The role of interleukin-19 in diabetic nephropathy

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Background
Proinflammatory cytokines play an important role in the establishment of arteriolosclerosis and kidney injury. Inflammatory cytokines are involved in the development of microvascular diabetic complications, including diabetic nephropathy (DN). Interleukin-19 (IL-19) has vital functions in many inflammatory processes and also can induce the angiogenesis of endothelial cells.
Objective
To investigate the role of IL-19 in the development of DN.
Patients and methods
A total of 112 participants were included and classified into four main groups: group I was the control group, which included 28 age-matched and sex-matched persons; group II included 28 patients with type 2 diabetes without nephropathy (normoalbuminuria); group III included 28 patients with type 2 diabetes with nephropathy (microalbuminuria); and group IV included 28 patient with type 2 diabetes with nephropathy (macroalbuminuria). All participants were subjected to complete blood count, complete urine analysis, fasting and random blood glucose, glycosylated hemoglobin (HbA1c), serum creatinine and urea, urinary albumin excretion rate (UAE), albumin-creatinine ratio (ACR), lipid profile, and serum IL-19 level assays.
Results
C-reactive protein (CRP) and serum IL-19 levels were significantly higher in diabetic patients compared with controls. IL-19 levels were significantly positively correlated with serum creatinine, ACR, UAE, HbA1c, and CRP. Multivariable logistic regression analysis showed that IL-19 levels were independently associated with patients with DN.
Conclusion
IL-19 levels were elevated in patients with DN and were positively correlated with ACR, UAE, HbA1c, and CRP. IL-19 may play an important role that contributes to the progression of DN.

Keywords:
diabetes, nephropathy, interleukin-19

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Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease and characterized by hyperglycemia, which is due to the deficiency in peripheral insulin effects (insulin resistance). Macrovascular and microvascular complications are the primary causes of morbidity and mortality in diabetes. It is important to understand the risk factors to prevent the development and progression of such complications [1]. Diabetic nephropathy (DN) or diabetic kidney disease is a syndrome characterized by the presence of pathological quantities of urine albumin excretion, diabetic glomerular lesions, loss of glomerular filtration rate, and arterial hypertension [2].

The pathophysiology of DN is caused by both metabolic alterations (hyperglycemia and possibly hyperlipidemia) and hemodynamic alterations (systemic and glomerular hypertension). Other factors, such as inflammation, endothelial dysfunction and oxidative stress, are also involved [3].

Inflammation plays some important roles in the pathogenesis of DN. Leukocytes, macrophages, and monocytes are all involved in the process of DN, and proinflammatory cytokines and inflammatory markers are strongly associated with the development of DN [4].

Interleukin-19 (IL-19) is a member of the IL-10 family of cytokines. IL-19 is composed of 159 amino acids that form α-helical structure. IL-19 is produced by activated monocytes, and to a lesser extent, by B cells [5]. IL-19 can promote the T-helper 2 response, which is associated with some allergic reactions (i.e. asthma and atopic dermatitis), and type 1 diabetes. IL-19 has indispensable functions

in many inflammatory processes and also can induce the angiogenic potential of endothelial cells [6]. A previous study also reported that IL-19 is closely related to T2DM with vascular complications. However, it has not been revealed clearly yet whether there are some associations between IL-19 concentration and DN [7].

Patients and methods

The study design

This is a case–control study that included 112 participants after their written and informed consents. The study was cleared by the institutional ethics committee on human research and has been conducted in the Departments of Internal Medicine and Clinical Pathology, Faculty of Medicine, Zagazig University, from September 2017 to August 2018.

Participants and groups

A total number of 112 persons were included and classified into four main groups: group I was the control group, which included age-matched and sex-matched persons, comprising 16 (57.1%) males and 12 (42.9%) females; group II included patients with type 2 diabetes without nephropathy (normoalbuminuria), comprising 16 (57.1%) males and 12 (42.9%) females, group III included patients with type 2 diabetes with nephropathy (microalbuminuria), comprising 12 (42.9%) males and 16 (57.1%) females; and group IV included patients with type 2 diabetes with nephropathy (macroalbuminuria), comprising 12 (42.9%) males and 16 (57.1%) females. Inclusion criteria were co-operative patients of both sexes with T2DM. Exclusion criteria were patients with type 1 diabetes, patients with confounding factors for proteinuria, those previously diagnosed with urolithiasis, patients with recent or current viral hepatitis or cirrhosis of liver, patients with medical history of clinical cardiovascular disease, patients with chronic lung disease, patients with acute or chronic infections, patients with autoimmune disorders or with malignancy, and pregnant or lactating women.

