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Serum CXCL16 in Relation to Diabetic Nephropathy in Type 2 Diabetes Egyptian Patients

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Abstract

Background: CXC chemokine ligand 16 (CXCL16) is both an oxidized low density lipoprotein receptor (ox-LDL) and a chemokine with a potential role in the pathogenesis of Diabetic Nephropathy (DN).

Aim of Study: The aim of this work is to evaluate the relationship between serum CXCL16 levels and (DN) in type 2 Egyptian diabetic patients.

Methods: This case-controlled study was conducted on 80 T2DM patients (group A1: 24 patients with normoalbuminuria; group A2: 28 patients with microalbuminuria, and group A3: 28 patients with macroalbuminuria) and 20 age- and sex-matched healthy controls. All were subjected to a complete clinical evaluation and laboratory investigations which included quantitative measurements of urinary albumin/creatinine ratio and serum CXCL16 levels by enzyme-linked immunosorbent assays.

Results: Serum CXCL16 levels were significantly higher in all T2DM groups compared with healthy controls. There was a positive correlation between CXCL16, creatinine and ACR (r=0.48, p:0.039 and r=0.53, p:0.019, respectively), whereas it was significantly negatively associated to eGFR (r=–0.46, p:0.05). Regression analysis indicated that CXCL16 levels were continued significantly correlated with creatinine, eGFR and ACR (p:<0.05, for all).

Conclusion: Egyptian type 2 DM patients are characterized by increased serum CXCL16 levels. There was a statistically significant correlation between CXCL16 levels and conventional renal markers reflecting disease progression.

Key Words: *Type 2 diabetes mellitus – Nephropathy – Urinary albumin/creatinine ratio – CXCL16.*

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Introduction

DIABETES is a snowballing health problem in Egypt with a harsh impact on health and economy. At present, the prevalence of Type 2 Diabetes (T2D) in Egyptian adults is around 15.6% **[1]**.

Diabetic Nephropathy (DN) is one of the commonest long-term diabetic complications and is the leading cause of End-Stage Renal Disease (ESRD) worldwide **[2]**. Currently, DN is defined in both type 1 and type 2 diabetes as the presence of persistently raised urinary Albumin/Creatinine Ratio (ACR) of ›_30mg/g, confirmed in at least 2 of 3 morning samples and/or sustained decrease in eGFR below 60ml/min per 1.73m^2 in a patient with known diabetes in the absence of signs of other forms of renal disease **[3]**. Though these assays are simple, give prognostic information, and are useful to guide treatment decisions; they have some restrictions that limit their application as markers for the early diagnosis of DN **[4]**. Albuminuria primarily reflects glomerular dysfunction, and is less sensitive to tubule-interstitial and vascular damages. In fact, tubule-interstitial and/or vascular histological changes are more common than glomerulopathy in DN of T2DM **[5]**. Therefore, current research pursues to develop new markers in blood or urine that could improve diagnostic accuracy of early DN **[6]**.

CXC chemokine ligand 16 (CXCL16) appertains to the CXC chemokine family and comprises of four distinctive domains: The CXC chemokine domain, mucin-like stalk domain, trans-membrane domain and cytoplasmic tail. It is mainly produced by Dendritic Cells (DCs) in lymphoid organ T-cell zones and by cells in the splenic red pulp **[7]**.

CXCL16 exists in two forms: Transmembrane and soluble. As a transmembrane molecule, CXCL 16 is expressed by human macrophages and dendritic cells and act as a scavenger receptor for phosphatidyl-serine and oxidized low-density lipoprotein (SR-PSOX), thus CXCL16 may play important roles in internalization and degradation of oxidized Low-Density Lipoprotein (ox-LDL) [8].

Evidence has been reported that early stages of DN is characterized by increased expression of CXCL16 scavenger receptor in human podocytes resulting in enhanced cellular uptake of ox-LDL. Accordingly, CXCL16 may represent a potential novel target for early diagnosis and therapeutic intervention in DN [9]. This study aimed to explore the relationship between serum CXCL 16 level and diabetic nephropathy in type 2 Egyptian diabetic patients.

