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Correlation of Interleukin-18 (IL-18) with the Degree of Nephropathy in Diabetic Type 2 Patients

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ABSTRACT

Background: *Diabetes mellitus (DM) is the world's most common non-communicable metabolic disease causing important morbidity and mortality due to its microvascular and macrovascular complications. Diabetic nephropathy is one of the most common microvascular problems that people with diabetes can have. Currently, there is a high focus on early detection of nephropathy in order to achieve the highest results for patients.* ***Aim of the study:*** *The present study was mainly aimed to the correlation IL-18, in serum as markers for primary detection of degree DN in a sample of Iraqi patients having type two diabetes mellitus (T2DM).* ***Subjects and Methods:*** *Between August 2023 and January 2024, a grand total of 120 patients with type II DM were investigated. patients selected from the Center of Diabetes and Endocrinology in Al-Sader Teaching Hospital in Najaf City were enrolled in this study. The patients were divided into three groups based on their albumin-to-creatinine ratio (ACR): normoalbuminuria, microalbuminuria, and macroalbuminuria. All participants underwent clinical evaluation along with a range of tests such as blood pressure, weight and height measurements, blood tests fasting blood sugar (FBS), glycated hemoglobin (HbA1c), serum urea and creatinine in addition to albumin and creatinine in urine. IL-18 were measured by the ELISA technique.* ***Results:*** *The prevalence of microalbuminuria and macroalbuminuria was 63.29% and 11.10% respectively in the group of patients in this research. This implies that diabetic nephropathy is present in about 74.39% of the diabetic populations in this research.*

Conclusions: *Based on the result of this study significantly high concentrations of IL-18 were discovered in diabetic patients with macroalbuminuria and microalbuminuria compared to diabetic groups with normoalbuminurin. IL-18 was found positively correlating with the age, gender urine creatinine and HbA1c.*

Keywords: Interleukin-18 (IL-18), T2DM, Nephropathy.

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INTRODUCTION

Diabetes mellitus (DM) is a sequence of metabolic diseases described as high blood sugar due to insulin excretion defects, insulin action or incorporation of both [1] Type 2 diabetes (T2DM) makes up around 90 percent of the condition of diabetes[2] Individuals with type two diabetic mellitus are at elevated risk of both microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (including cardiovascular comorbidity) due to hyperglycemia and individual insulin resistance (metabolic) syndrome components[3]. Complication from diabetes mellitus are numerous. The main reason of these problem is persistently high blood

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sugar levels.Increased blood glucose levels result in damage to small blood vesssels known as "microvascular diasease" and large arteries , known as "macrovascular disease ". Diabetic complication happen due to vascular damage,leading to damage to tissues and organs,These complication include nephropathy, neuropathy, retinopathy[5].

Diabetes nephropathy (DN): is a renal disease characterized by microangiopathy, which can lead to proyinuria, hypertension, and gradual decline in kidney function. Chronic hyperglycemia in diabetic patients causes an elevation in the glycation of basement membranes in the nephrons, resulting in impaired filtration function [6]. DN is a complication of both type 1 and type 2 diabetes mellitus, It is caused by microvascular alterations and can result in kidney faliure and cardiovascular disease [7].An increase in protein excretion in the urine is the traditional defintion of (DN),Also known as microalbuminuria , the early stage is marked by small rise in albumin levels in the urine.Proteinuria or macroalbuminuria is a sign of a more advanced disease,later cases are known as overt(DN).[8] Microalbuminuria is when you pee 30 to 299 mg of albumin per 24 hours, and macroalbumin is when you pee more than 300 mg of albumin per 24hours[9].diabetic nephrppaty is diagnosed when the amount of albumin in the urine exceeds 30 mg in a 24-hour period,or when the estimated glomerular filtration rate falls below 60mL/min per 1.73[10].

Albuminuria is a defining characteristic of diabetic nephropathy [11]. Interleukin-18 (IL-18) is a type of protein called a cytokine that acts as a bridge between the innate and adaptive immune responses in the body, Dendritic cells and macrophages secrete it ,and it has a supportive function in promoting the release of other cytokines and chemokines[12]. IL-18 is an inflammatory cytokine that noted in elevated levels in patients with diabetes type two and consider as important pathogenic intermediary in progressive diabetic nephropathy [13]. IL-18 is an inflammatory cytokine that noted in elevated levels in patients with diabetes type two and consider as important pathogenic intermediary in progressive diabetic nephropathy[14]. There was a close relationship among IL-18, albuminuria, and albumin excretion rate (AER); therefore, its association to the DN has been distinguished [15].

