UNIVERSITI PUTRA MALAYSIA

EXPRESSION PROFILING OF GENES RELATED TO ENDOTHELIAL CELL FUNCTION IN PRE-DIABETES AND TYPE 2 DIABETES SUBJCTS

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EXPRESSION PROFILING OF GENES RELATED TO ENDOTHELIAL CELL FUNCTION IN PRE-DIABETES AND TYPE 2 DIABETES SUBJCTS

By

SARA MORADIPOOR

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

March 2016

Dedicated to:

my beloved parents and siblings,

for their love, endless support, encouragement and for being a source of motivation and strength during moments of despair and discouragement.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of science

EXPRESSION PROFILING OF GENES RELATED TO ENDOTHELIAL CELL FUNCTION IN PRE-DIABETES AND TYPE 2 DIABETES SUBJECTS

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March 2016

Chairman : Prof. Patimah Ismail, PhD
Faculty : Medicine and Health Sciences

Type 2 diabetes mellitus (DM2) is a major chronic disease with high morbidity, mortality, and economic burden on public health. The term "endothelial dysfunction" refers to the inability of the endothelium to properly maintain vascular homeostasis. Substantial clinical and experimental evidence suggests that endothelial dysfunction occurs in T2DM patient, in both the resistance and conduit vessels of the peripheral circulation as well as in the coronary circulation. Endothelial dysfunction could be the mechanism in explaining the strong association observed between atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus. It has also been shown that patients with prediabetic conditions, such as impaired fasting glucose and impaired glucose tolerance, are at increased risk of cardiovascular disease as well. The first step of the adverse sequence of events that leads to the atherosclerotic process is thought to be endothelial dysfunction. Many genes have already been reported to be related to endothelial dysfunction in type 2 diabetes and prediabetic patients [e.g. endothelial nitric oxide synthase (eNOS)], but the identification of more genes is always a field of further investigation because of the potential finding of new targets for prevention of CVD in type 2 diabetes patients. The aim of this study was to evaluate the expression of a set of genes in peripheral blood associated with endothelial dysfunction in patients with type 2 diabetes mellitus and in those with impaired fasting glycaemia and impaired glucose tolerance (prediabetic patients), trying to find out the relationship between expression of this set of genes and these two pathological conditions. 45 subjects (22 men, 23 women), with a mean age of 48.9±5.71 years, were included in the study. We have recruited the participants after evaluation of fasting glucose and glucose tolerance and HbA1c. According to the results of fasting glucose, glucose tolerance and HbA1c, the participants were divided into three age-matched groups: group 1: diabetes, defined as fasting plasma glucose ≥ 126mg/dl or 2–h plasma glucose ≥ 200mg/dl and HbA1c ≥6.5 (n=15), group 2: Pre-diabetes, defined as fasting plasma glucose between 110 to 125 mg/dL or IGT 2h post-oral glucose load (75g) between 140mg/dl and 200mg/d and HbA1c between 5.7% to 6.4% (n=15), and group 3 (control group): healthy individuals with normal fasting plasma glucose and normal glucose tolerance (n=15). In patients with type 2 diabetes, we found 59 genes with increased expression. Decreased expression was observed for 4 genes. In pre-diabetes

patients, 2 genes were seen to be significantly down-regulated and 49 genes were significantly up-regulated. Our results indicate that diabetic and pre-diabetic condition may contribute to endothelial dysfunction by disrupting the expression of genes involved in the regulation of endothelial function.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Master Sains

