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Original Paper

Circulating CXCL16 in Diabetic Kidney Disease

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Key Words
Cardiovascular Risk • Chemokine • Chronic Kidney Disease • CXCL16 • Diabetes • Inflammation

Abstract
Background/Aims: Chronic kidney disease and, specifically, diabetic kidney disease, is among the fastest increasing causes of death worldwide. A better understanding of the factors contributing to the high mortality may help design novel monitoring and therapeutic approaches. CXCL16 is both a cholesterol receptor and a chemokine with a potential role in vascular injury and inflammation. We aimed at identifying predictors of circulating CXCL16 levels in diabetic patients with chronic kidney disease. ***Methods:*** We have now studied plasma CXCL16 in 134 European patients with diabetic kidney disease with estimated glomerular filtration rate (eGFR) categories G1-G4 and albuminuria categories A1-A3, in order to identify factors influencing plasma CXCL16 in this population. ***Results:*** Plasma CXCL16 levels were 4.0±0.9 ng/ml. Plasma CXCL16 increased with increasing eGFR category from G1 to G4 (that is, with decreasing eGFR values) and with increasing albuminuria category. Plasma CXCL16 was higher in patients with prior cardiovascular disease (4.33±1.03 vs 3.88±0.86 ng/ml; p=0.013). In multivariate analysis, eGFR and serum albumin had an independent and significant negative correlation with plasma CXCL16. ***Conclusion:*** In diabetic kidney disease patients, GFR and serum albumin independently predicted plasma CXCL16 levels.

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Introduction

Chronic Kidney Disease is the non-transmissible cause of death that increased the most worldwide over the past 20 years [1]. The increasing incidence of diabetic kidney disease is one of the key drivers of this trend. Cardiovascular disease (CVD) is one of the top causes of death in CKD patients [2]. However, the pathogenic mechanisms linking CKD with CVD remain poorly understood and thus, therapy is unsatisfactory. Chronic low grade systemic inflammation and lipid abnormalities are thought to play a role. Among inflammatory factors, chemokine (C-X-C) ligand 16 (CXCL16) is a small cytokine and cell surface receptor belonging to the CXC chemokine family that has been linked to lipid metabolism and to vascular disease [3-5].

CXCL16 is synthesized as a transmembrane molecule that is expressed as a cell surface-bound molecule, as well as a soluble chemokine [6]. CXCL16 interacts with the CXC-chemokine receptor CXCR6 in leukocytes and other cells promoting chemotaxis (soluble CXCL16) or cell adhesion (membrane-bound CXCL16) [7]. In addition, CXCL16 was originally described as a scavenger receptor for phosphatidylserine and oxidized low-density lipoprotein (oxLDL) and termed SR-PSOX [8]. Inflammatory cytokines such as interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα) promote CXCL16 expression [7]. CXCL16 has been implicated in the pathogenesis of vascular, kidney and lung injury. Upon cleavage of the mucin-like stalk, the CXCL16 chemokine is released and functions as a chemoattractant for CXCR6+ T, natural killer (NK), B, and dendritic cells [9-12].

CXCL16 is expressed in mouse and human injured kidneys and coronary and carotid atherosclerotic lesions, colocalizing with tubular cells, infiltrating macrophages, lipid-laden intimal macrophages and smooth muscle cells [13-15]. However, studies evaluating soluble CXCL16 as a potential biomarker of coronary artery disease have been inconsistent [16, 17]. A polymorphic variant of CXCL16 was associated with increased coronary artery stenosis in post-infarction patients [18].

The high stability of CXCL16 (e.g., little circadian variation, minor influence of food intake, and little variation after freeze and thaw cycle) further supports a potential role of CXCL16 as a biomarker in clinical samples [19]. High circulating CXCL16 levels within 24 hours of admission for myocardial ischemia predicted long-term mortality and congestive heart failure development [19]. However decreased or increased CXCL16 levels in both stable and unstable angina were reported in different studies [17, 20, 21]. A potential explanation for this variability is the presence of factors that are associated to both increased CXCL16 levels and adverse cardiovascular outcomes, as might be CKD. A majority of patients with ischemic heart disease may have reduced glomerular filtration rate (GFR): 76% had eGFR category G 2-5 in a recent prospective cohort [22]. In this regard, serum CXCL16 levels were significantly increased in CKD and gout subjects [23, 24]. These findings suggest that CXCL16 may be a marker of renal disease. No significant differences in serum CXCL16 levels between healthy and type 2 diabetes mellitus (DM) subjects were found.