MATERIAL AND METHODS

One hunderd twenty T2DM patients includin (86 females and 34 male) who attened the Center of Diabetes and Endocrinology in Al-Sader Teaching hospital in Najaf

The patients were split into three groups in relation to the albumin-creatinine ratio (ACR) :

- Group 1 including type two diabetic patients with normoalbuminuria patients (NA)
- Group 2 including type two diabetic patients with microalbuminuria (MA)
- Group 3 including type two diabetic patients with macroalbumiburia (CN clinical nephropathy)

The inclusion criteria include:

1- T2DM patients diagnosed with diabetes on the criteria for determing plasma glucose levels are based on both, fasting plasma glucose and the plasma glucose levels are tolerance test or a glycosylated hemoglobin test [17].
2- Both genders were included

Exclusion criteria involve:

1- Type 1 DM
2- Hypertension
3- Traumaor acute illness.

Enzyme –linked immunosorbent Assay (ELISA) (sunlong,China) was used to evaluate the blood levels of TNFR1 in people with

diabetic patient type two were evaluated using sandwich immunodetection method.

All information from both study groups was calm and exmined using the Statistical package for the Social Scinences (SPSS).

RESULT

This study showed significant difference in values for HbA1c , serum creatinine , serum urea, urine albumin, and urinary ACR between the patient groups (P< 0.05), also showed no significant difference in the mean values for BMI, age, FBS,urine creatinine , serum albumin and e GFR between the patients groups (P> 0.05) **Table 1.**

Areceiver operating characteristic (ROC) analysis was conducted to evaluate the diagnosis value of IL-18 and if it is more sensitive or specific than ACR , eGFR , and which of them is more sensitive or unique to diabetic nephropathy diagnosis.**Table 2.**

Table (3) reflects a correlation between IL-18 and eGFR output data for ROC curves. A cutoff value of eGFR (103). Nephropathy was prdicted by a serum level of IL-18 with 73.9% sensitivity , 51.4% specificity , and 0.588 accuracy. Aurine level of albumin with 85.1% sensitivity , 82.6% specificity , and 0.894 accuracy. Aurine level of creatinine with 59.5% sensitivity , 50% specificity , and 0.490 accuracy **Table (4).**

A serum level was of uria 55.4% sensitivity, 54.3% specificity and 0.561 accuracy. Level of serum creatinine was with 56.8% sensitivity, 50% specificty , and 0.554 accuracy **Table 5.**

Table 6 shows the Cutoff Points and Validity of The Studied Parameters in Diabetic Patients (S.Urea, S.Creatinine).

Table (7) person correlation analyses have revealed the no relationships between IL-18, eGFR and ACR variable studied in the diabetic patient with nephropathy.

Table -1 Baseline characteristic of the patients.

Characteristics	ACR ratio			P- value
	Normoalbuminuria N=46	Microalbuminuria N=63	Macroalbuminuria N=11	
Age, (year) Mean± S.D	54.33± 10.760	56.06± 11.153	51.36± 8.606	0.365
Body mass index (kg/m2)² Mean± S.D	29.75± 5.322	30.63± 5.080	34.06± 8.092	0.069
FBS (mg/dl) Mean± S.D	320.65± 100.082	318.27± 83.748	358.36± 111.946	0.413
HbA1c median (IQR)	10.00 (1.60)	10.00 (2.60)	11.00 (1.30)	**0.012***
U. Albumin (mg/L) median (IQR)	6.50 (22.00)	84.00 (58.00)	200.00 (4.00)	**<0.001****
U. Creatinine (mg/dl) median (IQR)	44.00 (55.25)	48.00 (54.00)	57.00 (15.00)	0.602
S. Creatinine (mg/dl) Mean± S.D	0.81± 0.365	0.82± 0.349	1.37± 0.469	**<0.001****
S. Urea(mg/dl) median (IQR)	31.00 (14.25)	31.00 (12.00)	43.00 (5.00)	**0.002****
e GFR Mean± S.D	111.93± 61.218	118.86± 56.703	99.09± 37.155	0.535
Urinary ACR Mean± S.D	17.71± 7.97	85.53± 60.54	376.82± 43.19	**<0.001****

****: highly significant difference, S.D.: Std. Deviation, N: number, IQR: Interquartile Range.**

Tables 2: Comparison of mean IL-18 of diabetic patients across albuminuria

Characteristics	ACR ratio			P-value
	Normoalbuminuria N=46	Microalbuminuria N=63	Macroalbuminuria N=11	
IL-18 (pg/ml) Mean± S.D	111.36± 216.252	93.06± 65.219	278.76± 120.889	0.001**

**** : Highly Significant difference, S.D.: Std. Deviation.**

Table 3. Cutoff Points and Validity of The Studied Parameters in Diabetic Patients (eGFR, IL-18).

Characteristic	eGFR	IL-18
AUC	0.527	0.588
SE	0.056	0.052
Sig.	0.616	0.106
95% Confidence Interval	0.418-0.636	0.486-0.690
Optimal Cut-Point Value	103	65.5
Sensitivity (%)	58.1%	73.9%
Specificity (%)	45.7%	51.4%
PPV (%)	63.23%	48.57%
NPV (%)	40.38%	76%
Diagnostic effectiveness (accuracy)	53.33%	60%

Table 4: Cutoff Points and Validity of The Studied Parameters in Diabetic Patients (FBS, HbA1c).