Physical examination and measurements

All participants of the study were subjected to the following: (a) full history talking and thorough physical examination. Fundus examination was performed to confirm diabetic retinopathy in participants with albuminuria to confirm the diagnosis of DN.

(b) Investigations (to verify the inclusion and exclusion criteria of studied patients) included (a) routine investigations such as complete blood count (by Sysmex KX21N, Sysmex America, Inc., One Nelson C. White Pkwy, Mundelein, IL, USA), fasting blood glucose (FBG) and random blood glucose (RBG), glycosylated hemoglobin (HbA1c), serum creatinine and urea, liver function tests, lipid profile, and C-reactive protein (CRP). Complete urine analysis by uriscane analyzer, determination of urinary albumin excretion (UAE) and creatinine then measuerment of albumin creatinine ratio (ACR), and urinary albumin were determined by Immunoturbidimetric assay, these parameters were measured by Cobas 8000 (Roche diagnostics, California, USA). (c) Special investigations included serum IL-19 levels determined by double antibody sandwich enzyme-linked immunosorbent assay kit provided by Glory Science Co. Ltd (Del Rio, Texas, USA).

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 24.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Data were tested for normal distribution using the Shapiro–Wilk test. Qualitative data were represented as frequencies and relative percentages. χ^2 and Fisher exact test were used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation). Analysis of variance by ANOVA and post hoc analysis with LSD tests were applied for comparing differences among groups. Friedman's rank test was used for non-normally distributed variables. Pearson's and Spearman's correlation coefficients were used for correlating normal and nonparametric variables, respectively. We considered values near to 1 as strong correlation and values near 0 as weak correlation. Regression analysis using the stepwise method was used to determine the association between IL-19 and DN. All statistical comparisons were two tailed with significance. Level of P value less than or equal to 0.05 indicates significant, P value less than 0.001 indicates highly significant difference, whereas P value more than 0.05 indicates nonsignificant difference.

Results

There is a high statistically significant difference among the four studied groups regarding BMI and systolic blood pressure (Table 1). A high statistically significant difference is found among the four studied groups regarding FBG, RBG, HbA1c, DM duration, serum creatinine, ACR, UAE, total cholesterol (TC), and triglycerides (TG) (Table 2). There is a high statistically significant difference among the four studied groups regarding CRP and serum IL-19, where they were increased in diabetic patients

Table 1 Demographic data of the four studied groups

Variables	Groups				F/χ^2	*P*
	Group I (*N*=28)	Group II (*N*=28)	Group III (*N*=28)	Group IV (*N*=28)		
Age (years) (mean±SD)	53.43±5.12	60.04±13.83	58.07±13.83	57.71±12.07	1.564	0.202
Sex [*n* (%)]						
Male	16 (57.1)	16 (57.1)	12 (42.9)	12 (42.9)	2.294	0.514
Female	12 (42.9)	12 (42.9)	16 (57.1)	16 (57.1)		
BMI (kg/m^2) (mean±SD)	24.36±1.32	27.88±1.43	26.82±1.69	29.12±1.46	25.698	<0.001
SBP (mmHg) (mean±SD)	113.57±6.22	119.64±13.39	123.75±14.95	118.75±11.59	3.402	0.020
DBP (mmHg) (mean±SD)	74.64±5.59	76.07±6.85	76.77±8.19	75.36±11.29	0.349	0.790

DBP, Diastolic blood pressure; SBP, systolic blood pressure. *P* value less than 0.05 is significant.

