The Role Of Sirtuin 1 in Diabetic Nephropathy

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Declaration

I declare that this thesis has been composed by myself and that the work of which it is a record has been done by myself. It has not been submitted for a degree at this or any other university.

Haidi Shebl Ahmed El-Ghandour

(2017)

Dedication

To my mother (GOD bless her soul)

Haidi Shebl Ahmed El-Ghandour

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Acknowledgement

First and foremost cordial thanks to GOD

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Abstract

Sirtuin 1(Sirt1) is a NAD-dependant class III protein deacetylase.Sirt-1 plays an important role in cellular processes, including gene expression, cell cycle regulation, cell metabolism, oxidative stress response, apoptosis, DNA repair and ageing. Sirt1 is also associated with inflammation and immune response. In addition, sirt1 also affects insulin secretion, and glucose and lipid metabolism. The aim of the present study was to investigate the role of Sirtuin-1 in diabetic nephropathy and its relation to AGEs.

One hundred subjects were included in this study; 80 patients and 20 healthy subjects, sex and age matched, used as controls (Gr.I). The patients were divided into: Gr. II (normoalbuminuric patients); Gr.III (patients with diabetic nephropathy); Gr.IIIa (patients with microalbuminuria) and Gr. IIIb (patients with macroalbuminuria).

Fasting blood glucose, fasting insulin, Homeostasis model assessment for insulin resistance (HOMA-IR), renal function tests, lipid profile, serum Sirt1,serum AGEs and urine microalbumin were evaluated by (ELISA) in this study.

Results indicated that serum Sirt1 level was significantly lowered in normoalbuminric patients ($p< 0.05$).While, serum level of AGEs was significantly increased in all diabetic patients ($p< 0.001$). Serum Sirt1 was negatively correlated with microalbumin in macroalbuminuric patients. Additionally, serum Sirt1 showed a positive correlation with insulin and AGEs levels in total diabetic patients ($p< 0.05$ and $p< 0.001$ respectively).

In conclusion**:** Serum Sirt1 may be associated with minimal renal impairment in type 2 diabetic nephropathy patients.

List of Abbreviations

2-OAADPr	:2-O- Acetyl-ADP-Ribose
3-DG	:3-Deoxyglucosone
A/C	:Albumin creatinine ratio
AceCS2	:Acetyl co-A synthetase 2
ADA	:American diabetic association
ADP	:Adenine diphosphate
ADPr	:Adenine diphosphate ribose
AGEs	:Advanced glycation end products
ARNT	: Aryl hydrocarbon receptor nuclear translocator
ASK	:Apoptosis Signal -regulating kinase
AT1R	:Angiotensin II type I receptor
ATP	: Adenine triphosphate
CD4	:Cluster of differentiation 4
CD8	:Cluster of differentiation 8
CKD	:Chronic kidney disease
CKD	:Chronic Kidney Disease
CML	:Nε -carboxymethyl-lysine
COX2	:Cyclo-oxygenase2
CTGF	:Connective tissue growth factor
DN	:Diabetic Nephropathy
DOLD	:Deoxyglucasone-lysine dimer
EMT	:Epithelial-mesenchymal transition
ESRD	:End stage renal disease

FFA	:Free fatty acid
FOXO1	: Forkhead box protein O1
FPG	:Fasting plasma glucose
FXR	:Farnesoid x receptor
GAD	:Glutamic acid decarboxylase
GDH	:Glutamate dehydrogenase
GDM	:Gestational diabetes mellitus
GFR	:Glomerular filtration rate
GLUT4	:Glucose transporter4
HDAC	:Histone deacetylase
HDL-C	:High density lipoprotein-c
HLA	:Human leucocyte antigen
Hst	: Histone
IAS	:Insulin antibodies
ICAs	: Islet cells
IDDM	:Insulin dependent diabetes mellitus
IDF	:International diabetes federation
IFG	:Impaired fasting glucose
IGT	:Impaired glucose tolerance
IKK	:Inhihibtor κB –kinase enzyme
IR	:Insulin receptor
IRS-1	:Insulin receptor substrate-1
JNK	: c-Jun N-terminal kinase
LDL-C	:Low density lipoprotein-c
LXR	:Liver x-receptor

MAPK	:Mitogen activated protein kinase
MCP-1	:Mononcyte chemoattractant protein-1
MGO	:Methylglycoxal
MHC	:Major histocomptability complex
MOLD	:Methyl Glyoxal Lysine Dimer
NAD^+	: Nicotinamide adenine dinucleotide
N-CoR	: nuclear receptor co-repressor
NF-Kb	:Nuclear factor kappa beta
OGTT	:Oral glucose tolerance test
OXPHOS	:Oxidative phosphorylation
PAI-1	:Plasminogen activator inhibitor
PGC-1α	:Peroxisome proliferator-activated receptor gamma coactivator1-alpha
PGE2	:Prostaglandins E2
PI3K	:Phosphoinositide3-kinase
PI3K	:Phosphotidyl-Inositol-3-OH Kinase
PKC	:Protein kinase c
PPAr	:Peroxisome proliferator activated-receptor
PTPB	: Protein tyrosine phosphatase
RAGE	:Receptor of advanced glycation end product
ROS	:Reactive oxygen species
RPF	:Renal protein flow
Sir2p	:Silent information regulation2 protein
Smad	:Small mother against decapentaplegic
SOD	:Superoxide dismutase

SP	:Specificity Protein
SREBP	:Sterol regulatory element binding protein
STAT	:Signal transducer activated transcription
T1DM	:Type1diabetes mellitus
T2DM	:Type2 diabetes mellitus
TGF-β	:Transforming growth factor beta
TNF-α	:Tumor necrosis factor alpha
UAE	:Urinary albumin excretion
UAE	:Urinary albumin excretion
UCP	:Uncoupling protein
UUO	: Unilateral ureteral obststruction
VEGF	:Vascular endothelial growth factor
WHO	:World health organization
α- SMA	:Alfa smooth muscles actin
α-ENaC	:Epithelial Na^+ channel α- subunit

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Introduction

Diabetic nephropathy (DN) is a serious complication of diabetes; it initially manifests with microalbuminuria and progresses towards end-stage renal failure. Sustained diabetes-related metabolic and haemodynamic perturbations can induce subclinical low-grade renal inflammation and drive kidney from repair response to damage process, eventually to renal fibrosis ***(Shirong et al., 2016)***.

Sirtuin-1(SIRT1) is the most conserved mammalian NAD^+ dependant protein deacetylase that has emerged as a key metabolic sensor in various metabolic tissues. SIRT1 directly links the cellular metabolic status to the chromatin structure and the regulation of gene expression, there by modulating a variety of cellular processes such as energy metabolism and stress response ***(Haigis et al., 2006)***.

During long standing hyperglycaemic state in diabetes mellitus, glucose forms covalent adducts with the plasma proteins through a non-enzymatic process known as glycation. Protein glycation and formation of advanced glycation end products (AGEs) ***(Jang et al., 2011)***.

Advanced Glycation End products (AGEs) accumulate in most sites of diabetes complications including the kidneys, retina, and artherosclerotic plaques. Glycation of proteins interferes with their normal functions by disrupting molecular conformation, altering enzymatic activity, reducing degradation capacity and interfering with receptor recognition ***(Zouboulis and Markrantonaki, 2011).***