STUDY OF TOLL – LIKE RECEPTOR 2 AND 4 EXPRESSION IN MONOCYTES IN TYPE 1 DIABETES MELLITUS WITH AND WITHOUT MICRO-VASCULAR COMPLICATIONS

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دراسة دور مستقبلات تول من النوع الثانى و الرابع فى الخلايا أحادية النواه فى الداء السكرى من النوع الاول مع وبدون مضاعفات الاوعية الدموية الدقيقة

رسالة

مقدمة توطئة للحصول على درجة الماجستير فى
أمراض الباطنة العامة

مقدمة من

وسام أحمد محمد
بكالوريوس الطب والجراحة
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SUMMARY AND CONCLUSION

Type 1 diabetes mellitus (T1DM) is associated with an increased risk of vascular complications, and T1DM patients with proteinuria and/or retinopathy have a significantly increased risk of fatal coronary artery disease . Inflammation plays a pivotal role in all stages of atherosclerosis. The monocyte-macrophage, a crucial cell in atherogenesis, is readily accessible for study. Several researches had demonstrated that patients with T1DM exhibit increased inflammation as evidenced by increased monocyte activity, and these are more pronounced in T1DM with microvascular complications.

Members of the toll-like receptors (TLRs) family play a critical role in the inflammatory components of atherosclerosis. Toll-like receptors are a family of pattern recognition receptors that are important in the regulation of immune function and inflammation. Their activation by various ligands triggers a signaling cascade leading to cytokine production and initiation of an adaptive immune response.

The aim of this study was to asses expression of toll-like receptor 2 and 4 in monocytes in type 1 diabetes mellitus and its relation to presence of diabetic micro vascular complications

بسم الله الرحمن الرحيم

وَأَنْزَلَ اللهُ عَلَيْكَ
الْكِتَابَ والْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ وَكَانَ
فَضْلُ اللهِ عَلَيْكَ
عَظِيمًا

صدق الله العظيم
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LIST OF ABBREVIATIONS

Abbrev.	Full term
AGE	Advanced glycation end-product
anti-Sm Ab	Anti –smooth muscle antibody
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CAECs	Coronary artery endothelial cells
CD80	Cluster of differantiation 80
CDI	Color doppler imaging
CHD	Coronary heart disease
CPG	Cytosine phosphate guanine
CPT	Cell preparation tubes
CRARI	The central retinal artery resistive index
CRP	C- reactive protein
CTLs	Cytotoxic T lymphocytes
CV	The cardiovascular risk facror
DAFNE	Dose Adjustment For Normal Eating
DNA	Dineucliec acid
dsDNA	Double stranded dineucliec acid
DSP	Distal symmetrical polyneuropathy
ENU	N-ethyl-N-nitrosourea
ESRD	End stage renal disease
GADA	Glutamic Acid Decarboxylase antibodies
GAS6	Growth arrest-specific 6 protein
GFR	Glomular filteration rate
GpIb	Glycoprotein Ib
HDL	High-density lipoprotein
HMGB1	High-mobility group box 1
HSF	Heat shock factor

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full term
HSP	Heat Shock Proteins
IA-2	Insulinoma-associated autoantibodies
ICA	Islet cell antibodies
IDDM	Insulin dependent diabetes mellitus
IMT	Carotid intima-media thickness
IMT	Intimal thickness
IP-10	Interferon-induced protein 10
IRAK	IL1 receptor associated kinase
IRS	Immunoregulatory sequences
IU	International unit
LPS	Lipopolysaccharides
MaL	MyD88 adaptor-like protein
MAPK	Mitogen-activated protein kinase
MD-2	Myeloid differentiation protein2
MI	Myocardial infarction
MODY	Maturity onset diabetes of young
MyD88	Myeloid differentiation primary response gene 88
NF-KB	Nuclear factor kappa B
NICE	National Institute for Health and Clinical Excellence
NKs	Natural killer cells
NLRs	Nucleotide oligomerization domain-like receptors
NO	Nitric oxide
NOS	Nitric oxidesynthase
NPH	Neutral protamine Hagedorn
ODN	Oligodeoxynucleotides
PAD	Peripheral artery disease
PAMPs	Pathogen-associated molecular patterns
PBMCs	Peripheral blood mononuclear cells
PGN	Peptidoglycan

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full term
PKC	Protein kinase C
PRR	Pattern recognition receptor
RAGE	Receptor for advanced glycation end-products
SLE	Systemic lupus erythromatosis
T2DM	Type 2 diabetes mellitus
T_H1	T helper 1 cell
TIR(Toll-IL-1)	Interleukin-1 Receptor/Toll-Like Receptor Superfamily
Tirap	Toll-interleukin 1 receptor (TIR) domain containing adaptor protein
TIRAP	TOLL-IL1R domain-containing adaptor protein
TLRs	Toll like receptors
Trif	TIR-domain-containing adapter-inducing interferon-β

INTRODUCTION

Type 1 Diabetes Mellitus (Insulin dependent Diabetes Mellitus. Or juvenile diabetes) is a form of diabetes mellitus that result from autoimmune destruction of insulin producing beta cells of the pancreas ***(Cooke and Plotnick, 2008).***

Type1 Diabetes is associated with an increased risk of micro-and macro vascular complications, micro vascular complications were defined as nephropathy, retinopathy and neuropathy. Patients with proteinuria and / or retinopathy have a significantly increased risk of fatal coronary artery disease ***(Libbyp et al., 2005)***.

About 20-30% of patients with type1diabetes develop diabetic nephropathy, the earliest clinical evidence of nephropathy is the appearance of low but abnormal level (≥30 mg / day or 20 mcg / minute) of albumin in urine, 80 % of subjects with type 1 diabetes mellitus who develop sustained micro albuminuria have their urinary albumin excretion increase at rate of 10 – 20 % per year to the stage of overt nephropathy or clinical albuminuria (≥ 300 mg / day or ≥ 200 mcg / minute) over a period of 10 – 15 years, End – stage renal disease (ESRD) develops in 50% of type 1 diabetic individuals with overt nephropathy within 10 years ***(Parving et al., 2007).***

Diabetic retinopathy is a devastating ocular complication of diabetes mellitus occur to some degree in

almost all patients who have diabetes, almost all patients with a 15 – year history of type 1 diabetes mellitus develop retinopathy ***(Fletcher, 2008)***.

Toll-like receptors (TLRS) are a class of Proteins that play a key role in the innate immune system. They are single, membrane, non catalytic receptors. They are expressed in multiple tissues; the predominant site of its expression is on cells of the innate immune system especially monocytes ***(Hansson and Edfel, 2008).***

They are important in regulation of immune function and inflammation. Their activation by various ligands triggers a signaling cascade lead to production of inflammatory cytokines and molecules that initiate adaptive immune response. They are up regulated in several inflammatory disorders ***(Uematsu and Akira, 2006)***.

Recent studies have shown that type 1 diabetes mellitus is a proinflammatory state characterized by increased levels of circulating biomarkers of inflammation and monocyte activity ***(Devarajs et al., 2009).***

Type1 diabetes mellitus may be associated with disorders of innate immune system. Toll like receptors are important mediators of the innate immunity with subsequent proinflammatory reaction that thought to be involved in diabetic micro vascular complications ***(Mullick et al., 2008).***