Table 2 Comparison of different variables among the four studied groups

Variables	Groups (mean±SD)				*F*	*P*
	Group I (*N*=28)	Group II (*N*=28)	Group III (*N*=28)	Group IV (*N*=28)		
FBG (mg/dl)	79.89±13.51	131.36±56.65	141.82±73.37	150.89±94.83	6.354	0.001
RBG (mg/dl)	92.07±8.23	160.93±93.86	194.64±98.85	180.14±66.26	10.020	<0.001
HbA1c (%)	5.19±0.335	7.77±1.74	8.64±1.49	8.49±1.18	18.428	<0.001
Duration of DM (years)	–	8.73±4.73	15.26±4.01	19.21±4.86	16.525	<0.001
S. Cr (mg/dl)	0.882±0.136	0.923±0.23	1.23±0.47	1.56±0.81	25.04	<0.001
ACR (mg/g)	18.54±4.39	25.82±4.26	39.79±4.4	64.46±2.52	76.012	<0.001
UAE (mg/24 h)	9.62±2.15	22.18±1.62	280.18±93.16	532.83±180.34	38.629	<0.001
TC (mg/dl)	163.32±34.91	186.71±25.48	201.12±67.85	218.50±54.17	6.490	<0.001
TG (mg/dl)	162.11±46.39	176.29±23.88	210.71±61.29	211.39±56.33	7.167	<0.001

ACR, albumin/creatinine ratio; S. Cr, serum creatinine; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; RBG, random blood glucose; TC, total cholesterol; TG, total triglycerides; UAE, urinary albumin excretion. *P* value less than 0.05 is significant.

Table 3 Comparison of different inflammatory markers of the studied groups

Variables	Groups (mean±SD)				*F*	*P*
	Group I (*N*=28)	Group II (*N*=28)	Group III (*N*=28)	Group IV (*N*=28)		
CRP (mg/l)	0.761±0.179	8.2±4.42	19.64±6.71	23.25±9.97	73.318	<0.001
IL-19 (pg/ml)	224.36±139.61	240.32±178.43	1013.57±1202.08	1457.64±1387.71	12.058	<0.001

CRP, C-reactive protein; IL-19, interleukin-19. *P* value less than 0.05 is significant.

(groups II, III, and IV) compared with controls (group I) (Table 3). A significant positive correlation was found between IL-19 and BMI, DM duration, serum creatinine, ACR, UAE, FBG, HbA1c, CRP, TC, and TG (Table 4). Multivariable logistic regression analysis shows that IL-19 levels are independently associated with patients with DN (Table 5).

Table 4 Correlation between interleukin-19 and other variables in all patients groups

IL-19 variables	*r*	*P*
Age	0.040	0.672
BMI	0.213	0.024
DM duration	0.447	<0.001
Serum creatinine	0.414	<0.001
Albumin/creatinine ratio	0.505	<0.001
Urinary albumin excretion	0.498	<0.001
Fasting blood glucose	0.323	0.001
HbA1c	0.375	0.001
C-reactive protein	0.467	<0.001
Total cholesterol	0.291	0.002
Total triglycerides	0.334	<0.001

DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; IL-19, interleukin-19. *P* value less than 0.05 is significant.

Discussion

DN is one of the most common microvascular complications of DM, leading to end-stage renal disease. It represents in ~20–30% in type 1 diabetic patients and ~10–20% of those with type 2 diabetes [8].

Pathogenesis of DN included genetic and environmental factors that initiate more complicated pathological processes [9]. Intensive research on molecular and cellular aspects revealed that many immunological and inflammatory factors can play important roles in development and progression of DN [10].

Table 5 Multivariable logistic regression analysis, to detect the association between interleukin-19 levels and diabetic nephropathy

	β	SE	Wald	*P* value	*B*	95% CI for *B*	
						Lower	Upper
IL-19	0.005	0.001	21.267	<0.001	1.005	1.003	1.007
Constant				–2.123			

CI, confidence interval; IL-19, interleukin-19. *P* value less than 0.05 is significant.

Inflammatory cytokines are involved in the development of microvascular complications of diabetes, including DN [11]. However, the role of inflammatory cytokines in development and progression of DN is still deficient. Extending the knowledge regarding the role of inflammation in the development and progression of DN is useful to find new strategies of therapy. So our study aimed to investigate the role of IL-19 in DN and its association with DN.