Subjects and Methods

This single-center, prospective, case-controlled study was conducted in Diabetes Clinic at Cairo Kidney Center (CKC), Cairo, in the period between October 2018 and June 2019. A total of 80 patients with T2DM were selected according to American Diabetic Association (2018) diagnostic criteria for T2DM [10]. In addition, 20 age-and sex-matched healthy volunteers were included as control group. The studied patients were classified into 3 groups according to their albuminuria measured by urinary Albumin/Creatinine Ratio (ACR): 24 patients with normo-albuminuria (ACR <30mg/g) as group A1, 28 patients with persistent microalbuminuria (ACR ≥30 to 300mg/g) as group A2, and 28 patients with persistent macroalbuminuria (ACR >300mg/g) as group A3. DN stages were classified according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) [11]. The control group underwent a routine health examination at the CKC, had no history of medical disorders, and were not taking regular medications.

Exclusion criteria were age under 18 years, type 1 diabetes, patients with ESRD, urinary tract infection, history of infectious diseases, coronary heart disease, liver disorders, thyroid dysfunctions, malignant tumors, current treatment with systemic corticosteroids, and pregnancy, or being on dialysis or transplantation. All participants were subjected to a complete clinical history and medical examination including medications and duration of diabetes, Body Mass Index (BMI) and arterial blood pressure measurement, and fundus examination to assess diabetic retinopathy. BMI was calculated as weight in kilograms, divided by height in meters squared (kg/m^2) [12]. Fasting blood samples were collected in a stable state and divided into EDTA and plain blood collection tubes. Thereafter, serum samples were immediately divided into 2 parts: The first was frozen at –80ºC until use for CXCL 16 assay, and the second part was used for estimation of biochemical variables (creatinine, fasting glucose, total cholesterol, Low-Density Lipoprotein-cholesterol (LDL-c), High-Density Lipoprotein-cholesterol (HDL-c) and triglycerides). All were measured with VITROS® 350 Chemistry Analyzer (Ortho Clinical Diagnostics). Glomerular Filtration Rate (GFR) was estimated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation: $eGFR=141 * \min(Scr/\kappa, 1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female]) X 1.159 [if black] and reported as ml/minute/1.73 m^2 where: Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 [13]. Moreover, glycosylated hemoglobin (HbA1c) was measured by nephelometry methodology (Mispa-i2, Agappe Diagnostics LTD, India).

Morning urine sample, obtained using sterile container without preservatives for assessment of urinary ACR. Serum CXCL16 concentration was assayed using commercially available quantitative sandwich Enzyme Linked Immunosorbent Assay (ELISA) according to the manufacturers' instructions (EIAab®, Wuhan EIAab Science, China). In addition, urinary ACR ELISA based kit was provided by MyBioSource, USA. All samples were analyzed in duplicate.

Compliance and ethical standards:

The protocol of this study was first approved by the scientific board of of CKC, and all patients provided written informed consent. The study protocol conforms to the provisions of the declaration of Helsinki 1946, as revised in 2013.

Statistical analysis:

Data analysis was performed using the statistical package SPSS version 15 software (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean ± standard error of the mean for quantitative variables and percentage for qualitative values. One way Analysis of Variance (ANOVA) followed by Tukey-Kramer multiple comparison test, and independent sample *t*-test were performed to compare continuous variables and Chi-square test was used to compare categorical variables in different groups. Pearson's correlation analysis was performed to determine the relationships between

CXCL16 levels and the different measured parameters, followed by calculation of coefficients of determination (r-squared, r^2) to test for a simple linear regression relationship. In all statistical tests, p-values ≤ 0.05 were considered significant **[14]**.

Results

Characteristics of the studied groups are summarized in (Table 1). Our data revealed no significant difference between healthy controls and DN groups, as well as between the three studied patient groups after segregation of controls from the analyses regarding age, sex, BMI, systolic and diastolic blood pressure, total cholesterol, triglyceride, and LDL-c levels. In lipid profile, only HDL-c level was significantly lower in A1 and A3 groups when compared with that of control group (p:0.09 and <0.001, respectively). Moreover, our findings indicated that the use of antihypertensive drugs; Angiotensin-Converting Enzyme (ACE) inhibitors; and insulin, diabetes duration (years) and % of retinopathy were similar in 3 studied patient groups ((Table 1), all p>0.05). As regard creatinine level, it was significantly higher in A2 and A3 groups than control group (p:0.07 and 0.09, respectively). Inversely, estimated GFR (eGFR) was significantly lower in A2 and A3 groups than in healthy controls (p:0.006 and 0.025, respectively). Nevertheless, there were no significant differences in creatinine and eGFR between A1 group and controls, as well as between 3 studied patient groups after segregation of controls from the analyses (p:>0.05, for all). Besides, Albumin/Creatinine Ratio (ACR) was progressively increased from A1group to A3 group (p:0.002), but no significant difference was detected between A1 group and controls (p:0.35). Concerning Fasting Blood Sugar (FBS) and glycated hemoglobin (HbA1C) levels, significant increases were seen in the three studied DN groups (A1, A2 and A3) when compared to controls (all p<0.05), but no significant differences were evident among the three patient groups (p:0.26 and 0.63, respectively).

