# *Study of the Relation between Inflammatory and Fibrogenic Cytokines in Diabetic Nephropathy*

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By

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# "دراسة العلاقة بين السيتوكينات المسببة للإلتهاب والتليف

## فى الإعتلال الكلوى السكرى"

كمتطلب جزئى لإستيفاء الحصول على درجة الماجستير فى العلوم الصيدلية
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# *Summary and Conclusion*

Diabetic nephropathy (DN) is a serious microvascular complication of diabetes mellitus (DM). Though the progression of DN is very slow, many of diabetic patients develop ESRD. Chronic hyperglycemia is considered as the major initiator of diabetic kidney disease, either by hemodynamic or metabolic pathways leading to induction of growth factors and cytokines.

The present study was undertaken to assess whether transforming growth factor beta 1 (TGF-$_1$), connective tissue growth factor (CTGF), monocyte chemoattractant protein-1 (MCP-1) and fibronectin (FN) levels in type 2 diabetic patients are associated with diabetic kidney disease as reflected by their albumin excretion rate (AER).

In order to fulfill our aim in this study, it was conducted on 82 subjects divided into two groups: group I: consists of 17 healthy volunteers served as control group, group II: consists of 65 diabetic patients subdivided into three subgroups: group II$_a$: consists of 18 diabetic patients with normoalbuminuria, group II$_b$: consists of 22 diabetic patients with microalbuminuria and grou II$_c$: consists of 25 diabetic patients with macroalbuminuria.

Fasting plasma glucose, glycated hemoglobin (HbA$_{1c}$) %, fasting serum insulin, serum creatinine, creatinine clearance, TGF-$_1$, plasma CTGF, MCP-1 and FN were determined. Also, urinary albumin, creatinine, albumin/creatinine ratio and N-Acetyl- -D-glucosaminidase (NAG) were determined in the different studied groups. Then, the correlations among these parameters were examined statistically to gain more insight into our results.

# بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا إلا ما

إنك أنت العليم الحكيم

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# List of Contents

# *List of Abbreviations*

| | |
|---|---|
| **ADA** | American Diabetes Association |
| **AER** | Albumin excretion rate |
| **AGEs** | Advanced glycation end products |
| **Akt** | Serine/threonine protein kinase |
| **AR** | Aldose reductase |
| **BMI** | Body mass index |
| **BMPs** | Bone morphogenetic proteins |
| **CAD** | Coronary artery diseases |
| **CCL2** | Chemokine [C-C motif] ligand 2 |
| **CCN** | Cysteine-rich 61 /CTGF/ nephroblastoma overexpressed protein |
| **CCR2** | Chemokine receptor 2 |
| **cFN** | Cellular fibronectin |
| **CIg** | Cold-insoluble globulin |
| **CKD** | Chronic kidney disease |
| **CR** | Chordin-like cysteine-rich |
| **CTGF** | Connective tissue growth factor |
| **DAG** | Diacylglycerol |
| **DG** | Deoxyglucosone |
| **DHAP** | Dihydroxyacetone phosphate |

| | |
|---|---|
| **DKA** | Diabetic ketoacidosis |
| **DM** | Diabetes mellitus |
| **DN** | Diabetic nephropathy |
| **ECM** | Extracellular matrix |
| **eGFR** | Estimated glomerular filtration rate |
| **EGFR** | Epidermal growth factor receptor |
| **EMT** | Epithelial–mesenchymal transformation |
| **ERK** | Extracellular signal-regulated kinase |
| **ESRD** | End-stage renal disease |
| **FBG** | Fasting blood glucose |
| **FN** | Fibronectin |
| **GAG** | Glycosaminoglycans |
| **GBM** | Glomerular basement membrane |
| **GDM** | Gestational diabetes mellitus |
| **GFAT** | Glutamine: fructose-6 phosphate amidotransferase |
| **GFR** | Glomerular filtration rate |
| **GOD** | Glucose oxidase |
| **GSH** | Reduced glutathione |
| **GSSG** | Oxidized glutathione |
| **HbA$_{1c}$** | Glycated hemoglobin |
| **IDDM** | Insulin dependent diabetes mellitus |
| **IGFBP** | Insulin-like growth factor binding |

| | |
|---|---|
| | protein |
| **IL-8** | Interleukin-8 |
| **JNK** | c-Jun N-terminal kinase |
| **K/DOQI** | Kidney Disease Outcomes Quality Initiative |
| **LAP** | Latency associated peptide |
| **LLC** | Large latent complex |
| **LTBP** | Latent TGF- binding protein |
| **MAbs** | Monoclonal antibodies |
| **MAPK** | Mitogen activated protein kinase |
| **MCP-1** | Monocyte chemoattractant protein-1 |
| **MG** | Methylglyoxal |
| **MMP-2** | Matrix metalloproteinase-2 |
| **MNP-GlcNAc** | 2-methoxy-4-(2' nitrovinyl) phenyl 2-acetamido-2-deoxy- -D-glucopyranoside |
| **NAD$^+$** | Nicotinamide adenine dinucleotide |
| **NADP$^+$** | Nicotinamide adenine dinucleotide phosphate |
| **NADPH** | Reduced nicotinamide adenine dinucleotide phosphate |
| **NAG** | N-Acetyl- -D-glucosaminidase |
| **NF- B** | Nuclear factor-kappa beta |
| **NIDDM** | Non insulin dependent diabetes mellitus |
| **NO$^\cdot$** | Nitric oxide |
| **NOV** | Nephroblastoma overexpressed protein |

| | |
|---|---|
| $O_2^{\cdot-}$ | Superoxide anion |
| OHAs | Oral hypoglycemic agents |
| $ONOO^-$ | Peroxynitrite |
| PAP | Para-aminophenazone |
| pFN | Plasma fibronectin |
| PI3K | Phosphoinositide-3-OH kinase |
| PKB | Protein kinase B |
| PKC | Protein kinase C |
| POD | Peroxidase |
| RAGEs | Receptors of advanced glycation end products |
| RER | Rough endoplasmatic reticulum |
| ROS | Reactive oxygen species |
| R-Smad | Receptor Smads |
| SDH | Sorbitol dehydrogenase |
| SGK-1 | Serine/threonine glucocorticoid kinase-1 |
| SLC | Small latent complex |
| SP | Signal peptide |
| TAK-1 | TGF- -activated kinase 1 |
| TGF- $_1$ | Transforming growth factor beta-1 |
| TIMP-2 | Tissue inhibitor of metalloproteinase-2 |
| TMB | Tetra methyl benzidine |

| UAE | Urinary albumin excretion |
|---|---|
| UDPGlcNAc | Uridine diphosphate N-acetyl glucosamine |
| VEGF | Vascular endothelial growth factor |
| vWC | Von Willebrand factor type C |

# *List of Tables*

| Table No. | Table Title | Page |
|:---:|:---|:---:|
| 1 | Different stages of diabetic nephropathy | 7 |
| 2 | Measurement and significance of albumin excretion rate (AER) | 11 |
| 3 | Demographic characteristics of studied groups | 70 |
| 4 | Diabetic markers of studied groups | 71 |
| 5 | Kidney function tests of studied groups | 74 |
| 6 | TGF- 1, CTGF, MCP-1 and FN of studied groups | 77 |
| 7 | Summary of the results of the studied parameters | 84 |
| 8 | Individual data of healthy control group I | I |
| 9 | Individual data of diabetic normoalbuminuric group $II_a$ | II |
| 10 | Individual data of diabetic microalbuminuric group $II_b$ | III |
| 11 | Individual data of diabetic macroalbuminuric group $II_c$ | IV |

# *List of Figures*