Our findings showed that there was a highly significant difference among the studied groups regarding BMI, where it was higher in patients with albuminuria than in normoalbuminuric patients. Another study reported that obesity-associated glomerular hyperfiltration, renal vasodilation, increased glomerular filtration rate and intraglomerular capillary pressure, and high blood pressure are characteristics of DN [12].

In this study, there was a highly significant difference among the studied groups regarding systolic blood pressure, where it was higher in macroalbuminuric and microalbuminuric patients than normoalbuminuric patients. In agreement with this study, a previous study suggested that microalbuminuria precedes hypertension more commonly in T1DM than T2DM [13].

A highly significant difference was found among the studied groups regarding DM duration which was higher in macroalbuminuric and microalbuminuric patients than normoalbuminuric patients. Moreover, a previous study reported that a long duration of diabetes and poor glycemic control is associated with increased production of glycosylation end products, metabolic derangements, endothelial injury, and oxidative products [14].

Regarding serum creatinine, a highly significant difference among the studied groups was observed, where it was higher in macroalbuminuric and microalbuminuric patients than in normoalbuminuric patients. In agreement with this result, another study reviewed aspects of the association of diabetes with renal disease, emphasizing that chronic kidney disease and albuminuria are associated with increased rates of cardiovascular disease and mortality [15].

Regarding serum TG and TC, they were higher in macroalbuminuric and microalbuminuric patients than in normoalbuminuric patients. Moreover, a previous study stated that DN is associated with an altered lipid profile characterized by elevated TG-rich lipoproteins even in the early stages of the renal disease [16].

In the current study, FBG, RBG, HbA1c, ACR, and UAE in the microalbuminuric and macroalbuminuric diabetic group were significantly increased compared with normoalbuminuric and control groups. This study is in agreement with a previous study, which has suggested that hyperglycemia is the driving force for the development of DN [7].

There was a positive correlation between IL-19 and BMI, DM duration, serum creatinine, ACR, UAE, FBG, HbA1c, CRP, TC, and TG. Our results suggested that long-term hyperglycemia may increase the expression of IL-19 via stimulating endothelial cells inducing local inflammation and accelerating endothelial damage and atherosclerosis. Similarly, another study demonstrated a positive correlation between IL-19 and HbA1c and UAE [7].

Our findings showed that there was a highly significant difference regarding CRP among studied groups, where it was higher in macroalbuminuric and microalbuminuric patients than in normoalbuminuric patients. CRP, which is a marker of inflammation, has been reported to be associated with the risk of DM complications [17]. This result is consistent with a previous study that showed that CRP may deteriorate the inflammatory cascade in tissue injury in addition to initiating endothelial damage and atherosclerosis [18].

IL-19 concentrations were significantly higher in macroalbuminuric and microalbuminuric patients than in normoalbuminuric patients. Similarly a previous study reported that inflammatory cytokines and inflammatory stimuli can induce IL-19 expression, and this expression

is attributed to injured and stimulated vascular smooth muscle cells [19]. Moreover, another study revealed the roles of IL-19 in the development of vascular inflammatory diseases such as atherosclerosis, restenosis, and coronary artery transplant vasculopathy [8]. Similar observations were reported by another study which documented that chronic inflammation, characterized by elevated circulating levels of inflammatory markers, appears to play a critical role in the pathogenesis of T2DM and its associated complications [20].

Similarly, a previous study reported that proinflammatory cytokines play an important role in the establishment of arteriolosclerosis and kidney injury, and inflammatory cytokines are involved in the development of microvascular diabetic complications, including DN [11].

Multivariable logistic regression analysis showed that IL-19 levels were independently associated with DN, which is similar to another study that reported the same results [7]. These results suggest that IL-19 is involved in the inflammatory reaction and can play a significant role in development and progression of DN.

Conclusions

The previous findings of this study showed that IL-19 levels were significantly high in patients with DN and were correlated with CRP, ACR, UAE, and HbA1c. The results suggest that IL-19 has a possible role in the pathophysiology and progression of DN, providing further concepts as a therapeutic target for prevention or delaying of progression of DN.

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Conflicts of interest

There are no conflicts of interest.