Table (1) and Fig. (1A) showed that patients in the three DN groups (A1, A2 and A3) had significantly higher serum CXCL16 levels than control group (p:0.04, 0.006, and 0.03 respectively). Although there was a significant difference in serum levels of CXCL16 in A1 group as compared to both A2 and A3 groups, no significant difference was evident between A2 group and A3 group (p: 0.42).

To investigate the relationship between serum CXCL 16 and conventional markers of kidney function in subjects with DN, Pearson's correlation analysis was performed. As shown in Figs. (2A,C) serum CXCL16 demonstrated moderate positive relationship with serum creatinine and ACR (r= 0.48, p:0.039 and r=0.53, p:0.019, respectively), whereas it was significantly negatively associated to eGFR (r=–0.46, p:0.05) Fig. (2B). To determine if any markers correlated with CXCL 16 level, we examined the linear correlation between selected renal biomarker and CXCL16 levels. Table (2) showed that eGFR, creatinine and urinary ACR were continued significantly correlated with serum CXCL16 (r^2=0.21; p:0.0048, r^2=0.24; p:0.04 and r^2=0.28; p:0.02, respectively). Of note, all other variables involving lipid profile, FBS, and HbA1C were all ruled out during regression analysis (p >0.05, for all).

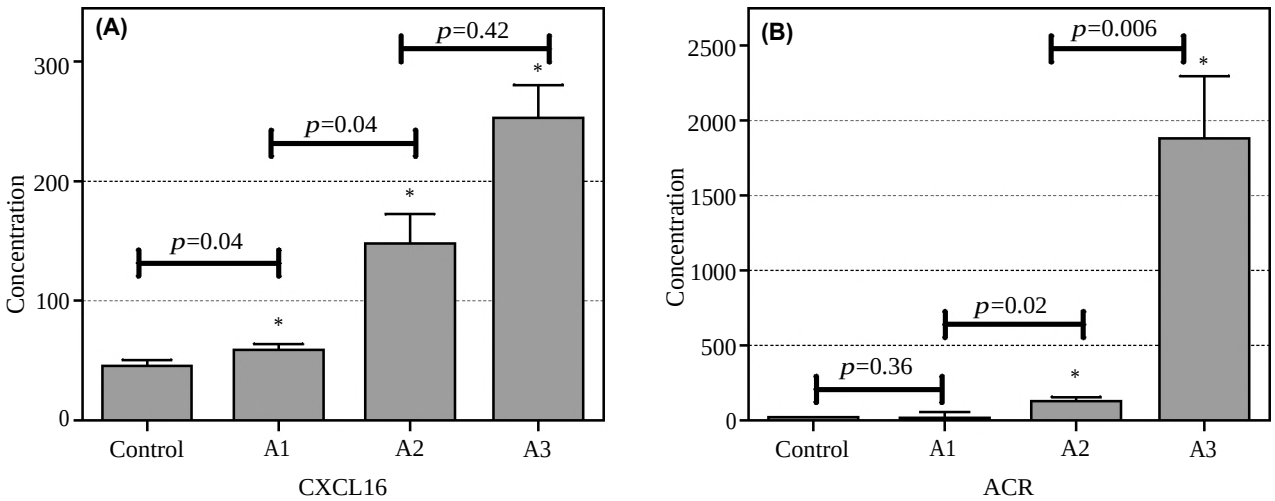

Fig. (1): Serum CXCL16 level (A) and albumin-to-creatinine ratio; ACR (B) in different studied groups.

*: Significant difference with control.