PEMPROFILAN EKSPRESI GEN YANG BERKAITAN DENGAN FUNGSI SEL ENDOTHELIAL DALAM SAMPEL PRE-DIABETES DAN DIABETES JENIS 2

Oleh

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Kencing manis jenis 2 (DM2) merupakan penyakit kronik utama dengan morbiditi, mortaliti, dan beban ekonomi yang tinggi ke atas kesihatan awam. Istilah "disfungsi endotelial" merujuk kepada ketidakupayaan endotelium untuk mengekalkan homeostasis vaskular dengan betul. Bukti klinikal dan eksperimen yang cukup banyak menunjukkan bahawa disfungsi endotelial berlaku kepada pesakit T2DM, terdapat rintangan di dalam kedua-dua saluran pembuluh peredaran periferi dan juga dalam peredaran koronari. Disfungsi endotelial diperhatikan boleh menjadi mekanisme yang menjelaskan perkaitan yang kuat di antara penyakit aterosklerotik kardiovaskular (CVD) dan kencing manis jenis 2. Penyakit ini juga telah menunjukkan bahawa pesakit yang menghidap kencing manis peringkat awal, seperti glukosa berlapar terjejas dan toleransi glukosa terjejas, turut mempunyai risiko peningkatan penyakit kardiovaskular. Langkah awal urutan perkembangan yang berlawanan membawa kepada proses aterosklerotik yang dianggap sebagai disfungsi endotelial. Banyak gen yang telah dilaporkan berkaitan dengan disfungsi endotelial bagi pesakit kencing manis jenis 2 dan pesakit kencing manis peringkat awal [contohnya Endotelial Nitrik Oksida Sintesis (eNOS)], tetapi bagi mengenal pasti lebih banyak gen, kajian lanjut di lapangan sering dijalankan kerana potensi dapatan sasaran baru untuk pencegahan penyakit CVD bagi pesakit kencing manis jenis 2. Tujuan kajian ini adalah untuk menilai ekspresi satu set gen dalam pereferi darah yang berkait dengan disfungsi endotelial pada pesakit kencing manis jenis 2 dan pada pesakit yang mengalami glycaemia berlapar terjejas dan toleransi glukosa terjejas (pesakit kencing manis peringkat awal), dan berusaha untuk mengetahui hubungan antara ekspresi set gen ini dan kedua-dua keadaan patologi tersebut. Seramai 45 pesakit (22 lelaki, 23 wanita), umur purata 48.9±5.71 tahun, telah dilibatkan dalam kajian ini. Kami memilih peserta selepas penilaian glukosa berlapar dan toleransi glukosa dan HbA1c. Berdasarkan kepada hasil penilaian glukosa berlapar, toleransi glukosa dan HbA1c, para peserta dibahagikan kepada tiga kumpulan umur yang dipadankan: Kumpulan 1: kencing manis, ditakrifkan sebagai plasma glukosa berlapar ≥ 126mg/dl atau 2-h plasma glukosa ≥200mg/dl dan HbA1c ≥6.5 (n = 15), kumpulan 2: Pesakit kencing manis peringkat awal, ditakrifkan sebagai plasma glukosa berlapar antara 110 hingga 125mg/dl atau IGT 2h beban glukosa bedah oral (75g) antara 140mg/dl dan 200mg/d

dan HbA1c antara 5.7% hingga 6.4% (n = 15), dan kumpulan 3 (kumpulan kawalan): individu yang sihat memiliki plasma glukosa berlapar normal dan toleransi glukosa normal (n = 15). Pada pesakit kencing manis jenis 2, kami mendapati 59 gen dengan ekspresi meningkat. Ekspresi menurun diperhatikan untuk 4 gen. Bagi pesakit-pesakit kencing manis peringkat awal, kami mendapati 49 gen dengan ekspresi meningkat. Ekspresi menurun diperhatikan untuk 2 gen. Keputusan kami menunjukkan bahawa keadaan kencing manis dan kencing manis peringkat awal boleh menyebabkan disfungsi endotelial melalui gangguan ekspresi gen yang terlibat dalam peraturan fungsi endotelial.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ADA	American diabetes association
AGE	Advanced glycation end products
AKT	Protein kinase B
ALOX5	Arachidonate 5-lipoxygenase
ANXA5	Annexin A5
AR	Aldose reductase
B2M	Beta-2 micoglobulin
BH4	Tetrahydrobiopterin
BMI	Body mass index
°C	Centigrade
Ca	Calcium
CASP1	Caspase-1
CCL2	Chemokine (C-C motif) ligand 2
cDNA	Complementary Deoxyribonucleic acid
CI	confidence interval
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
C_T	threshold cycle
CVD	Cardio vascular disease
DAG	Diacylglycerol
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
EC	Endothelial cell
ECM	Extracellular matrix
EDCFs	Endothelium-derived constricting factors
EDRFs	Endothelium-derived relaxing factors
eNOS	Endothelial nitric oxide synthase
ERK	Extracellular signal-regulated kinases
ET-1	Endothelin-1
F-6-P	Fructose 6-phosphate
FC	Fold change
FFA	Free fatty acids
FPG	Fasting plasma glucose
GFAT	Glucosamine-fructose-6-phosphate aminotransferase
GFPT	Glucosamine-fructose-6-phosphate aminotransferase
GlcNAc	N-acetylglucosamine
GlucN-6-P	Glucosamine-6-phosphate
GlucNAc-1-P	N-acetylglucosamine-6-phosphate
GluN	Glutamine
GLUT1	Glucose transporter 1
HAEC	Human aortic endothelial cell
HbA1c	Glycated haemoglobin
HBP	Hexosamine biosynthetic pathway
HDL	High-density lipoprotein