However, CXCL16 levels were higher in Chinese patients with diabetic kidney disease (DKD) than in CKD patients without diabetes [24]. In this regard, there are differences between Asians and Caucasians in terms of prevalence of proteinuric DKD (higher in Asians), progression of CKD (faster in Asians) and CKD-associated mortality (lower in Asians) [25, 26]. Thus, information derived from other ethnicities is required to better understand the predictors of CXCL16 levels in DKD.

We have now explored the determinants of circulating CXCL16 levels in diabetic CKD patients in a European setting.

Material and Methods

Study population

The study was performed at Fundación Jiménez Díaz University Hospital—Autonomous University of Madrid and approved by the IIS-Fundacion Jimenez Diaz Ethics Committee. Before enrollment, the study was fully explained to all participating patients and an informed consent was signed. This cross-sectional observational study assessed baseline data from 134 Caucasian European diabetic patients with CKD. Patients not on dialysis attending the monographic outpatient diabetic kidney disease clinic were offered to participate. No limits were provided for estimated glomerular filtration rate (eGFR) or urinary albumin:creatinine ratio (UACR). The CKD-EPI formula was used for eGFR calculation [27]. Exclusion criteria were age under 18 years, positive serology for Hepatitis C Virus (HCV), Hepatitis B Virus surface Antigen (HbsAg) or Human Immunodeficiency Virus (HIV), being on dialysis or transplantation or refusal to participate or sign an informed consent. All individuals were subjected to a complete clinical history, including assessment of current pharmacological treatment, blood and urine analysis, and transthoracic echocardiogram. Plasma samples were obtained in a stable state, in the absence of superimposed inflammatory conditions beyond the systemic inflammation associated with diabetes, CKD or cardiovascular disease. Plasma samples were collected after a 12 h fast and immediately processed and frozen at 80ºC until use. Plasma CXCL16 was assessed by ELISA (R&D Systems, Minneapolis, USA). The limit of detection was 0.017 ng/ml, and the coefficients of inter- and intra-assay variability were 9.6 % and 4.2 %.

Statistical Methodology

Data analyses were performed using statistical software R version 3.0.1. Quantitative variables were described by mean and standard deviation or by median and inter-quartile ranges (IQR); 25% percentile and 75% percentile. Qualitative variables were described by frequency tables and contingency tables. Associations between quantitative and qualitative variables were assessed using Student's t test or Mann-Whitney test when comparing two groups, and ANOVA or Kruskal-Wallis test when comparing three or more groups. Correlations between quantitative variables were evaluated using Spearman correlation coefficient. In order to identify potential predictors of quantitative outcomes, multivariable linear regression models were fitted. Models were built using forward stepwise procedures in order to maximize R-Squared with the smallest number of predictor variables. The statistical significance of variables in the models was assessed by ANOVA test.

Results

We performed a cross-sectional analysis of baseline data from patients with diabetic CKD not on dialysis on regular follow-up visits in the diabetic nephropathy clinic at Fundación Jiménez Díaz University Hospital. Plasma CXCL16 was assessed in 134 patients; all of them were diabetic and most (130/134) had CKD (Table 1). Most patients were in eGFR category G3 (63/134, 47%). Mean age was 67.9±13.9 years and a majority was male (92/134, 69%). This population was borderline obese with mean BMI 29.7±4.2 kg/m^2.

