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**Evaluation of the role of cytokine gene
polymorphisms in diabetic nephropathy among
Kuwaiti patients with type 2 diabetes mellitus**

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➤ الملخص
➤ المستخلص

This thesis has not been submitted
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Ashraf Elsaid Hafez Elhelaly

List of abbreviations

| Abbreviation | Full name |
|--------------|--|
| Alb | Albumin |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| Ca | Calcium |
| CAD | Coronary artery disease |
| CCD | Charge coupled device |
| cDNA | complementary DNA |
| CE | Capillary electrophoresis |
| CHF | Congestive heart failure |
| CI 95% | Confidence interval 95% |
| Cl | Chloride |
| Cr | Creatinine |
| CRP | C-reactive protein |
| CVDs | Cardiovascular diseases |
| CVS | Cardiovascular system |
| DCCT | Diabetes control and complications trial |
| DCs | Dendritic cells |
| DKA | Diabetic ketoacidosis |
| DKD | Diabetic kidney disease |
| DM | Diabetes mellitus |
| DN | Diabetic nephropathy |
| EDIC | Epidemiology of diabetes interventions and complications study |
| EDTA | Ethylenediaminetetraacetic acid |
| eGFR | Estimated glomerular filtration rate |

| | |
|---------------|--------------------------------------|
| ELISA | Enzyme-linked immunosorbent assay |
| ESRD | End-stage renal disease |
| FP | Forward primer |
| FPG | Fasting plasma glucose |
| GDM | Gestational diabetes mellitus |
| GFR | Glomerular filtration rate |
| HbA1c | Hemoglobin A1c |
| HDL-C | High-density lipoprotein cholesterol |
| HLA | Human leucocyte antigens |
| HRP | Horseradish peroxidase |
| HTN | Hypertension |
| HWE | Hardy-Weinberg equilibrium |
| IFG | Impaired fasting glucose |
| IFN- γ | Interferon gamma |
| IGH | Impaired glucose homeostasis |
| IGH | Impaired glucose homeostasis |
| IGT | Impaired glucose tolerance |
| IL-10 | Interleukin-10 |
| IL-12 | Interleukin-12 |
| IL-13 | Interleukin-13 |
| IL-2 | interleukin-2 |
| IL-4 | Interleukin-4 |
| IL-5 | Interleukin-5 |
| IL-6 | Interleukin-6 |
| IQR | Interquartile range |
| K | Potassium |
| LA | Lactic acidosis |
| LD | Linkage disequilibrium |
| LDL-C | Low-density lipoprotein cholesterol |
| MA | Microalbumin |
| MGB | Minor groove binder |
| MHC | Major histocompatibility complex |
| MI | Myocardial infarction |

| | |
|---------------|---|
| mRNA | Messenger RNA |
| Na | Sodium |
| NFQ | Non-fluorescent quencher |
| NK | Natural killer cells |
| NPDR | Non- proliferative diabetic retinopathy |
| NPV | Negative predictive value |
| OD | Optical density |
| OGTT | Oral glucose tolerance test |
| P | Phosphorous |
| PAF | platelet activating factor |
| PCR | Polymerase chain reaction |
| PDR | Proliferative diabetic retinopathy |
| POP | Performance optimized polymers |
| PPV | Positive predictive value |
| ROC | Receiver operating characteristic |
| ROS | Reactive oxygen species |
| RP | Reverse primer |
| SD | Standard deviation |
| SDS | Sequence detection system |
| SLE | Systemic lupus erythematosus |
| SNPs | Single nucleotide polymorphisms |
| SPSS | Statistical package for the social sciences |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| TAE | Tris-Acetate-EDTA-Na ₂ |
| Taq | <i>Thermus aquaticus</i> |
| TB | Total bilirubin |
| TC | Total cholesterol |
| TG | triglycerides |
| TH1 | T-lymphocyte helper cell type 1 |
| Th2 | T-lymphocyte helper cell type 2 |
| TMB | 3,3',5,5'-tetramethylbenzidine |
| TNF- α | Tumor necrosis factor alpha |

| | |
|------|--------------------------------------|
| TP | Total protein |
| UACR | Urinary albumin-to- creatinine ratio |
| UAE | Urinary albumin excretion |

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ABSTRACT

Abstract

Background: Data from previous studies on the role of inflammatory cytokines as biomarkers for diabetic kidney disease (DKD) are contradictory. The association of a particular inflammatory cytokine single nucleotide polymorphism (SNP) with susceptibility to DKD has not been consistently replicated. We aimed to investigate the utility of inflammatory cytokines as biomarkers for DKD in type 2 diabetes mellitus (T2DM) patients. Association of inflammatory cytokine gene SNPs with the development of DKD was also explored. **Subjects & Methods:** One hundred and fifty-nine Kuwaiti subjects were recruited in this study, including 50 T2DM patients without DKD, 67 diabetic DKD patients and 42 healthy subjects. Plasma levels of interleukin-6 (IL-6), IL-10, interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) were measured by enzyme-linked immunosorbent assays. Nine SNPs, including 2 SNPs in *IL-6*, 3 SNPs in *IL-10*, 1 SNP in *IFN- γ* and 3 SNPs in *TNF- α* , were genotyped using TaqMan SNP genotyping assays. **Results:** Diabetic DKD patients showed higher IL-6, IL-10, IFN- γ and TNF- α levels than those without DKD. Diabetic DKD patients had a significantly higher frequency of *IL-10* -1082A allele than those without DKD ($P=0.001$). No significant association of *IL-6* -174/-597 haplotypes with DKD risk was detected ($P=0.188$). Distribution of *IL-10* -592/-819/-1082 haplotypes differ significantly between T2DM patients with/without DKD ($P=0.014$). Diabetic DKD patients had a significantly lower frequency of *IL-10* -592C/-819C/-1082G haplotype than those without DKD ($P=0.002$). **Conclusion:** Although inflammatory cytokine genotypes and, more importantly, haplotypes may have the potential to identify those patients at risk of DKD, hence, improving DKD predisposition prediction, further investigations regarding their real clinical significance is warranted in a large cohort of patients.