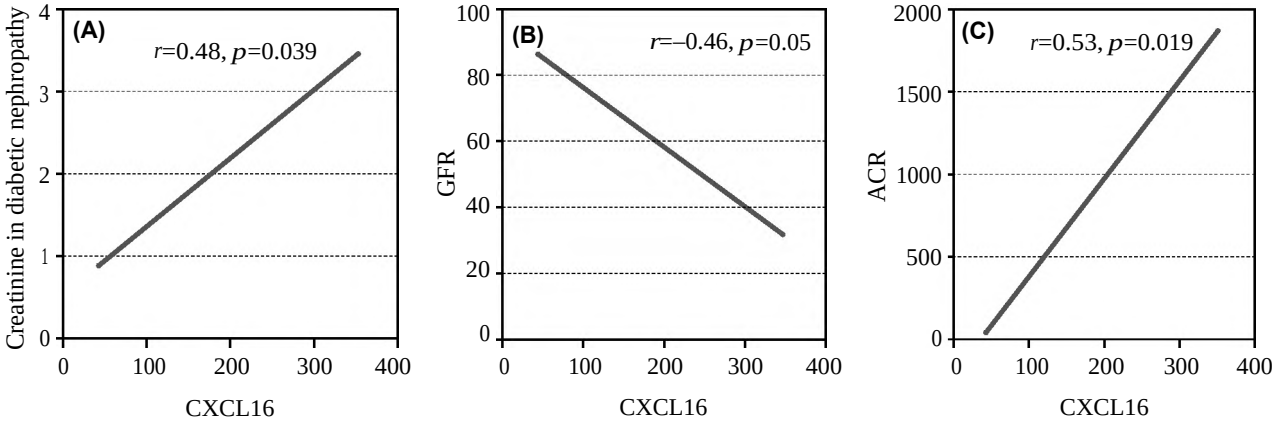

Fig. (2): Statistically significant Pearson's correlations with serum CXCL16. A) CXCL16 and serum creatinine. B) CXCL16 and estimated glomerular filtration rate; eGFR. C) CXCL16 and albumin-to-creatinine ratio; ACR.

Table (1): Characteristics of controls and diabetic cases grouped according to the albuminuria categories.

Variables	Controls (n=20)	A1 (n=24)	A2 (n=28)	3 (n=28)	*p*-value (A1/A2/A3
Age (years)	50.10±2.8	55.60±8.80a	62.86±4.20a	54.4±40a	0.49
Sex, female (%)	32.50%	35.00%a	40.00%a	37.00%a	0.34
BMI (kg/m^2)	24.50±1.36	31.50±2.58a	31.46±1.96a	30.19±2.35a	0.89
Clinical markers:					
Systolic BP, mmHg	113.0±2.3	127.0±8.0a	142.1±10.23a	140±10.77a	0.56
Diastolic BP, mmHg	77.5±1.29	79.0±6.4a	87.14±6.15a	82.86±7.38a	0.72
Antihypertensive use, %	–	80%a	71 %a	71 %a	0.93
ACE inhibitors use, %	–	40%a	85%a	57%a	0.24
Insulin use, %	–	20%a	43%a	57%a	0.42
Diabetes duration, years	–	8.70±8.75a	13.64±8.72a	16.43±8.01a	0.46
DR, %	–	14%a	40%a	43%a	0.46
Kidney function markers:					
Creatinine, mg/dl	0.88±0.09	1.10±0.24a	1.43±0.40a*	2.84±0.90a*	0.14
eGFR, ml/min/1.73m^2	109.0±4.95	77.1±16.25a	69.06±8.97a*	53.17±19.17a*	0.56
ACR, mg/g	12.40±1.96	17.80±3.90a	129.7±31.90b*	1885.0±413.9c*	0.002
Glycemic markers:					
Fasting glucose, mg/dl	88.2±2.15	133.0±9.37a*	136±11.47a*	174.9±27.75a*	0.26
HbA1C, %	4.86±0.14	7.13±0.44a*	7.17±0.49a*	7.90±0.82a*	0.63
Lipid markers:					
Cholesterol, mg/dl	148.1±5.80	164.2±21.07a	149.3±15.22a	171.0±13.77a	0.61
Triglycerides, mg/dl	120.0±10.48	180±35.3a	127.6±33.59a	149.1±33.83a	0.59
HDL-c, mg/dl	40.80±1.58	31.2±3.15a*	37.14±5.39a	26.57±1.56a*	0.159
LDL-c, mg/dl	85.4±17.7	97±32.9a	90.7±30.2a	114±40.6a	0.29
Cxcl16 (pg/ml)	45.90±5.30	52.0±8.90a*	118.3±64.40b*	181.4±6.4b*	0.07

Data are expressed as mean ± standard error (SE) or (%).
Mean values in the same raw bearing the same superscript letter do not differ significantly whereas those bearing.
* : Superscript means significant difference compared to controls.
BMI : Body Mass Index.
ACE : Angiotensin-Converting Enzyme.
DR : Diabetic Retinopathy.
eGFR : Estimated Glomerular Filtration Rate.
BMI : Body Mass Index.
ACE : Angiotensin-Converting Enzyme.
DR : Diabetic Retinopathy.
eGFR : Estimated Glomerular Filtration Rate.