Mean eGFR was 56.0±25.1 ml/min/1.73 m^2 and the median (IQR) UACR was 123.6 (27.1, 386.7). In 17 (13%) patients UACR was >1000 mg/g). All patients were on anti-hypertensive agents and most on RAAS blockade (131, 98%), anti-platelet agents (90, 67%), oral hypoglycemic agents (84, 63%), insulin (90, 67%) and lipid lowering agent (113, 84%). Only 48 (36%) were on vitamin D or VDR activators, 12 (9%) on phosphate binders and 7 (5%) on erythropoiesis stimulating agents.

Mean±SD plasma CXCL16 levels were 4.0±0.9 ng/ml. We explored the association of plasma CXCL16 levels with clinical, echocardiogram, therapeutic and laboratory parameters. Plasma CXCL16 increased with increasing eGFR category (that is, with decreasing eGFR) (Figure 1) and with increasing UACR (Figure 2). Table 2 shows CXCL16 values according to GFR (G) and albuminuria (A) categories.

Plasma CXCL16 was higher in patients with prior CVD (4.33 ±1.03 vs 3.88± 0.86 ng/ml; p=0.0132). The univariate analysis of plasma CXCL16 (ng/ml) with quantitative variables disclosed positive correlations between CXCL16 and age, pulse pressure, UACR, serum phosphorus, alkaline phosphatase and intact PTH. CXCL16 had a negative correlation with diastolic blood pressure, eGFR, hemoglobin, serum total iron binding capacity, serum albumin, CO_2, serum calcium, $1,25(OH)_2D$ and folic acid (Figure 3) (Table 3).

In multivariate analysis, eGFR and serum albumin remained independently and significantly negatively correlated with plasma CXCL16, while UACR was independently positively correlated with plasma CXCL16 when serum albumin was not part of the equation (Table 4). The best R squared obtained was 0.30.

Discussion

The main findings from this study are that in a European, non-dialysis DKD population, eGFR and serum albumin were independent predictors

Table 1. Patient characteristics (n=134 diabetic CKD patients). Quantitative data expressed as mean ±SD or median (interquartile range) as appropriate

Variable		Value
Age (years)		67.9±13.9
Males n (%)		92 (68.7)
DM n (%)		134 (100)
Hypertension n (%)		128 (95.5)
CVD n (%)		35 (26)
Albuminuria category n (%)	A1	35 (26)
	A2	56 (42)
	A3	43 (32)
GFR category n (%)	G1	16 (11.9)
	G2	36 (26.9)
	G3a	29 (21.6)
	G3b	33 (24.6)
	G4	20 (14.9)
Body Mass Index (kg/m^2)		29.7±4.2
Systolic BP (mmHg) (134)		143.1±17.8
Diastolic BP (mmHg) (134)		75.2±11.8
Pulse Pressure (mmHg) (134)		67.9±17.1
Serum Creatinine (mg/dl) / (134)		1.4±0.6
eGFR (CKD-EPI) (ml/min/1.73 m2) / (134)		56.0±25.1
Serum Uric Acid (mg/dl) / (134)		6.5±1.7
Serum Glucose (mg/dl) / (134)		141.9±50.2
Serum HbA1C (%) / (134)		7.5±1.2
Haemoglobin (g/dl) / (134)		13.6±1.7
Serum Albumin (g/dl) / (134)		4.1±0.4
Serum hsCRP (mg/dl) / (63)		1.2±3.3
Serum Prealbumin (mg/dl) / (114)		27.3±6.7
Serum CO2 (mEq/L) / (127)		27.4±3.6
Serum Calcium (mg/dl) / (134)		9.5±0.5
Serum Phosphorus (mg/dl) / (134)		3.5±0.6
Serum Alkaline Phosphatase (IU/l) / (134)		84.0±32.6
Serum TIBC (μg/dl) / (134)		320.6±67.6
Serum intact PTH (pg/ml) / (131)		52.7 (35.0, 93.6)
Serum 25(OH)D (ng/ml) / (131)		20.1±10.3
UACR (mg/g) / (134)		123.6 (27.1, 386.7)

