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Serum Chemerin Level: Does It Have a Role in Progression of Diabetic Nephropathy

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Abstract: *Background:* Diabetic nephropathy has become the leading cause of end-stage renal failure in Europe, the United States and Japan (25-44%). Chemerin is a chemoattractant expressed in white adipose, liver and lung tissues. Chemerin is shown to be associated with inflammation which is involved in the pathogenesis of diabetic nephropathy. The aim of the present work is to estimate serum chemerin level and to correlate its level in the patients with the stage of the diabetic nephropathy disease. *Patients and Methods:* The present study included 60 subjects who were divided into 4 groups *Group I:* included 15 diabetic patients with norm albuminuria *Group II:* included 15 diabetic patients with microalbuminuria *Group III:* included 15 diabetic patients with macroalbuminuria *Group IV:* included 15 normal subjects as a control group. All patients and controls were subjected to estimation of body mass index. Blood urea, serum creatinine and estimated GFR, Urinary albumin to urinary creatinine ratio, complete lipid profile (LDL, HDL, TG) and Serum chemerin level by ELIZA. *Results:* Serum chemerin level was higher in diabetic than non-diabetic persons and was higher in patients with macroalbuminuria than those with normo and microalbuminuria and its level is correlated with markers of impaired renal function. *Conclusion:* chemerin could have a role in progression of diabetic nephropathy or its level could be elevated due to impaired renal excretion which should be further investigated.

Keywords: Diabetic Nephropathy, Chemerin, Albuminuria

1. Introduction

Diabetic nephropathy is a complication seen in long standing diabetes mellitus where progressing impairment of kidney function leads to end-stage renal disease (ESRD). It affects both type 1 and type 2 diabetes patients and is the most common kidney condition requiring dialysis [1]

Diabetic nephropathy passes to several stages, stage I (Hyperfiltration), characterized by renal enlargement, intrarenal hypertension and high glomerular filtration rate (GFR), may be seen early in the course of diabetes. [2]

Stage II, During this so-called silent phase early histological abnormalities in the kidney may be seen, including glomerular hypertrophy and subtle thickening of the glomerular basement membrane, best seen by electronmicroscopy.[1]

Stage III Albumin excretion rates of 20-200 μg/min, is defined as microalbuminuria (also called incipient nephropathy) as these levels are not detectable by conventional urine dipstick analysis. [3]

Stage IV Albumin excretion rates above 200 μg/min or 300 mg/day are dipstick positive and defined as overt nephropathy. This is usually associated with a relentless loss of GFR (by 1-24 mL/min per year) until end-stage renal failure. [4]

Stage V, End-stage renal disease (ESRD), is a progressive, irreversible deterioration in renal function in which the body's ability to maintain metabolic and fluid and electrolyte balance fails, resulting in uremia or azotemia (retention of urea and other nitrogenous wastes in the blood. [5]

Chemerin is a multifunctional protein implicated in chemotaxis of immune cells, regulation of differentiation and metabolic function of adipocytes, and glucose homeostasis.[6,7]

Chemerin levels have also been shown to be higher in obesity and some features of Metabolic syndrome, diabetes, also it induces insulin resistance (IR) in skeletal muscle, the

major site of peripheral IR. [8, 9]

Significant positive association was found between circulating chemerin and body mass index (BMI), waist-to-hip ratio, glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and serum triglycerides in women with polycystic ovary syndrome. These studies suggest that chemerin may play a potential role in obesity induced insulin resistance and the development of type 2 diabetes mellitus. [10]

Recently, serum chemerin levels were found to be significantly higher in patients on chronic hemodialysis compared with controls, suggesting that determinants of renal function are independently related to circulating chemerin levels.[11] Therefore, serum chemerin concentration might be altered in patients with diabetic nephropathy. So we conducted this study with the aim to evaluate serum chemerin level in different stages of DN.