Table (2): Coefficients of determination for regression models describing CXCL16 level versus different variables in diabetic nephropathy patients.

Variable	R Square	*p*-value
Fasting blood sugar	0.07	0.29
HbA1C	0.01	0.78
eGFR	0.21	0.05
Creatinine	0.24	0.04
ACR	0.28	0.02
Cholesterol	0.01	0.68
Triglycerides	0.01	0.69
HDL	0.04	0.43
LDL	0.01	0.69

Discussion

Diabetic nephropathy is a potentially disastrous complication of diabetes causing end stage renal disease. Although the albumimuria is considered to be the golden standards for forecasting DN onset and progression **[15]**, there are some limitations that limit its application as an early indicator of DN risk. Therefore, new alternative markers are being explored, such as inflammatory chemokines. CXCL16 is both an oxidized low density lipoprotein receptor (ox-LDL) in human podocytes and a chemokine with a potential role in the pathogenesis of renal dysfunction in diabetes patients. Lately, a lot of interest has evolved in studying CXCL16 as an alternative to ACR for the early diagnosis of DN. To the best of knowledge, there is paucity of data on the value of serum CXCL 16 in type 2 Egyptian diabetic patients with nephropathy; however, it has been tested in European patients with diabetic kidney disease with different eGFR (G1-G4) and albuminuria (A1-A3) categories as well as in a Chinese setting **[16,17]**. As it was the aim of the current study to explore the relationship between serum CXCL16 level and diabetic nephropathy in type 2 Egyptian diabetic patients, only patients with DN ranging from normal to severely increased albumin excretion were included.

Our study showed that serum CXCL16 level was increased in normoalbuminuric diabetic patients, even without early signs of glomerular injury; compared with age-and sex-matched healthy control subjects indicating usefulness of serum CXCL 16 as a marker of DN at a very early stage, even before the presence of microalbuminuria. Also, this study reported that CXCL16 levels increased per albuminuria stratum; though, the difference between A2 and A3 group was insignificant. Our results suggest that CXCL16 is involved in the pathogenesis of renal dysfunction in diabetes patients as supported by three findings. First, serum CXCL16 levels were significantly increased in diabetes patients with renal disease when compared with healthy subjects. Secondly, correlation analysis revealed that serum CXCL16 levels were moderately associated with creatinine, ACR, and eGFR in DN patients Fig. (2), implying that serum CXCL16 levels could be a usable marker for reflecting the progression of renal damage caused by diabetic disease. Thirdly, coefficients of determination (r^2) for regression analysis indicate that the variability of CXCL16 level is well explained by independent conventional kidney markers in DN patients.

Alike; Zhao and colleagues **[17]**, studied association of serum CXCL16 levels with diabetic subjects with and without renal disease in 120 Chinese patients. They reported that serum CXCL16 levels were significantly higher in DN subjects compared to T2DM and healthy control groups ($p<0.05$). Similarly, in another study by Elewa and Colleagues **[16]** who examined predictors of serum CXCL16 levels in diabetic CKD patients in a European setting. They demonstrated that CXCL16 levels increased with increasing eGFR category, as well as with increasing ACR category. Moreover, in agreement to our findings, Zhao and Colleagues **[17]**, showed that serum CXCL16 levels were positively correlated with Blood Urea Nitrogen (BUN), creatinine, and uric acid and negatively correlated with Creatinine Clearance Rate (CCR), eGFR, and thus may serve as an indicator of renal injury in Chinese patients with DN. Also, our results were in consensus with Elewa and colleagues **[16]** findings, which revealed through multivariate analysis that low eGFR may serve as an independent predictor of serum CXCL 16 level in European diabetic patients with chronic kidney disease.

Tight glucose control has clearly been shown to reduce onset and progression of diabetic kidney disease in both Type 1 and Type 2 diabetic patients **[18]**. Though, this study showed that CXCL16 was not significantly associated with glycemic control markers. Correspondingly, previous reports disclosed insignificant correlations between serum CXCL16 and glycemic markers (FBS, 2-hours blood glucose and HbA1C) **[16,17]**. Of note, this finding warrant added study in larger populations before results can be generalizable.

