بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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MONA MAGHRABY

Study of Neutrophil-Lymphocyte Ratio, Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α) in Type 2 Diabetes with Diabetic Nephropathy

A Thesis

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✍ *Marwa Mohamed Ali Ahmed*

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List of Abbreviations

Abb.	Full term
8oHdG	8-oxo-7,8-dihydro2-deoxyguanosine
A1C	Glycated hemoglobin
ACE	Angiotensin-converting enzyme
ADA	American Diabetes Association
AGE	Advanced Glycation End products
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ARBs	Angiotensin receptor blockers
ARE	Antioxidant response element
BMI	Body mass index
BMP-7	Bone morphogenic protein-7
CBC	Complete blood counts
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
DM	Diabetes mellitus
DN	Diabetic nephropathy
EDTA	Ethylenediamine tetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ERK	Extracellular related kinase
ESRD	End-stage renal disease
FPG	Fasting plasma glucose
G-CSF	Granulocyte colonystimulating factor
GFR	Glomerular filtration rate
GSH	Glutathione
GSH	Glutathione Rreductase
GST	Glutathione S Ttransferase

List of Abbreviations Cont...

Abb.	Full term
HAAF	Hypoglycemia-associated autonomic failure
H-FABP	Heart fatty-acid binding protein
HNS	Hyperosmolar nonketotic state
HO-1	Heme oxygenase
IFG	Impaired fasting glucose
IFTA	Interstitial fibrosis and tubular atrophy
IGT	Impaired glucose tolerance
IkB	Inhibitory kappa B protein
IKK	Inhibitory kappa B kinase
IL1	Interleukin-1
KIM-1	Kidney molecule injury 1
L-FABP	Liver-type fatty acid binding protein
L-PGDS	Lipocalin-type prostaglandin synthase
MAPK	Mitogen-activated protein kinase 42/44
MCP-1	Monocyte chemoattractant protein-1
MODY	Maturity onset diabetes of the young
NAG	N-acetyl-β-D-glucosaminidase
NF-kb	Nuclear Factor Kappa
NGAL	Neutrophil gelatinase-associated lipocalin
NGSP	National Glycohemoglobin Standardization Program
NHANES	National Health and Nutrition Examination Survey
NIK	NF-kB-inducing kinase
NLR	Neutrophil lymphocyte ratio
NLR	Neutrophil-lymphocyte ratio
Nrf2	Nuclear Factor (erythroid-1) related factor
OGTT	Oral glucose tolerance test
PI3	Phosphatidylinositol 3

List of Abbreviations Cont...

Abb.	Full term
PKC	Protein Kinase c
PTF	Pentoxifylline
RAAS	Renin-angiotensin-aldosterone system
ROS	Reactive Oxygen Species
SOD	Super Oxide Dismutase
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TGF-beta	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-α
TRADD	TNFR associated death domain
TWBC	total white blood cell
UKPDS	U.K. Prospective Diabetes Study
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

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INTRODUCTION

Type 2 diabetes mellitus (DM) can have serious socio-economic effects due to its many potential complications, which include microvascular (diabetic nephropathy (DN), neuropathy and retinopathy) and macrovascular complications (atherosclerosis, ischemic heart disease, stroke and peripheral vascular disease which frequently results in amputation) ***(Kahraman et al., 2016).***

Several studies have shown the relationship between systemic inflammation and insulin resistance, where an altered immune system plays a decisive role in the pathogenesis of DM..These immunological alterations result in elevated circulating levels of acute-phase proteins and pro-inflammatory cytokines that play a major role in the development of chronic inflammation-induced organ dysfunction in DM ***(Abhijit et al., 2014).***

Diabetic nephropathy (DN) is a major cause of end-stage kidney disease, and therefore early diagnosis and intervention may help reverse renal damage ***(Ahmet et al., 2013).*** Early pathophysiologic changes of DN include renal hyperfiltration and extracellular accumulation in both the glomerular and the tubule interstitial compartments, and these effects are associated with deterioration of renal function ***(Yachun et al., 2013).***

Elements of the diabetic mellitus (hyperglycaemia, AGEs, immune complexes) can activate kidney cells via induction of SAPK signaling, resulting in the release of chemokines and up regulation of cell adhesion molecules. These events facilitate the kidney infiltration of monocytes and lymphocytes, which become activated in the diabetic kidney and secrete injurious molecules ***(Andy and Lim, 2016).***

The neutrophil-lymphocyte ratio (NLR) is a marker of systemic inflammation, which is calculated by dividing the neutrophil count by the lymphocyte count. NLR has been shown to have predictive and prognostic utility in a variety of diseases including acute myocardial infarction, autoimmune disease, and chronic kidney disease (CKD) ***(Hiroyuki et al., 2017).***

DN in T2DM has an inflammatory pathology. Many inflammatory markers have been found to be related to DN, such as interleukin-1 (IL1), IL6, IL8, transforming growth factor beta 1, tumor necrosis factor-alpha (TNF-α), and cytokines. However, their measurement is not used routinely as it is not easy to do it. In this respect, NLR has emerged as a novel surrogate marker ***(Sagar et al., 2017)***.