2. Subjects & Methods

The study population was classified into two groups' cases and controls. The control group involves 15 non diabetic persons (5 males and 10 females) with a mean age of 31.33±8.19 years. The other group consists of 45 type 2 diabetic patients (27 males and 18 females) with a mean age of 30.83±6.43 years. The latter group further subdivided into three groups according to (presence of albumin in urine), these are normo-albuminuric group (group 1, n=15), micro-albuminuric group (group 2, n=15) and macroalbuminuric group (group 3, n=15). They were recruited from Internal Medicine Department of Alexandria Main University Hospital. All patients and controls were subjected to the followings: Full history taking and complete clinical examination, Estimation of body mass index,[12] Blood urea, serum creatinine and creatinine clearance,[13] Urinary albumin to urinary creatinine ratio,[14] and Complete lipid profile (LDL, HDL, TG).

Serum chemerin level was detected using ELIZA.[15,16]The human chemerin ELISA, standards and samples were incubated in microtitration wells pre-coated with polyclonal anti-human chemerin antibody. Incubation was followed by washing, then biotin labelled polyclonal anti-human chemerin antibody was added and incubated with the captured chemerin. After another washing, streptavidin-HRP conjugate was added. After the last washing step, the remaining conjugate was allowed to react with the substrate solution. The reaction was stopped by addition of acidic solution and absorbance of the resulting yellow product was measured. The absorbance was proportional to the concentration of chemerin. A standard curve was constructed by plotting absorbance values against chemerin concentrations of standards, and concentrations of unknown samples were determined using this standard curve.

3. Results

No significant difference was found between cases and controls as regard their age.

Plasma chemerin level among diabetic patients (293.33±162.360) was higher than that among controls (124.44±26.509) and this difference was statistically significant (P<0.001). Other biochemical parameters showed a significant difference between cases and controls namely Blood urea, serum creatinine, albumin creatinine ratio (ACR), fasting blood sugar and post prandial blood sugar level. They were significantly higher among cases. On the other hand eGFR was significantly higher among controls. No difference was found between both groups as regards TG, LDL, and HDL.

Mean BMI among cases (25.19±2.75) was significantly higher than that among controls (21.89±2.26) as P<0.001.

Comparing the three subgroups of diabetic patients regarding plasma chemerin level using krauskal wallis test, a significant difference between the groups was found as $\chi 2$=9.92 P=0.007.

Using Mann Whitney test to compare chemerin level in two groups interchangeable showed that: A significantly higher level of chemerin among group 3 (488.67±214.67) as compared to that among group 2 patients (318.67±198.3) as Z = -2.28 (P=0.022.). There was a significantly higher level of chemerin among group 3 (488.67±214.67) as compared to that among group 1 patients (268.00±117.85) as Z= -3.05 P=0.002. No statistically significant difference was found between plasma chemerin level among group 2 (318.67±198.3) as compared to that among group 1 patients (268.00±117.85) as Z= -0.45 P=0.647. (Table I).

Within type 2 diabetic patients bivariate correlation (Spearman Correlation) showed that (Table II): A significant positive correlation between plasma chemrin level and blood urea with r= 0.55 and P<0.001, A significant positive correlation between plasma chemerin level and serum creatinine with r= 0.36 and p=0.014, A significant positive correlation between plasma chemerin level and ACR with r= 0.38 and p=0.010, A significant positive correlation between plasma chemerin level and HbA1c with r=0.64 and P<0.001, A significant negative correlation between plasma chemerin level and eGFR with r=- 0.42 and p= 0.004,A significant positive correlation between chemerin and triglyceride: r=0.44 P=0.003, and a significant positive correlation between chemerine and BMI: r=0.36 P=0.015.

Table (I). *Biochemical parameters among diabetic patients.*

	Normo (n=15)	**Micro (n=15)**	**Macro (n=15)**
Blood urea			
Min. – Max.	15 – 50	15.0 – 60.0	70-200
Mean ± SD.	29.27 ± 12.28	32.2 ± 16.78	115.67±31.73
Median	30	30	107

