UNIVERSITI PUTRA MALAYSIA

COMPARISON OF THE EXPRESSION OF PI3K/AKT PATHWAY COMPONENTS IN TYPE 2 DIABETIC AND NON- DIABETIC HUMAN VOLUNTEERS *EX VIVO*

SOMAYEH ALSADAT HOSSEINI KHORAMI

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By

SOMAYEH ALSADAT HOSSEINI KHORAMI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

July 2018

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree of Doctor of Philosophy

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July 2018

Chair : Huzwah Khaza'ai, PhD
Faculty : Medicine and Health Sciences

Insulin resistance in T2DM has been characterized by several defects in insulin signalling. Insulin-stimulated glucose transport occurs via PI3K/AKT-dependent pathway which results in GLUT4 translocation from intracellular vesicles to the plasma membrane and increased glucose uptake. Upon stimulation of insulin, PI3K phosphorylates membrane phospholipids and converts PIP2 to PIP3. This complex phosphorylates/activates PDK1 leading to activation of AKT and co-localization at plasma membrane. PTEN phosphatase antagonizes PI3K/AKT signalling by converting PIP3 to PIP2. Overexpression of PTEN in T2DM, results in inhibition of AKT signalling pathway and GLUT4 translocation. The present cross-sectional study was performed to investigate the underlying transcription level of gene of interest in insulin signalling mechanism responsible for these defects based on the characterization of socio-demographic, biochemical properties, serum vitamin D and calcium level. Hence, real time-PCR was employed in this study to investigate the interaction on the gene of interest (GOIs) such as IRS1, PI3K, PDK1, AKT2, GLUT4, GSK3 and PTEN of fifty non-diabetic and fifty T2DM respondents. Findings provide evidence that the gene expression level of IRS and GSK3 was preserved while PI3K, AKT2, PDK1 and GLUT4 were expressed significantly ($P < 0.05$) lower in T2DM respondents compared to non-diabetic respondents. Glucose levels (HbA1c and FBS), lipid profiles (TC, TG, LDL and HDL) were tested by colorimetric enzymatic method, serum vitamin D and calcium were measured by HPLC and C-peptide levels were determined by ELISA. Glucose levels (HbA1c and FBS) in diabetic were significantly higher ($P < 0.05$) compared to non-diabetic respondents and C-Peptide did not show any significant difference. The average level of TC was found to be significantly higher

in diabetic respondents and LDL was significantly lower in diabetic respondents compared to non-diabetic. Current study indicates, only PTEN expression level had a significant relation with duration of diabetes. This finding suggests that PTEN may not be the cause of the reduced gene expression level of PI3K/AKT pathway in Type II diabetes. As the findings of the present study showed reduced gene expression level of PI3K, PDK, AKT2, GLUT4 in diabetic respondents compared to non-diabetic respondents, therefore, the impaired gene expression of PI3K/AKT pathway may play a primary role in the pathogenesis of the disease while PTEN is not the primary cause and it is up-regulated by the years of having diabetes.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
Sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PERBANDINGAN EKSPRESI MEKANISME PI3K/AKT DI ANTARA PESAKIT DIABETIK JENIS 2 DAN RESPONDEN BUKAN DIABETIK DALAM EX VIVO