Characteristic	FBS	HbA1C
AUC	0.526	0 .556
SE	0.054	0.052
Sig.	0.631	0.304
95% Confidence Interval	0.420-0.632	0.453-0.659
Optimal Cut-Point Value	306	9.9
Sensitivity (%)	50%	65.2%
Specificity (%)	48.6%	40.5%
PPV (%)	37.7%	40.54%

NPV (%)	61.02%	65.22%
Diagnostic effectiveness (accuracy)	49.17%	50%
Youden's index	-0.01	0.06

Table 5 Cutoff Points and Validity of The Studied Parameters in Diabetic Patients (U.albumin, U.Creatinine)

Characteristic	U. albumin	U. Creatinine
AUC	0.894	0.490
SE	0.029	0.056
Sig.	<0.001**	0.859
95% Confidence Interval	0.837-0.951	0.381-0.599
Optimal Cut-Point Value	44.5	43.5
Sensitivity (%)	85.1%	59.5%
Specificity (%)	82.6%	50%
PPV (%)	88.73%	65.67%
NPV (%)	77.55%	43.39%
Diagnostic effectiveness (accuracy)	84.17%	55.83%
Youden's index	0.68	0.1

Table 6 Cutoff Points and Validity of The Studied Parameters in Diabetic Patients (S.Urea, S.Creatinine) .

Characteristic	S. Urea	S. Creatinine
AUC	0.561	0.554
SE	0.054	0.055
Sig.	0.265	0.322
95% Confidence Interval	0.455-0.667	0.446-0.662
Optimal Cut-Point Value	31.5	0.75
Sensitivity (%)	55.4%	56.8%
Specificity (%)	54.3%	50%
PPV (%)	66.13%	64.62%
NPV (%)	43.10%	41.82%
Diagnostic effectiveness (accuracy)	55%	54.17%
Youden's index	0.1	0.07

Table 7: Correlations of IL-18, eGFR, and ACR Ratio in type II Diabetic Patients.

Parameter	Statistics	eGFR	IL-18 (pg/ml)
eGFR	*R*	-	-0.132
	P. value	-	0.075
Urinary ACR	*R*	-0.084	0.320
	P. value	0.180	<0.001**
IL-18 (pg/ml)	*R*	-0.132	-
	P. value	0.075	-

R: Pearson's correlation coefficient, *: Correlation is significant at the 0.05 level (1-tailed), **: Correlation is significant at the 0.01 level (1-tailed).

DISCUSSION

Diabetic kidney disease is the primary microvascular complication of diabetes mellitus (DM) and the main reason why people get end-stage kidney disease worldwide [17]. The current study showed that the BMI was not a significant between study group the mean of BMI higher in macroalbuminuria followed by microalbuminuria and lastly normoalbuminuria group,something that has been discussed in previous study [18][19]. Age was not a significant between study group, the result was similar to the findings reported by [20][21], The persent study has showed that age is not significant correlation with the degree DN. This present research indicates a mean high level of HbA1c macroalbuminuria followed by microalbuminuria then by normoalbuminuria group (P=0.012) comparable findings are consistent with other research,suggesting that hyperglycemic is the driving force for DN development [22][23].

Blood urea levels increase in conjunction with albuminuria ,greater levels were recorded in macroalbuminuria followed by microalbuminuria and normoalbuminuria(p=0.002) , Similar results have been noted [24][25]. High blood urea indicates kidney function abnormality, Abnormal urea is a symptom of nephropathy, there is a need for early detection of nephropathy [26]. The serum creatinine significant change in mean among patients group (p=0.001) Macroalbuminuria was the greatest mean followed by microalbuminuria and , finally , normoalbuminuria. The study results were similar to those of the studies [27][28], Increased creatinine in blood indicates nephron abnormality [29].

The present study showed that there is highly significant increase (P value =0.001) in the levels of IL-18 (mg/dL) in patients with macro–albuminuria compared to normo and micro–albuminuria**.** however, the role of IL-18 seems to be more specific than other cytokines in the inflammatory process. IL-18 is expressed in renal tissue and is upregulated by several stimuli including hyperglycemia [30]. IL-18 showed a significant positive correlation with the urine albumin, while it showed a significant negative correlation and no correlation with HbA1c. This result agrees with [31].

CONCLUSIONS

1-The majority of patients with type II diabetes in AL-Najaf city and AL-Chibaish district exhibit either microalbuminuria or normoalbuminuria.

2-There is no significant correlation between the duration of diabetes and the occurrence of diabetic nephropathy. Additionally, there is no significant correlation between age, gender, BMI,and the occurrence of diabetic nephropathy.

3-There is a significant association (strong correlation) between diabetic nephropathy and HbA1c, serum urea, and serum creatinine, eGFR.However, there is a weak correlation between fasting blood sugar and diabetic nephropathy.

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