Serum Chemerin Level as Biomarker for Renal Dysfunction in Type II Diabetes

Ahmed Mohammed Abdel- Rahman Tahoun[1], Ahmed Abdou El lawah [2], Magdy Abdel-kareim EL dahshan[2], Ahmed Mohammed El sayed Shalaby*[1]
[1]Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University
[2]Department of Internal Medicine, Faculty of Medicine, Al-Azhar University
*Corresponding author: Ahmed Mohammed El sayed Shalaby; **Mobile:** (+20)0100 621 4169;
Email: drahmedshalaby1981@yahoo.com

ABSTRACT

Background: Type 2 diabetes mellitus is the most common form of diabetes. Millions of patients worldwide have been diagnosed as type 2 diabetes and many more are unaware they are at high risk. It represents a major public health threat and constitutes an important contributor to the predicted decline in life expectancy.

Objective: The aim of the present work was to evaluate serum chemerin level and its association with kidney functions in patients with type 2 diabetes mellitus.

Patients and methods: This case control study was conducted at Clinical Pathology Departments of Al-Azhar University Hospitals. It was carried out on 80 subjects of matched age and sex divided as 60 type 2 diabetic patients and 20 apparently healthy volunteers (hospital staff) serving as control group.

Results: In a correlation study between serum chemerin and other studied parameter in diabetic patients, a significant positive correlation was found between serum levels of chemerin, FBS, ACR, serum creatinine, serum urea, fasting insulin, HOMA-IR index and BMI. On the other hand, a highly significant negative correlation between serum chemerin and eGFR was observed in patients' group. Furthermore, we evaluated the diagnostic performance of chemerin for discriminating patients with macroalbuminuria from those without. The best diagnostic cutoff for chemerin was 100.1 ng/mL. This had a diagnostic sensitivity of 85%, specificity 75%, negative predictive value 63%, positive predictive value 90.9%. The area under the curve (AUC) was 78.3%.

Conclusion: These findings suggested that serum chemerin can be used as a predictive marker for diabetic nephropathy.

Keywords: Serum chemerin, Renal dysfunction, Type 2 diabetes mellitus.

INTRODUCTION

The incidence of diabetes, particularly type 2 diabetes is increasing at alarming rate. About 347 million people worldwide have diabetes [1]. Diabetes is predicted to become the seventh leading cause of death in the world by the year 2030 [2].

In Egypt, it is estimated that by the year 2030 Egypt will have at least 8.6 million adults with diabetes, however little data are available on the epidemiology of diabetes in Egypt [3].

Diabetic nephropathy (DNP) is by far the most common cause of end stage renal disease (ESRD). Approximately one third of individuals with diabetes develop DNP with a high likelihood of progression to ESRD. In addition, DNP is associated with considerably increased cardiovascular disease risk and mortality. Thus, the public health burden from DNP is enormous. Current evidence suggests that both genetic and environmental factors determine susceptibility to develop DNP and the risk for and rate of progression of DNP [4]. The decrease in renal function in diabetic nephropathy is characterized by glomerular dysfunction, which is closely related to elevated urinary albumin excretion. Increased urinary albumin excretion has been demonstrated to be strongly associated with insulin resistance in type 2 diabetes patients [5].

Chemerin, a recently discovered adipocytokine [6], is a multifunctional protein implicated in chemotaxis of immune cells, regulation of differentiation and metabolic function of adipocytes, and glucose homeostasis [7]. Chemerin expression was significantly elevated in adipose tissue of obese and type 2 diabetic compared to lean and normoglycemics [8]. Chemerin has been shown to induce insulin resistance in skeletal muscle cells [9]. Significant positive association was found between circulating chemerin and BMI, waist-to-hip ratio, glucose and insulin homeostasis model assessment of insulin resistance (HOMA-IR). These studies suggest that chemerin may play a potential role in obesity-induced insulin resistance and the development of type 2 diabetes [10]. Serum chemerin levels were found to be significantly higher in patients on chronic hemodialysis compared to controls, suggesting that determinants of renal function are independently related to circulating chemerin levels. Therefore, serum chemerin concentration might be altered in patients with diabetic nephropathy [11].

AIM OF THE WORK

The aim of the present work was to evaluate serum chemerin level and its association with kidney functions in patients with type 2 diabetes mellitus.

SUBJECTS AND METHODS

I. Subjects:

This case control study was conducted at Clinical Pathology Departments of Al-Azhar University Hospitals. It was carried out on 80 subjects

of matched age and sex divided as 60 type 2 diabetic patients and 20 apparently healthy volunteers (hospital staff) serving as control group.

Subjects under study were classified into the following groups:
* **Group I (Control Group):** This group included 20 apparently healthy volunteers selected from those working in auxiliary jobs in Al-Azhar University Hospitals, (11 males and 9 females) whose ages range from 45-70 years (57.80 ± 6.4 years).
The control group of healthy volunteers was selected so as to have no history of arterial hypertension, diabetes, neoplastic, cardiovascular, lung, renal, endocrine or central nervous system disorders. None of these subjects were under any medical treatment.
* **Group II (Patients' group):** This group included 60 adult patients with type 2 DM under medical treatment (35 males and 25 females) whose ages range from 40-81 years (59.72 ± 8.38 years). The diagnosis was based on the ADA criteria for diagnosis of DM [12].