Diabetic dyslipidemia [high triglycerides (TGs) and/or low HDL-cholesterol (HDL-C) levels)] has been shown to play pivotal roles in the pathogenesis of DN **[19]**. Two mechanisms were proposed to explain how dyslipidemia-induced CXCL 16 pathway may contribute to lipid nephrotoxicity in DN,

including the increased uptake of ox-LDL through CXCL16 receptors on human podocytes, which result in glomerular injury and albuminuria, as well as inflammation-induced CXCL 16 pathway, which induce tubulointerstitial injury in mouse diabetic nephropathy **[20,21]**. Our results contrast with a significant body of research revealing that serum cholesterol, TG, HDL-c, and LDL-c significantly related to the level of albuminuria in type 2 DM patients **[22]**. In addition, the present work does not imply that increased CXCL16 level is related to lipid profile abnormalities in different stages of DN.

There were some limitations in this study, firstly, it was a single center-based study with a small sample size and inherent selection bias. Secondly, the case-controlled nature of this study does not permit a causal link between CXCL 16 and pathogenesis of DN. Lastly, we do not perform adjustment for creatinine, ACR, or eGFR as confounding factors.

In conclusion, this study verifies the significant increase of serum CXCL 16 in patients with diabetic nephropathy and its correlation with creatinine, ACR, and eGFR as markers of disease severity and albuminuria progression. Furthermore, CXCL16 could be used as a diagnostic marker of early DN in Egyptian patients with T2DM. Nonetheless, it was not significantly correlated with anthropometric, disease-related variables, dyslipidemia, or impaired glycemic control in studied subjects. Further studies are recommended on a large number of cases of both types of diabetes, using multiple logistic regression analysis to do adjustment for any confounding factors, and drawing Receiver Operator Characteristic curve (ROC) curve to evaluate the clinical performance characteristics of serum CXCL16 in relation to ACR as a diagnostic marker of early DN.

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Compliance with ethical standards:

Conflicts of interest: The authors declare that they have no conflicts of interest to disclose.

Ethical approval: The study protocol was approved by the corresponding ethical committee.

Informed consent: Informed consent was obtained from all participants.

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علاقة سى اكس سى ال١٦ فى المصل بمرضى إعتلال الكلى السكرى لدى المرضى المصريين المصابين بداء السكرى من النوع الثانى

تشير بعض الدراسات إلى أهمية دور الكيموكين CXCL16 كمستقبل للبروتينات الدهنية المؤكسدة منخفضة الكثافة وكذلك فى تطور مرض إعتلال الكلية السكرى.

تم عمل هذا البحث بغرض دراسة مستوى الكيموكين CXCL16 فى الدم فى المرضى المصريين المصابين بإعتلال الكلى السكرى الناتج عن النوع الثانى من داء السكرى.

تم تصميم هذا البحث ليشمل عدد ٨٠ مريض مصابين بالنوع الثانى من داء السكرى تم تقسيمهم إلى ٣ مجموعات من المرضى على حسب كمية بيلة الألبومين وكذلك مجموعة ضابطة تشمل ٢٠ شخصاً أصحاء. وتم إجراء البحث على المرضى المترددين على عيادة مرضى السكرى بمركز القاهرة لأمراض الكلى بالقاهرة. خضع جميع المرضى للفحص الطبى الشامل وفحوصات معملية شملت مستوى الجلوكوز، سكر الخلية، الدهون بأنواعها المختلفة، نسبة الزلال إلى الكرياتينين فى البول وكذلك مستوى الكيموكين CXCL16 فى الدم.

أظهرت نتائج البحث إرتفاع مستوى CXCL16 فى مجموعات المرضى الثلاث مقارنة بالمجموعة الضابطة ووجود ترابط إيجابى بين ومستوى الكرياتينين بالدم ونسبة الزلال إلى الكرياتينين فى البول، بينما توجد ترابط سلبى مع معدل الترشيح الكلوى.

الإستنتاج: يتضح من نتائج هذا البحث أن مستوى CXCL16 يتزايد فى مرضى إعتلال الكلى السكرى ويترابط بطريقة ذات أهمية إحصائية مع وظائف الكلى التقليدية والتى تعكس تطور هذا المرض.