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipoatrophic diabetes 5. Others C. Diseases of the exocrine pancreas 1. Pancreatitis 2. Trauma, pancreatectomy 3. Neoplasia 4. Cystic fibrosis 5. Hemochromatosis 6. Fibrocalculous pancreatopathy 7. Others D. Endocrinopathies 1. Acromegaly 2. Cushing's syndrome 3. Glucagonoma 4. Pheochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronoma 8. Others	**III. Other specific types (cont'd)** E. Drug- or chemical-induced 1. Vacor (rat poison) 2. Pentamidine 3. Nicotinic acid 4. Glucocorticoids 5. Thyroid hormone 6. Diazoxide 7. Beta-adrenergic agonists 8. Thiazides 9. Phenytoin 10. Alpha-interferon 11. Others F. Infections 1. Congenital rubella 2. Cytomegalovirus 3. Others G. Uncommon forms of immune-mediated diabetes 1. Stiff-man syndrome 2. Anti-insulin receptor antibodies 3. Others H. Other genetic syndromes sometimes associated with diabetes 1. Down's syndrome 2. Klinefelter's syndrome 3. Turner's syndrome 4. Wolfram's syndrome 5. Friedreich's ataxia 6. Huntington's chorea 7. Laurence-Moon-Biedl syndrome 8. Myotonic dystrophy 9. Porphyria 10. Prader-Willi syndrome 11. Others **IV. Gestational diabetes mellitus (GDM)**

HNF = hepatic nuclear factor

IPF = Insulin promoter factor

➢ Type 1 Diabetes Mellitus:

This form of diabetes is immune mediated in more than 90% of cases and idiopathic in less than 10%. It is a catabolic disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, pancreatic β cell fail to respond to all insulinogenic stimuli ***(Eisenbarth GS 2007).***

Diabetes mellitus type 1 occurs at any age but most commonly arises in children and young adults. Patients with type 1 diabetes have an absolute requirement for insulin therapy and will develop diabetic ketoacidosis (DKA) if not given insulin ***(American Diabetes Association 2008).***

Etiology of Type 1 Diabetes Mellitus

Type 1 diabetes is characterized by destruction of the pancreatic beta cells, leading to absolute insulin deficiency. It is classified into two subtypes (Type 1A and 1B) ***(Atkinson MA, Maclaren NK 1994).*** Type 1A diabetes mellitus results from autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans. This process occurs in genetically susceptible subjects is probably triggered by one or more environmental agents as infection with certain viruses as coxsackievirus B, cytomegalovirus, adenovirus, and mumps virus, and usually progresses over many months or years during which the subject is asymptomatic and euglycemic. This long latent period is a reflection of the large number of functioning

beta cells that must be lost before hyperglycemia occurs. Type 1B diabetes mellitus refers to non-autoimmune islet destruction (idiopathic) ***(Atkinson MA, Maclaren NK 1994).***

Since the discovery of autoantibodies directed against pancreatic beta-cell antigens, it has been recognized that some adults who considered having type 2 diabetes probably have type 1 diabetes. Among adults with apparent type 2 diabetes, approximately 7.5 to 10% have type 1 diabetes as defined by the presence of circulating islet-cell antibodies (ICA), antibodies to glutamic acid decarboxylase (GAD). This is sometimes referred to as "latent autoimmune diabetes in adults" (LADA) ***(Leslie RD et al 2006).***

Latent autoimmune diabetes in adults (LADA) is defined as adult-onset diabetes with circulating islet antibodies but not requiring insulin therapy initially. Currently, there are no recommendations for islet antibody testing in type 2 diabetes. Five clinical features were more frequent in LADA compared with type 2 diabetes at diagnosis: 1) Age of onset < 50 years. 2) Acute symptoms. 3) Body Mass Index (BMI) < 25 kg/m^2. 4) Personal history of autoimmune disease. 5) Family history of autoimmune disease. The presence of at least two of these distinguishing clinical features (LADA clinical risk score ≥ 2) had a 90% sensitivity and 71% specificity for identifying LADA, so at least two distinguishing clinical features are found in a majority of patients with LADA at diagnosis and can be

used to identify adults with diabetes at higher risk for LADA ***(Fourlanos S et al 2006).***

LADA often does not require insulin at the time of diagnosis and may even be managed with changes in lifestyle in its early stages, but beta cells continue to be destroyed and LADA patients should be closely monitored. Some studies have demonstrated that the use of sulfonylureas and the insulin sensitizing drug as metformin may increase the risk of severe metabolic disorder in persons with LADA ***(A G Unnikrishnan et al 2004).***

Once blood glucose can no longer be managed through lifestyle and medications, daily insulin injections will be required ***(A G Unnikrishnan et al 2004).***

80% of persons initially diagnosed with type 2 but test positive for GAD (an indication of LADA) progress to insulin dependency within 6 years, but those who test positive for both GAD and islet antigen will progress more rapidly to insulin dependence ***(A G Unnikrishnan et al 2004).***

Studies on monozygotic twins suggest that genetic influences are less marked in type 1 diabetes than in type 2 diabetes and environmental factor is required for induction of diabetes in these cases. At least half of the familial aggregation of type 1 diabetes is accounted for by genes in the major histocompatibility locus on the short arm of chromosome 6. The