Those patients were further classified according to their albumin/creatinine ratio into three subgroups:
1) Subgroup IIa (n=20): Patients with type 2 diabetes and had normoalbuminuria (Alb/Creat ratio < 30 mg alb/g creat). Subgroup IIa included twenty patients (12 males and 8 females) whose ages ranged from 40-70 years (57.70 ± 9.25 years).
2) Subgroup IIb (n=20): Patients with type 2 diabetes and had microalbuminuria (Alb/Creat ratio 30-300 mg alb /g creat). Subgroup IIb included twenty patients (10 males and 10 females) whose ages range from 47-70 years (58.75 ± 8.02 years).
3) Subgroup IIc (n=20): Patients with type 2 diabetes and had macroalbuminuria (Alb/Creat ratio >300 mg alb/g creat). Subgroup IIc included twenty patients (13 males and 7 females) whose ages ranged from 55-81 years (62.90 ± 7.7 years).

Ethical consideration and written informed consent:
An approval of the study was obtained from Al-Azhar University Academic Ethical Committee. Every patient signed an informed written consent for acceptance of the operation.

* **Inclusion criteria:** all patients were type 2 diabetes.
 *** Exclusion criteria:** The following patients were excluded from the study:-
1. Patients with type 1 diabetes mellitus.
2. Patients with any hepatic affection.
3. Patients with active inflammatory diseases.
4. Patients with malignant diseases of any origin.
5. Patients with other known major diseases.

All individuals included in this study were subjected to the following:
1-Full history taking.
2- Laboratory investigations.

II. Sampling:
A- Serum samples:
 Five milliliters of venous blood were collected after 6-8 hours fasting under complete aseptic precautions in plain vacutainer (red-topped) tubes. After clotting, samples were centrifuged (at 1000 xg for 15 minutes). The separated serum was divided into two equal aliquots. One was designated for the immediate assay of fasting glucose, serum creatinine and urea. The other aliquot was stored at -20ºC for subsequent assay of chemerin and fasting insulin. Hemolysed samples were discarded. Repeated freezing and thawing was avoided.
B- Urine Samples:
 Ten milliliters (10 mL) of morning urine sample were collected. Urine strips were used for protein detection then urine samples were used for immediate estimation of microalbumin in all subjects.
III- Analytical Methods:
A- Serum glucose.
B- Serum Creatinine.
C- Serum urea.
D- Estimation of Glomerular Filtration Rate (GFR).
E- Estimation of Urinary microalbumin.
F- Serum insulin.
G- The homeostasis model assessment-insulin resistance index (HOMA-IR).
H- Serum Chemerin.

Statistical analysis
        Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:
- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
    - P-value <0.05 was considered significant.
    - P-value <0.001 was considered as highly significant.
    - P-value >0.05 was considered insignificant.

RESULTS

Table (1): Age and sex distribution of the studied group

	Control group (20)	Subgroup IIa (Normoalb) (n=20)	Subgroup IIb (Microalb) (n=20)	Subgroup IIc (Macroalb) (n=20)	Student's *t*-test	P value
	Mean ±SD	Mean ± SD	Mean ± SD	Mean ± SD		
Age Mean ± SD	57.80 ± 6.4	58.45 ± 7.78	57.0 ± 7.55	61.05 ± 7.19	X^2= 2.22	0.529
Range	45-70	40-70	43-70	51-81		
Sex N (%) Male Female	11(55.0) 9(45.0)	12(60.0) 8(40.0)	10(50.0) 10(50.0)	13(65.0) 7(35.0)	X^2= 1.02	0.80

There was no statistically significant difference ($p > 0.05$) among studied and control groups as regards age and sex.

Table (2): Comparison between group I and group II regarding BMI

	Group I (Control Group) (n=20)	Group II (Patient group) (n=60)	Student's *t*-test	p-value
	Mean ± S D	Mean ± S D		
BMI(kg/m²)	25.9 ± 3.43	41.8 ± 5.4	4.4	<0.001

There was a highly statistically significant increase in the mean of BMI in patients' group compared to control group ($p < 0.001$).

Table (3): Comparison between group I and group II regarding renal function tests (serum urea, creatinine, urinary microalbumin, ACR and eGFR)

	Group I (Control Group) (n=20)	Group II (Patient group) (n=60)	Student's *t*-test	p-value
	Mean ± S D	Mean ± S D		
serum urea(mg/dl)	27.95 ± 5.83	70.47 ± 4.17	4.75	<0.001**
serum creatinine (mg/dl)	0.795 ± 0.16	2.59 ± 0.85	2.69	0.007**
microalbumin in urine(mg/l)	3.70 ± 1.48	226.7 ± 21.41	6.35	<0.001**
ACR(mg/g)	9.46 ± 1.96	412.79 ± 78.96	5.12	<0.001**
eGFR(ml/min)	110.3 ± 10.60	80.68 ± 1.28	2.58	0.01*

There was a highly statistically significant increase in the mean of urinary microalbumin, urea and ACR in patients' group compared to control group ($p < 0.001$). Also, there was a statistically significant difference between patients' group and control group as regards serum creatinine and eGFR.