CKD A and G categories were defined according to KDIGO [32] as follows: Albuminuria A1: UACR <30 mg/g; A2: UACR 30 – 300 mg/g; A3: UACR >300 mg/g. GFR: G1: eGFR ≥90 ml/min/1.73m^2; G2: eGFR 89 – 60 ml/min/1.73m^2; G3a: eGFR 59 – 45 ml/min/1.73m^2; G3b: eGFR 44 – 30 ml/min/1.73m^2; G4: eGFR 29 – 15 ml/min/1.73m^2; G5: eGFR <15 ml/min/1.73m^2

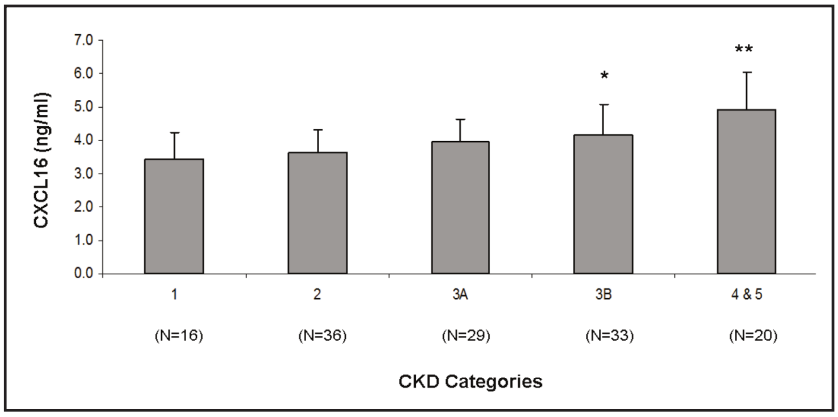

Fig. 1. Plasma CXCL16 values according to estimated glomerular filtration rate (eGFR) G category. * p<0.05 vs CKD category G1 and p<0.002 vs CKD categories G1+G2; ** p<0.01 vs stage 1 and p <0.0001 vs CKD categories G1+G2.

of CXCL16 that together with UACR explain around 30% of the variability in CXCL16 levels. While in univariate analysis, higher CXCL16 levels were associated with CVD and a number of other markers, these associations were no longer significant when eGFR was in-

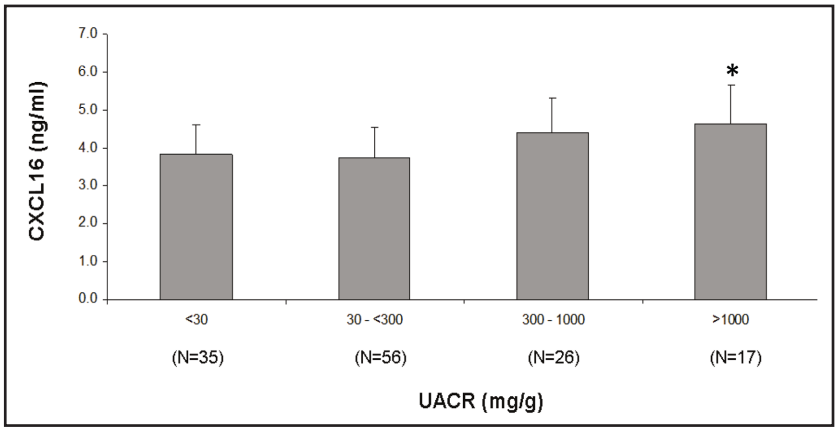

Fig. 2. Plasma CXCL16 values according to UACR. * p <0.01 vs UACR <30 mg/g.

Table 2. Circulating CXCL16 levels (ng/ml) according to CKD G and A categories. Median [IQR] (n)

		Albuminuria category			
		A1	A2	A3	Total
eGFR category	G1/G2	3.50 [3.25, 3.86] (14)	3.56 [3.02, 3.87] (29)	3.64 [3.32, 3.84] (9)	3.58 [3.03, 3.88]
	G3/G4	3.77 [3.33, 4.15] (21)	3.81 [3.52, 4.07] (27)	4.65 [4.24, 5.05] (34)	4.08 [3.57, 4.74]
	Total	3.66 [3.26, 4.13]	3.60 [3.15, 3.95]	4.38 [3.67, 3.94]	

