Study of selenoprotein p as a possible marker of insulin resistance in type 2 diabetes and chronic hepatitis C

Thesis

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قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ
الْحَكِيمُ

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Contents

List of Abbreviations

AACE	American Association of Clinical Endocrinologists
ALB	Albumin
ALT	Alanine amino transferase
AMPK	5′ Adenosine monophosphate- activated protein kinase
AST	Aspartate amino transferase
BMI	Body mass index
CHOL	Cholesterol
CVD	Cardiovascular disease
DM	Diabetes mellitus
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GLUT	Glucose transporter
GSK-3	Glycogen synthase kinase-3
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HDL	High density lipoprotein
HNF	Hepatic nuclear factor
HOMA-IR	Homeostasis model assessment estimate of insulin resistance
IDDM	Insulin - dependent diabetes mellitus
IDF	International diabetic federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IR	Insulin Resistance
IRS-I	Insulin Receptor substrate I
LADA	Latent autoimmune diabetes in adults
LDL	Low density lipoprotein
MAP	Mitogen-activated protein
MODY	Maturity onset diabetes in the young
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
PI3-K	Phosphatidylinositol 3-kinase
PPG	Postprandial plasma glucose
SeP	Selenoprotein P
T2DM	Type 2 diabetes mellitus

TG	Triglycerides
WHO	World Health Organization

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Introduction

Insulin resistance has been defined as a condition in which cells become resistant to the action of insulin; such that higher levels of insulin are needed to evoke the same cellular response. Insulin resistance is thus evaluated by the ability of insulin to control glycaemia ***(Lawrence and Jacqueline, 2009).***

Resistance to insulin-mediated glucose uptake plays a major role in the pathogenesis and clinical course of patients with type 2 diabetes mellitus ***(Reaven, 2011).***

The world prevalence of diabetes among adults (aged 20–79 years) is 6.4%, affecting 285 million adults, in 2010, and will increase to 7.7% and 439 million adults by 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries ***(Shaw et al., 2010)***.

Both insulin sensitivity and β-cell function predict conversion to diabetes in different ethnic groups and various states of glucose tolerance, family history of diabetes, and obesity. The prevention of type 2 diabetes should focus on interventions that improve both insulin resistance and insulin secretion ***(Marian et al., 2010).***

Hepatitis C virus (HCV) infection is gaining increased attention and is a global health crisis. Egypt reports the highest prevalence of HCV worldwide, ranging from 6% to more than 40% among regions and demographic groups ***(Lehman and Wilson, 2009).***

Chronic HCV can be considered a metabolic disease in view of its interaction with lipid metabolism leading to steatosis, and also its impairment of glucose metabolism leading to insulin resistance and diabetes. Indeed, there is a strong epidemiological link between HCV infection and diabetes, the prevalence of diabetes in patients with chronic hepatitis C has ranged from 20 to 50%; and This is higher than that reported for patients with other chronic liver diseases such as chronic HBV ***(Lawrence and Jacqueline, 2009).***

Furthermore ***Kerry et al., 2010 ;***considered hepatitis C is a liver disease that not only lead to cirrhosis and cancer but also makes people three to four times more likely to develop type 2 diabetes .

Selenoprotein P (SeP), a liver-derived secretory protein, causes insulin resistance. Hepatic SeP mRNA levels correlated with insulin resistance in humans. Administration of purified SeP impaired insulin signaling and dysregulate glucose metabolism in both hepatocytes and myocytes these results demonstrate a role of SeP in the

regulation of glucose metabolism and insulin sensitivity and suggest that SeP may be a therapeutic target for type 2 diabetes mellitus ***(Hirofumi et al., 2010)*** **.**

Circulating SeP concentrations were elevated in patients with glucose metabolism dysregulation and were related to various cardio metabolic parameters including insulin resistance, inflammation, and atherosclerosis ***(Yang et al., 2011).***

Aim of work

- To assess the relationship between insulin resistance and selenoprotein p in type 2 diabetes mellitus and chronic hepatitis C.

Diabetes mellitus

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels ***(American Diabetes Association, 2011).***

Several pathogenic processes are involved in the development of diabetes, these ranges from autoimmune destruction of B cells of the pancreas with consequent insulin deficiency to abnormalities that result to resistance to insulin action. The basis of abnormalities in carbohydrate, fat and protein metabolism in diabetes is deficient action of insulin on target tissues ***(American Diabetes Association, 2009).***

Diabetes mellitus (DM) comprises a group of common metabolic disorders sharing the phenotype of hyperglycemia. Several distinct types of DM exist caused by interaction of genetics, environmental factors and life style choices, Factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization and increase glucose production ***(Larry, 2006).*** The resulting hyperglycemia is associated with disorder of carbohydrate, fat and protein metabolism and can lead to