	Normo (n=15)	Micro (n=15)	Macro (n=15)
Serum creatine			
Min. – Max.	0.6 – 1.5	1.0 – 3.0	1.7-4.3
Mean ± SD.	1.19 ± 0.27	1.44 ± 0.50	3.07±0.74
Median	1.2	1.3	3.1
eGFR			
Min. – Max.	64.30 – 160.0	50.0 – 160.0	15.8-65.0
Mean ± SD.	105.06 ± 27.92	89.05 ± 32.77	33.61±15.23
Median	93	77.8	26.9
ACR			
Min. – Max.	5.0 – 30.0	114 – 300	350-2000
Mean ± SD.	17.97 ± 7.86	191.00 ± 69.46	838.67±440.67
Median	19	198	700
Plasma chemrine			
Min. – Max.	100.0-500.0	100-720	190-800
Mean ± SD.	268±117.85	318.67±198.34	488.67±214.67
Median	280	280	400
Fasting blood sugar			
Min. – Max.	95.0-265.0	98-288	
Mean ± SD.	147±44.04	159.33±55.45	
Median	148	145	
Post prandial			
Min. – Max.	145.0-340.0	165-340	
Mean ± SD.	218.6±49.92	235.6±51.36	
Median	230	230	
Serum Triglyceride			
Min. – Max.	140-300	135-280	130-330
Mean ± SD.	193.6±40.59	195.0±39.64	211.67±50.05
Median	185	185	220
LDL Cholesterol			
Min. – Max.	85-140	95-130	90-165
Mean ± SD.	109.0±14.57	115.4±11.86	119.4±22.16
Median	110	120	120
HDL Cholesterol			
Min. – Max.	32-55	34-59	35-55
Mean ± SD.	42.4±7.17	44.4±6.8	41.4±5.6
Median	40	45	40
HBA1c			
Min. – Max.	6.50-9.20	6-10	7.5-9,6
Mean ± SD.	218.60±49.92	7.97±1.10	8.23±0.71
Median	8	7.9	8

Table (II). *Correlation between plasma chemerin with age and different biochemical parameters among diabetics.*

	Plasma Chemrin level	
	r_s	p
Age	0.26	0.93
FBS	0.16	0
PPS	0.18	0.056
Blood Urea	0.55	<0.001*
Serum creatine	0.36	0.019*
ACR	0.38	0.042*
eGFR	-0.42	0.011*
TG	0.436	0.003*
HDL	-0.15	0.245
LDL	0.03	0.214
HBA1c	0.53	<0.001*
Body Mass Index	0.361	0.015*

r_s: Spearman coefficient

* Correlation is significant at level less than 0.05

4. Discussion

In the present study there was a higher serum chemerin level in diabetic patients than the control this is in agreement with the work of Yang M et al [17] who found that serum chemerin is higher in diabetic and hypertensive patients than in diabetic and normotensive but in our study we did not put hypertension in our concern.

Also in the same study, they found HbA1c and waist circumference were independently related factors influencing plasma chemerin levels, we found a strong correlation between HbA1c and BMI with serum chemerin.

Our results demonstrate that a significant elevation in serum chemerin concentrations in patients with macroalbuminuria was observed compared with normal controls and patients with normoalbuminuria and microalbuminuria. Elevated serum chemerin levels in the

macroalbuminuria group in this study concur with the results of previous studies about other adipocytokines.[18,19] Chemerin, as well as other adipocytokines, might be impaired at a relatively late stage of diabetic nephropathy.

The Results of this study indicate a strong association of high chemerin levels with decreased renal function as indicated by positive correlation between serum chemerin and serum creatinine and its negative correlation with eGFR. A possible explanation is that elevated chemerin levels may be a consequence of impaired kidney function in patients with renal failure. Impaired clearance or catabolism of chemerin in the kidney may lead to the accumulation of chemerin in the plasma. This suggests that elevated plasma chemerin levels are significantly associated with macroalbuminuria in type 2 diabetes patients. Recently, serum chemerin levels were reported to be significantly elevated in patients on chronic hemodialysis as compared with healthy subjects, indicating that determinants of renal function are independently related to circulating chemerin levels. [20]

In the present study, there was no correlation between serum chemerin level and lipid profile including LDL, HDL and TG.

When reviewing the literature regarding this point, controversy in the results was found, many authors [21-23] have suggested that elevated serum chemerin levels are related to HDL-c. Other studies did not find a relationship between serum chemerin levels and HDL-c. [24] Further studies will be necessary to elucidate the exact relationship of serum chemerin and HDL-c.

In conclusion, this study showed that serum chemerin levels were elevated in diabetic patients with macroalbuminuria. Both creatinine clearance and serum creatinine were significantly associated with serum chemerin levels. Our results indicate that elevated serum chemerin levels could be considered as an independent predicting marker for progression of diabetic nephropathy.

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