Oleh

SOMAYEH ALSADAT HOSSEINI KHORAMI

Julai 2018

Pengerusi : Huzwah Khaza'ai, PhD
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Rintangan insulin dalam Diabetes Mellitus Jenis 2 (DMJ2) telah disifatkan oleh beberapa faktor gangguan dalam isyarat insulin. Pengangkutan glukosa dirangsang oleh insulin melalui laluan PI3K/AKT yang mencetuskan translokasi GLUT4 dari vesikel intrasel kepada membran plasma dan menggalakkan pengambilan glukosa ke dalam sel. Apabila insulin dirangsang, PI3K akan memfosforilasikan fosfolipid pada membran sel, dan menukarkan PIP2 kepada PIP3. Proses fosforilasi kompleks/pengaktifan gen PDK1, akan menyebabkan pengaktifan protein AKT dan ko-lokasi pada membran plasma. Walaubagaimanapun, gen PTEN menyebabkan kerencatan laluan PI3K/AKT dengan menukarkan semula PIP3 kepada PIP2. Di dalam penyakit DMJ2, gen PTEN akan terhasil secara banyak menyebabkan kerencatan terhadap laluan AKT dan translokasi pengangkutan GLUT4. Kajian keratan rentas ini dilakukan untuk menyiasat tahap transkripsi genetik dalam mekanisme isyarat insulin yang bertanggungjawab ke atas kecacatan ini dengan mengambil maklum demografik masyarakat, penelitian data biokimia, aras vitamin D serum dan kalsium. Oleh itu, kaedah "Real time-PCR" digunakan dalam kajian ini untuk menyiasat interaksi genetik (GOI) seperti IRS1, PI3K, PDK1, AKT2, GLUT4, GSK3 dan PTEN dalam darah lima puluh responden bukan diabetik dan lima puluh responden DMJ2. Penemuan kajian ini memberikan bukti bahawa tahap ekspresi gen IRS dan GSK3 dipelihara manakala PI3K, AKT2, PDK1 dan GLUT4 diekspresi lebih rendah dengan ketara ($P < 0.05$) dalam responden DMJ2 berbanding dengan responden bukan diabetik. Aras glukosa (HbA1c dan FBS), profil lipid (TC, TG, LDL dan HDL) telah diuji dengan kaedah enzim kolorimetrik manakala aras vitamin D dan kalsium dalam plasma diukur oleh HPLC dan tahap C-peptida ditentukan dengan menggunakan kaedah ELISA. Aras glukosa (HbA1c dan FBS) dalam pesakit DMJ2 adalah lebih tinggi ($P < 0.05$) berbanding dengan responden bukan diabetik dan C-Peptida tidak menunjukkan sebarang perbezaan yang ketara. Purata aras kolesterol adalah tinggi di dalam responden DMJ2 manakala LDL-C rendah

berbanding dengan responden bukan diabetik. Kajian semasa menunjukkan hanya ekspresi gen PTEN mempunyai hubung-kait yang signifikan dengan tempoh menghidap diabetes. Dapatan ini menunjukkan bahawa gen PTEN bukan penyebab utama yang mempengaruhi tahap ekspresi genetik pada mekanisme PI3K / AKT di T2DM. Penemuan kajian menunjukkan tahap pengurangan gen PI3K, PDK, AKT2, GLUT4 dalam responden DMJ2 berbanding dengan responden bukan diabetik, oleh itu, ekspresi gen laluan PI3K/AKT yang terganggu boleh memainkan peranan utama dalam patogenesis DMJ2, sementara gen PTEN bukanlah penyebab utama dan ia dipengaruhi oleh faktor tempoh pesakit menghidap diabetes.

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I certify that a Thesis Examination Committee has met on 6 July 2018 to conduct the final examination of Somayeh Alsadat Hosseini Khorami on her thesis entitled “Comparison of the Expression of PI3K/AKT Pathway Components in Type 2 Diabetic and Non-Diabetic Human Volunteers Ex Vivo” in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U. (A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

aPKC	Atypical Protein Kinase C
AKT	Protein Kinase B
AMV	Avian Myeloblastosis Virus
CETP	Cholesteryl Ester Transfer Protein
cDNA	Complementary Deoxyribonucleic Acid
Ct	Threshold Cycle
DAG	Diacylglycerol
DBP	Vitamin D–binding protein
DEPC	Diethyl Pyrocarbonate
dNTP	Deoxynucleotide
EDTA	Ethylenediaminetetraacetic acid
FA	Formaldehyde
FBS	Fasting Blood Sugar
GAPDH	Glyceraldehyde 3-Phosphate Dehydrogenase
gDNA	genomic DNA
GLUT	Glucose Transporter
GS	Glycogen Synthase
GSK	Glycogen Synthase Kinase
HbA1C	Hemoglobin A1C
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HKG	House Keeping Gene
HPLC	High Performance Liquid Chromatography
IGT	Impaired Glucose Tolerance
IL	Interleukin
IR	Insulin receptor
IRS	Insulin-receptor substrate
LDL	Low Density Lipoprotein
LPL	Lipoprotein Lipase
MMLV	Moloney Murine Leukemia Virus
MOPS	Morpholino Propane Sulfonic Acid
mRNA	Messenger ribonucleic acid
NaOH	Sodium hydroxide
NTC	No Template Control
25(OH) D	25-hydroxycholecalciferol
Oligo-dT	Deoxy-Thymidine Nucleotides
PDK	Phosphoinositide-Dependent Kinase
PHLPP	PH-domain leucine-rich repeat protein Phosphatase
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphotidylinositol-4,5-bisphosphate
PIP3	Phosphotidylinositol-3,4,5-triphosphate
PKB	Protein Kinase B (also known as AKT)
PKC	Protein Kinase C
PP1	Protein Phosphatase 1
PTPs	Protein Tyrosine Phosphatases