HG	High glucose
HGEC	Human glomerular endothelial cell
HNF-1α	Hepatocyte nuclear factor 1 alpha
HUVEC	Human umbilical vein endothelial cells
ICAM	Intercellular adhesion molecule
IFG	Impaired fasting glucose
Ig	Immunoglobulin
IGT	Impaired glucose tolerance
IL-1B	Interleukin 1, beta
IL-1Ra	Interleukin-1 receptor antagonist
IL-6	Interleukin 6
IL7	Interleukin-7
IMR	Institute for Medical Research
iNOS	Inducible nitric oxide synthase
IR	Insulin resistance
IRS	Insulin receptor substrate
ITGA5	Integrin alpha-5
ITGAV	Integrin, alpha V
Kg	Kilogram
L	Litter
LAM	Leukocyte adhesion molecule
LKB1	Liver kinase B1
MAPK	Mitogen activated protein kinase
mg	Milligram
min	Minute
mmol	Millimole
MMP	Matrix metallopeptidase
MREC	Medical Research Ethic Committee
mRNA	Messenger Ribonucleic acid
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor-kappa B
ng	Nanogram
NIDDM	Noninsulin-dependent diabetes mellitus
nm	Nanometer
NO	Nitric oxide
NOS3	Nitric oxide synthase 3
nx	plate number of test group
ny	plate number of control group
O^{2-}	superoxide anion
O-GlcNAc	O- linked- N-acetylglucosamine
OGT	O-linked N-acetylglucosamine transferase
OGTT	Oral glucose tolerance test
$ONOO^-$	Peroxynitrite anion
PAI-1	Plasminogen activator inhibitor-1
PBS	Phosphate-buffered saline
PDK-1	pyruvate dehydrogenase kinase, isozyme 1
PECAM1	Platelet endothelial cell adhesion molecule
PGH2	Prostaglandin H2
PI3K	Phosphoinositide 3 kinase

PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PKC	Protein kinase C
PKC-β	Protein kinase C beta
PLAU	Urokinase-type plasminogen activator
PLG	plasminogen
PPAR-γ	Peroxisome proliferator-active receptor gamma
PTEN	phosphatase and tensin homolog
RAGE	Advanced glycation end products receptor
RCF	Relative centrifugal force
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RPLP0	Ribosomal protein, large, P0
RT-PCR	Reverse transcription polymerase chain reaction
SD	Standard deviation
SDH	Sorbitol dehydrogenase
SELL	Selectin L
SELPLG	Selectin P ligand 1
SMC	Smooth muscle cell
SP1	Specificity protein 1
T2DM	Type 2 diabetes mellitus
TGFB1	Transforming growth factor beta-1
TIMP1	Tissue inhibitor of metalloproteinase
TNF-α	Tumor necrosis factor alpha
TXA2	Thromboxane A2
UCP	Uncoupling protein
UDP-GalNAc	Uridine diphosphate N-acetylgalactosamine
UDP-GlucNAc	Uridine diphosphate N-acetylglucosamine
uPA	Urokinase-type plasminogen activator
UPM	University Putra Malaysia
USA	United states of america
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
vWF	von Willibrand's factor
WHR	Waist-hip ratio
μ	Micro
σx	standard deviation of Delta Ct of test group
σy	standard deviation of Delta(Ct) of control group

CHAPTER 1

INTRODUCTION

1.1 Research Background

Diabetes is a group of metabolic diseases that are characterized by glucose level, chronically elevated above the normal range. Undiagnosed, or poorly controlled, it can lead to complications such as blindness, renal insufficiency, stroke, and amputation of extremities. Diabetes is associated with a decrease in life expectancy (Malecki, 2005). There are several distinct types of diabetes, but two most common types are type 1 diabetes and type 2 diabetes (T2DM), of which type 2 diabetes constitutes more than 90% of cases of diabetes. The worldwide prevalence of diabetes has been dramatically increasing, particularly in developing countries like India. Current estimates of diabetes suggest that 285 million of the world's adult population (6.4%) is suffering from diabetes. India has 50.8 million and China has 43.2 million diabetics. The largest age group involved is 40–59 years. By 2030 it is projected that 438 million of the world's adult population (7.8%) will be diabetics with major chunk from India and China. The largest age group affected will be between 60 and 79 years. T2DM is caused by complex interactions between adverse environmental factors and certain genetic factors. Several risk factors, including common, easily measurable phenotypic features (such as obesity, hypertension, low HDL cholesterol levels, elevated triglyceride levels and impaired fasting glucose) as well as parental history of diabetes are already used efficiently to predict the development of T2DM (Kota, Meher, Jammula, Kota, & Modi, 2012). According to the American Diabetes Association (ADA), the term 'pre-diabetes' is defined as a metabolic clinical condition able to predispose affected individual to a future development of diabetes (American Diabetes Association, 2014). The endothelium, which is originally considered to be simply a physical barrier between the blood and vascular wall, is now recognized as the most important component of normal vascular homeostasis, because it serves to maintain the anticoagulant, antiplatelet, and fibrinolytic phenotypes of vascular cells (J. Xu & Zou, 2009). The term endothelial dysfunction refers to a condition in which the endothelium loses its physiological properties: the tendency to promote vasodilation, fibrinolysis and antiaggregation (Avogaro, Fadini, Gallo, Pagnin, & de Kreutzenberg, 2006). Endothelial dysfunction plays a critical role in the development of diabetic vasculopathy, which is associated with reduced NO bioavailability resulting from ROS overproduction, lipid peroxidation, and increased generation of adhesion molecules (W. T. Wong, Wong, Tian, & Huang, 2010). Several evidences indicate that pre-diabetes conditions may be associated with an increased cardiovascular risk profile of individuals (Ciccone et al., 2014). Ying Su et al. considered 30 patients with IFG, 38 with IGT, 46 with normal glucose tolerance, and 44 with T2DM and they confirmed that endothelial dysfunction, an early marker of macrovascular disease, is present in subjects with pre-diabetes, indicating endothelial damage in these stages (Su et al., 2008).

