



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكرو فيلم

# بسم الله الرحمن الرحيم



**MONA MAGHRABY**



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التوثيق الإلكتروني والميكرو فيلم



# شبكة المعلومات الجامعية التوثيق الإلكتروني والميكرو فيلم



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التوثيق الإلكتروني والميكروفيلم

# جامعة عين شمس

## التوثيق الإلكتروني والميكروفيلم

### قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



### يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



**MONA MAGHRABY**



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

*A Thesis*

*Submitted for partial fulfillment of Master degree  
in Endocrinology and Metabolism*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

# قَالَ

سَبَّحَانَكَ لَا إِلَهَ إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

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# *List of Abbreviations*

| Abb.        | Full term                                |
|-------------|--|
| 8oHdG.....  | 8-oxo-7,8-dihydro-2-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 colony-stimulating factor    |
| GFR .....   | Glomerular filtration rate               |
| GSH .....   | Glutathione                              |
| GSH .....   | Glutathione S-transferase                |
| GST.....    | Glutathione S-transferase                |



## *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- $\beta$ -D-glucosaminidase                |
| NF-kb.....   | Nuclear Factor Kappa                                |
| NGAL .....   | Neutrophil gelatinase-associated lipocalin          |
| NGSP.....    | National Glycohemoglobin Standardization<br>Program |
| NHANES ..... | National Health and Nutrition Examination<br>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- $\alpha$ ..... | Tumor necrosis factor- $\alpha$      |
| 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- $\alpha$ ), 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*).