PTEN	Phosphatase with sequence homology to protein-tyrosine phosphatases and the cytoskeleton protein tensin
rRNA	Ribosomal Ribonucleic Acid
RNase	Ribonuclease
RNFD	Recombinant Electron Transport Complex Protein
Rpm	Revolutions per minute
RT	Reverse Transcriptase
RT-PCR	Real Time Polymerase Chain Reaction
Ser	Serine
SHIP	SH2-domain containing protein tyrosine Phosphatase
TC	Total Cholesterol
T2DM	Type 2diabetes Mellitus
TE	Tris-EDTA
TG	Triglyceride
TNF	Tumor Necrosis Factor
Tris•Cl	Tris base. HCl
3T3L1	a Cell line derived from mouse
Tyr	Tyrosine
UV	Ultraviolet
VDR	Vitamin D Receptor
VLDL	Very Low Density Lipoprotein
UPM	Universiti Putra Malaysia

CHAPTER 1

INTRODUCTION

1.1 Background of Study

WHO estimates that 364 million people have diabetes globally, and is expected to reach indefinite proportions by 2030 (Mathers & Loncar, 2006). The rapid increased phenomenon of Type 2 diabetes mellitus worldwide is termed as "tsunami of diabetes". Due to its insidious onset, diabetes remains undiagnosed which makes populations susceptible to life-threatening complications thus reduces the quality of life.

The prevalence of diabetes mellitus among Malaysians adults above 30 years of age has increased considerably during 1986 to 2012 (about four times over a 20-year period). In 1986 there were around 6.3% of the young populations with diabetic. This number escalated to approximately 8.3% in 1996, then rose dramatically to more than 14.9% in 2006. Since 2006 there has been a steady increase, with around 22.6% in 2012. In addition, a similar percentage of the population has been considered as pre-diabetes (with the prevalence of 21.7%). In the absence of immediate and effective interventions, these individuals are at very high risk of developing not only diabetes, but also cardiovascular disease, and all associated complications (Wan Nazaimoon et al., 2013). In consequent, without immediate and effective public health interventions, the current situation is enough to severely paralyze the healthcare system of this country.

Diabetes mellitus is a group of metabolic diseases with heterogeneous etiology, characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both. Two major forms of diabetes were identified as type 1 and type 2. Shortage or lack of insulin secretion due to autoimmune or viral destruction of β cells is responsible for type I diabetes that includes 5-10% of diabetic patients. Type 2 diabetes which is more prevalent covers more than 90% of diabetic patients (Olefsky et al., 2001) and usually begins as insulin resistance state (the cells do not use insulin properly). As the requirement for insulin rises, the pancreas gradually loses its ability to produce it (Barnard et al., 2006). In Type 2 diabetic patients, lack of insulin action and/or secretion induces hepatic glucose output by stimulating gluconeogenesis and glycogenolysis and inhibiting glycogen synthesis which causes development of hyperglycemia, especially during fasting time (Jensen et al., 2011). In addition, lipolysis in adipose tissue elevates circulating levels of free fatty acids. Liver converts fat into fatty acids and ketone bodies to produce energy. High production of ketones resulting in ketosis in uncontrolled diabetes (Manninen, 2004). Extra fatty acids in serum will be converted to phospholipid and cholesterol ester in liver which along with excess production of triglycerides in liver may be released to the blood as lipoproteins (Mittendorfer, 2011). In addition, disorders in serum urea and creatinine has been revealed in Type 2 diabetic patients (Nain et al., 2012).

Therefore, one of the functions of insulin is control of cellular glucose uptake in muscle and adipose tissue which is performed through the insulin signal transduction (Wasserman & Ayala, 2005). Insulin binds insulin receptor, which causes receptor autophosphorylation and activation. Activated insulin receptor then phosphorylates insulin receptor substrate-1 (IRS1), which subsequently forms a complex with phosphatidylinositol-3-kinase (PI3K) to produce phosphatidylinositol triphosphate (PIP3) which then interacts allosterically with phosphosinositide-dependent kinase 1 (PDK1). The PIP3-PDK1 complex phosphorylates protein kinases AKT and trigger glucose transporter (GLUT4) translocation to the cell membrane in order to absorb glucose. This pathway is regulated by the action of a number of other proteins such as PTEN (lipid phosphatases) which dephosphorylates activated insulin receptors (IR) and IRS1 and consequently convert PIP3 into PIP2. There are several feedback loops that modulate the effects of the insulin signalling pathway. AKT phosphorylates/ deactivates PTEN hence, impairs the function of PTEN as a negative signalling element, resulting in net positive feedback (Colomiere et al., 2009).