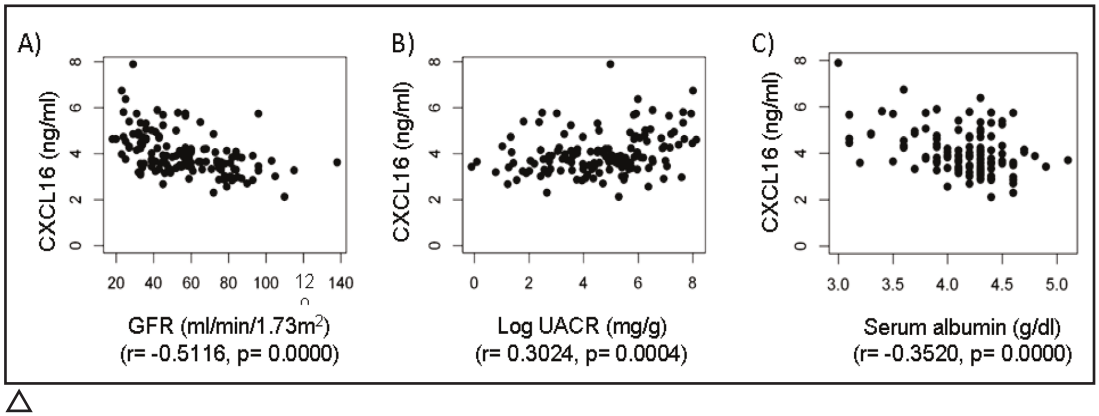

Fig. 3. Statistically significant univariate correlations with plasma CXCL16 that were also significant in at least some multivariate models. A) CXCL16 and estimated glomerular filtration rate (eGFR). B) CXCL16 and UACR. C) CXCL16 and serum albumin.

Table 3. Correlations between plasma CXCL16 (ng/ml) and quantitative variables in univariate analysis. Only statistically significant (p< 0.05) results are shown

Variable	N	Coefficient	P value
Age (years)	134	0.1942	0.0246
Diastolic BP (mmHg)	134	- 0.2089	0.0154
Pulse Pressure (mmHg)	134	0.1865	0.0310
eGFR (ml/min/1.73 m^2)	134	- 0.5116	0.0000
UACR (mg/g)	134	0.3024	0.0004
Hemoglobin (g/dl)	134	- 0.3017	0.0004
Serum Albumin (g/dl)	134	- 0.3520	0.0000
Serum CO_2 (mEq/l)	127	- 0.1911	0.0314
Serum Calcium (mg/dl)	134	- 0.2284	0.0079
Serum Phosphorus (mg/dl)	134	0.2230	0.0096
Serum Alkaline phosphatase (IU/l)	134	0.2929	0.0006
Serum TIBC (µg/dl)	134	- 0.2399	0.0052
Serum intact PTH (pg/ml)	131	0.3612	0.0000
Serum 1,25 $(OH)_2D$ (pg/ml)	87	- 0.2172	0.0433
Serum Folic acid (ng/ml)	121	- 0.1992	0.0285

Table 4. Multivariate models for predictors of CXCL16 (ng/ml) levels

	Model 1		Model 2		Model 3	
	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Intercept	4.658 (4.281, 5.036)	<0.0001	7.153 (5.394, 8.912)	<0.0001	8.281 (6.043, 10.519)	0.0000
eGFR (ml/min/ 1.73 m2)	-0.014 (-0.020, -0.009)	<0.0001	-0.013 (-0.018 -0.007)	<0.0001	-0.016 (-0.022, -0.009)	0.0000
UACR (mg/g)	0.000 (0.000, 0.001)	0.0016	0.000 (-0.000, 0.000)	0.0893	0.000 (-0.000, 0.000)	0.1861
Serum albumin (g/dL)	---	---	-0.609 (-1.029, -0.189)	0.0048	-0.680 (-1.106, -0.253)	0.0020
Age (years)	---	---	---	---	-0.010 (-0.022, 0.002)	0.1123
R squared	0.2518		0.2909		0.2993	

troduced in multivariate models. The strong association between eGFR and CXCL16 levels may underlie the disparate observations regarding the relationship between CXCL16 and CVD or outcomes.