References

1 Fujita T, Ogihara N, Kamura Y, Satomura A, Fuke Y, Shimizu C, *et al.* Interleukin-18 contributes more closely to the progression of diabetic nephropathy than other diabetic complications. Acta Diabetol 2012; 49:111–117.

2 Lim A. KH. Diabetic nephropathy – complications and treatment. Int J Nephrol Renovasc Dis 2014; 7:361–381.

3 Bennett K, Aditya BS. An overview of diabetic nephropathy: epidemiology, pathophysiology and treatment. J Diabet Nurs 2015; 18:61–67.

4 Nguyen D, Ping F, Mu W, Hill P, Atkins RC, Chadban SJ. Macrophage accumulation in human progressive diabetic nephropathy. Nephrology (Carlton) 2006; 11:226–231.

5 Hofmann SR, Rösen-Wolff A, Tsokos GC, Hedrich CM. Biological properties and regulation of IL-10 related cytokines and their contributionto autoimmune disease and tissue injury. Clin Immunol 2012; 143:116–127.

6 Ellison S, Gabunia K, Richards JM, Kelemen S, England R, Rudic D, *et al.* IL-19 reduces ligation-mediated neo intimal hyperplasia by reducing vascular smooth muscle cell activation. Am J Pathol 2014; 184:2134–2143.

7 Li L, Jiang XG, Hu JY, Yu ZQ, Xu JY, Liu F, *et al.* The association between interleukin-19 concentration and diabetic nephropathy. BMC Nephrol 2017; 18:65.

8 Zhenhua H. Diagnosis and treatment of diabetic nephropathy in type1 and type 2 diabetes patients. J Mol Biomark Diagn 2016; 7:295.

9 Martini S, Eichinger F, Nair V, Kretzler M. Defining human diabetic nephropathy on the molecular level: integration of transcriptomic profiles with biological knowledge. Rev Endocr Metab Disord 2008; 9:267–274.

10 Mora C, Navarro JF. Inflammation and diabetic nephropathy. Curr Diabetes Rep 2006; 6:463–468.

11 Yin Q, Zhai Q, Wang D, Hai J, Cao M, Wang J, *et al.* Investigation on the association between inerleukin-10 –592C/A, 819C/T and –1082A/G gene polymorphisms and development of diabetic nephrophathy. Int J Clin Exp Pathol 2015; 8:15216–15221.

12 Klessens CQ, Woutman TD, Veraar KA, Zandbergen M, Valk EJ, Rotmans JI, *et al.* An autopsy study suggests that diabetic nephropathy is under diagnosed. Kidney Int 2016; 90:149–156.

13 Freedman B, Bostrom M, Daeihagh P, Bowden DW. Genetic factors in diabetic nephropathy. Clin J Am Soc Nephrol 2007; 2:1306–1131.

14 Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, *et al.* Normalizing mitochondrial superoxide production blocks three pathways of hyperglycemic damage. Nature 2000; 404:787–790.

15 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2044; 351:1296–1305.

16 Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. Diabetics Metab 2016; 26:254–264.

17 Arık HO, Yalcin AD, Gumuslu S, Genç GE, Turan A, Sanlioglu AD. Association of circulating sTRAIL and CRP with type 2 diabetic nephropathy and foot ulcers. Med Sci Monit 2013; 29:712–715.

18 Yamaoka-Tojo M, Tojo T, Masuda T, Machida Y, Kitano Y, Kurosawa T, *et al.* C-reactive protein-induced production of interleukin-18 in human endothelial cells: a mechanism of orchestrating cytokine cascade in acute coronary syndrome. Heart Vessels 2003; 18:183–187.

19 Cuneo AA, Herrick D, Autieri MV. IL-19 reduces VSMC activation by regulation of mRNA regulatory factor HuR and reduction of mRNA stability. J Mol Cell Cardiol 2010; 49:647–654.

20 Fujita H, Taniai H, Murayama H, Ohshiro H, Hayashi H, Sato S, *et al.* DPP-4 inhibition with alogliptin on top of angiotensin II type 1 receptor blockade ameliorates albuminuria via up-regulation of SDF-1α in type 2 diabetic patients with incipient nephropathy. Endocr J 2014; 61:159–166.