Besides molecular researches, there have been relatively little systematic investigations into the effects of specific vitamins and minerals on insulin sensitivity. Epidemiological investigations into the role of dietary factors and insulin resistance generally focus on specific nutrients, notably macronutrients (fat, carbohydrate, protein and, to a lesser extent, alcohol) or micronutrients (vitamins and minerals) while it is difficult to separate the health effects of specific nutrients. Epidemiological analysis reveals several candidates such as vitamin D, but in each case the evidence for specific physiological effects is limited (Choi et al., 2014).

1.2 Problem Statement

Overexpression of PTEN in T2DM, results in inhibition of AKT signaling pathway and GLUT4 translocation to the cell membrane, hence decrease the glucose uptake. In contrast, decreasing of PTEN expression, enhance insulin stimulated AKT and GSK3 phosphorylation (Leslie et al., 2012). Therefore, regulation of insulin function is performed by the balance between phosphorylation and dephosphorylation.

Moreover, based on tremendous results of some recent studies, there is a relationship between vitamin D and insulin sensitivity not only in both *in vitro* and *in vivo* studies but also in epidemiological and clinical studies. It has been documented that vitamin D deficiency and obesity in adult C57BL/6 mice entailed hyperinsulinemia and impaired expression level of the PI3K/AKT pathway components which caused impaired glucose homeostasis and insulin resistance (Borges et al., 2016). Also it has been demonstrated that vitamin D-induced activation of PI3K/AKT pathway through the down regulation of PTEN (Yang et al., 2015). .

However, the mechanism underlying the effects of vitamin D on insulin sensitivity has not been clarified. Vitamin D may modulate PTEN and/or other components of the AKT/PI3K pathway hence, affects insulin sensitivity and glucose homeostasis. Therefore, present research was aimed to investigate the gene transcription level of insulin signal transduction components and underlying mechanism responsible for the alterations and defects in Type 2 diabetic patients and also examine the plausible relationship between vitamin D and related GOIs as well as biochemical markers measured in the study.

1.3 Significance of Study

The proposed study is aimed to elucidate the plausible relationship between serum vitamin D ($25(OH)D_3$ concentration and the expression level of genes involved in insulin signal transduction in non-diabetic and diabetic respondents. Results from the proposed study will contribute to current understanding of the role that vitamin D may play in the development of T2DM and it should be elucidated that whether altered insulin signalling gene expression in Type 2 diabetes mellitus is influenced by the regulatory transcriptional properties of vitamin D. The information provided by this study may assist in finding a new diabetes screening marker for Type 2 diabetes and developing an effective strategy to prevent T2DM also this study could be a possible new gateway for controlling diabetes by regulating PTEN level.

1.4 Objectives

1.4.1 General Objective

To investigate the gene expression level of insulin signal transduction markers in Type 2 diabetic respondents and compare it with non-diabetic respondents.

1.4.2 Specific Objectives

1) To assess and compare the socio-demographic characteristics (age, gender, medical backgrounds, anthropometric measurement and lifestyle behaviours) and biochemical measurements (FBS, HbA1c, LDL, HDL, TC, TG and C-peptide) in Type 2 diabetic and non- diabetic respondents.
2) To assess serum vitamin D and calcium in respondents and compare both groups.
3) To determine gene expression level of IRS1/ PI3K/ PDK1/ AKT2/ GLUT4/ GSK3/ PTEN and to investigate the underlying mechanism in this pathway in Type 2 diabetic and non- diabetic respondents.
4) To ascertain the association between IRS1/ PI3K/ PDK1/ AKT2/ GLUT4/ GSK3 and PTEN expression and biochemical parameters, serum vitamin D and calcium in respondents and compare both groups.

1.5 Hypothesis

1) High level of PTEN expression as a modulator of insulin sensitivity could be seen among Type 2 diabetes.
2) Overexpression of PTEN in diabetic respondents is associated with lower expression of GLUT4.
3) Lower expression of GLUT4 among Type 2 diabetic respondents would be due to lower level of IRS1/ PI3K/ PDK1/ AKT2 expression as consequences of increased expression of PTEN.
4) Higher expression of GSK3 among Type 2 diabetic respondents is associated with lower level of AKT2 expression and increased level of PTEN.
5) Lower vitamin D status is associated with impaired insulin signaling and decreasing GLUT4 expression.

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