Increasing CXCL16 levels with decreasing eGFR may represent an aspect of the systemic inflammation associated with uremia. Indeed, mean plasma CXCL16 levels were 4.0±0.9 ng/ml in European patients with DKD. This compares with previously reported mean values in Asia of 1.30±0.05 ng/ml for the general population, 2.65±0.11 ng/ml for CKD patients, 3.04±0.16 ng/ml for DKD patients and 1.23±0.04 ng/ml for type 2 DM patients [28].

In multiple regression analysis, the independent predictors of high plasma CXCL16 were low eGFR and low serum albumin. Thus, a relationship was found between CXCL16 and parameters of renal function (eGFR) and a marker of nutrition, serum albumin, that is also a negative acute phase reactant. UACR was also an independent predictor of plasma CXCL16 when adjusted for eGFR, but not when serum albumin was included in the equation, suggesting that UACR and serum albumin may represent, in part, different aspects of the same phenomenon. While high albuminuria will lead to low serum albumin levels, the fact that serum albumin is a stronger predictor suggests a further additional relationship between serum albumin and CXCL16. In this regard, CXCL16 is a promoter of inflammation and, as such, may contribute to lower serum albumin levels independently form proteinuria.

A study of 146 Chinese patients with CKD of diverse etiologies observed a correlation between plasma CXCL16 levels and eGFR [24]. A smaller study of 30 Chinese DKD patients disclosed that plasma CXCL16 levels were independently associated with eGFR and proteinuria and negatively correlated with serum albumin [28]. Thus, we have confirmed in a large White DKD population that eGFR and serum albumin are independent predictors of plasma CXCL16 levels across several ethnicities, while albuminuria has a milder association. In this regard, plasma CXCL16 was positively correlated with 24-hour urine protein but negatively correlated with serum albumin in 50 active nephrotic syndrome patients [29].

This study has established a correlation between decreased GFR and serum albumin and high circulating CXCL16 levels. This observational study can only be hypothesis generating. The clinical implications will depend on which hypothesis is correct, but may even include circulating CXCL16 being a target for therapy if experimental interventional studies confirm data suggesting a pathogenic role for CXL16 in kidney injury [5]. In this regard, several hypotheses may explain the relationship between parameters of kidney function and plasma CXCL16. The association between plasma CXCL16 and GFR may be related to either a low clearance of CXCL16 when renal function deteriorates or to the presence of inflammation in CKD. In this regard, it is not known how CXCL16 is cleared from the circulation. The fact that CXCL16 correlated with proteinuria in nephrotic syndrome suggests that circulating CXCL16 is not excreted in great amounts in urine or that synthesis is higher than potential urinary losses. Furthermore, there is also evidence that CXCL16 is expressed by injured tubular cells

in the course of acute or chronic interstitial inflammation, as that caused by proteinuria [13]. Thus, the kidney may be source of circulating CXCL16 in proteinuric nephropathies, especially if advanced to the point where GFR is decreased. Finally, there is experimental evidence that CXCL16 may cause glomerular injury, adding a further potential explanation between the observed association between circulating CXCL16 and markers of severity of kidney injury [5]. In this regard, CXCL16 is the main scavenger receptor for ox-LDL in human podocytes [30, 31].

Some limitations should be acknowledged. Thus, as is the case for other cross-sectional studies, only one baseline determination is available, and variability of CXCL16 levels over time was not assessed. Furthermore, the number of sample was relatively small.

Conclusion

In diabetic CKD patients, decreased GFR and serum albumin are independent predictors of circulating CXCL16 levels. However, plasma CXCL16 was not associated with CVD in multivariate analysis. Unraveling cause-and effect relationships for this observation may help guide therapy, since there is experimental evidence that kidney injury may increase CXCL16 levels and also that high CXCL16 levels may promote kidney injury. In this regard, the strong association between eGFR and CXCL16 levels may underlie the disparate observations regarding the relationship between CXCL16 and CVD or outcomes.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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