1.2 Statements of Problem

The prevalence of diabetes, constituted chiefly by type 2 diabetes (T2D), is a global public health threat. Asian countries contribute to more than 60% of the world's diabetic population as the prevalence of diabetes is increasing in these countries. The prevalence among adults aged 20-70 years is expected to rise from 285 million in 2010 to 438 million by the year 2030. While T2D poses a huge economic burden to all nations, developing countries bear the highest burden since more than 80% of cases occur in these countries. Prevalence estimates of diabetes and impaired glucose tolerance (IGT) are high in all Asian countries and are expected to increase further in the next two decades. The present trend indicates that more than 60% of the world's diabetic population will be in Asia (Guo, He, Zhang, & Walton, 2012). Malaysia has one of the world's highest number of diabetes cases among its population with 2.6 million registered patients (Kearney, Whelton, Reynolds, Whelton, & He, 2004). The total estimated cost of diagnosed diabetes in 2012 is $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity. This figure represents a 41 percent increase over a five-year period ($174 billion in 2007 dollars) (American Diabetes Association, 2013). Micro- and macro-vascular dysfunctions are the major causes of morbidity and mortality in patients with diabetes mellitus (W. T. Wong et al., 2010). Type 2 diabetes is characterized by a two- to fourfold increased risk of cardiovascular disease. It has also been shown that patients with pre-diabetic conditions, such as impaired fasting glucose and impaired glucose tolerance, are at increased risk of cardiovascular disease as well (Kirpichnikov & Sowers, 2001). Pre-diabetic condition is a further expression of incipient atherosclerosis development. The synergy between a systemic inflammatory condition and the presence of high blood glucose concentrations are able to impair vascular endothelium in its function, thus predisposing to atherosclerotic lesions (Ciccone et al., 2014). The first step of the adverse sequence of events that leads to the atherosclerotic process is thought to be endothelial dysfunction (Avogaro et al., 2006).

According to the above studies, diabetes and pre-diabetes are costly diseases with high prevalence worldwide, mostly Asian countries including Malaysia. It has also been shown that patients with type 2 diabetes and patients with pre-diabetes are at increased risk of cardiovascular disease, and endothelial dysfunction is thought to be the most important event that leads to the atherosclerotic process and cardiovascular disease. Therefore, research on expression of endothelial cells-related genes in type 2 diabetes and pre-diabetes patients seems to be important in prevention of atherosclerosis and cardiovascular disease in these metabolic disorders.

1.3 Hypothesis:

H1: The rate of expression of genes regulating the endothelial cells function, is related to endothelial dysfunction in type 2 diabetes patients.

H2: The amount of expression of genes regulating the endothelial cells function, is related to endothelial dysfunction in pre-diabetic condition.

1.4 Objectives:

General Objective:

To determine the expression of genes related to endothelial cells function in peripheral blood of patients with type 2 diabetes, and pre-diabetic patients.

Specific Objectives:

1. To compare the expression level of seven groups of genes – angiogenesis, vasoconstriction & vasodilation, inflammatory response, apoptosis, cell adhesion, coagulation, platelet activation – which are related to endothelial cells function, between type 2 diabetes patients and control.

2. To compare the expression level of seven groups of genes – angiogenesis, vasoconstriction & vasodilation, inflammatory response, apoptosis, cell adhesion, coagulation, platelet activation – which are related to endothelial cells function, between pre-diabetes patients and control.

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