Table (4): Comparison between group I and group II regarding fasting FBS, insulin and HOMA-IR

	Group I (Control Group) (n=20)	Group II (Patient group) (n=60)	Student's *t*-test	p-value
	Mean ± S D	Mean ± S D		
FBS(mg/dl)	85.6 ± 2.77	217.13 ± 56.12	St t= 10.35	<0.001**
Fasting Insulin (µIU/ml)	11.73 ± 2.98	8.76 ± 2.12	1.96	<0.05*
HOMA_IR Index	1.77 ± 0.21	5.05 ± 0.94	3.54	<0.001**

There was a highly statistically significant increase in the mean of HOMA-IR and FBS in patients' group compared to control group ($p < 0.001$). Also, there was a statistically significant increase in the mean Fasting insulin in patients' group compared to control group ($p < 0.001$).

Table (5): Comparison between group I and group II regarding serum chemerin

	Group I (Control Group) (n=20)	Group II (Patient group) (n=60)	Student's t-test	p-value
	Mean ± S D	Mean ± S D		
serum chemerin (ng/ml)	43.7 ± 4.22	135.5 ± 11.07	5.60	<0.001**

There was a highly statistically significant increase in the mean of serum chemerin in patients' group compared to control group (p < 0.001).

Table (6): Comparison between patients' subgroups and control group regarding renal function tests (serum urea, creatinine, urinary microalbumin, ACR and eGFR)

	Control group (n=20)	Subgroup IIa (Normoalb) (n=20)	Subgroup IIb (Microalb) (n=20)	Subgroup IIc (Macroalb) (n=20)	Student's t-test	P value
	Mean ± S D	Mean ± SD	Mean ± S D	Mean ± S D		
serum urea(mg/dl)	27.95 ± 5.83	38.95 ± 1.43	35.6 ± 1.19	136.85 ± 4.01	F= 97.36	<0.001**
serum creatinine (mg/dl)	0.795 ± 0.16	0.795 ± 0.20	0.875 ± 0.21	6.11 ± 1.36	F= 97.96	<0.001**
microalbumin in urine (mg/l)	3.70 ± 0.48	9.84 ± 2.39	78.3 ± 6.56	591.95 ± 17.55	X^2=71.7	<0.001**
ACR(mg/g)	9.46 ± 2.96	12.92 ± 3.34	80.0 ± 2.16	1145.45 ± 42.04	X^2=67.27	<0.001**
eGFR(ml/min)	110.3 ± 10.60	120.45 ± 9.70	101.8 ± 2.55	19.78 ± 3.6	X^2=47.78	<0.001**

There was a statistically highly significant elevation in serum levels of urea, creatinine, urinary microalbumin and ACR in patients with macroalbuminuria (subgroup IIc) versus control group (p<0.001). In addition, a highly statistically significant elevation in serum levels of urea, creatinine, urinary microalbumin and ACR in patients with microalbuminuria (subgroup IIb) versus control group (p<0.001). Concerning comparison between patients with normoalbuminuria (subgroup IIa) versus control group no statistically significant difference was detected in sub groups IIa versus control group. As regards eGFR, a highly statistically significant decrease was observed in patients with macroalbuminuria (subgroup IIc) versus control group (p < 0.001). However, no statistically significant difference was detected in other subgroups (sub groups IIa, IIb) versus control group.

Table (7): Comparison between patients' subgroups and control group regarding serum FBS, fasting insulin and HOMA-IR.

	Control group (n=20)	Subgroup IIa (Normoalb) (n=20)	Subgroup IIb (Microalb) (n=20)	Subgroup IIc (Macroalb) (n=20)	Student's t-test	P value
	Mean ± S D	Mean ± SD	Mean ± S D	Mean ± S D		
FBS (mg/dl)	85.6 ± 2.77	169.45 ± 20.06	199.5 ± 26.16	282.45 ± 8.52	F= 193.4	<0.001**
Fasting Insulin (µIU/ml)	11.73 ± 2.98	5.96 ± 1.27	4.56 ± 5.17	15.77 ± 1.61	X^2=18.85	<0.001**
HOMA_IR Index	1.77 ± 0.21	2.56 ± 0.74	2.57 ± 1.41	10.02 ± 2.63	X^2=43.72	<0.001**

There was a highly statistically significant elevation in FBS as well as HOMA-IR index in patients with macroalbuminuria (subgroup IIc) versus control group (p < 0.001). There was no statistically significant difference in patients with microalbuminuria (subgroup IIb) and normoalbuminuria (subgroup IIa) versus control group as regards fasting insulin or HOMA-IR.

Table (8): Comparison between patients' subgroups and control group regarding serum chemerin

	Control group (n=20)	Subgroup IIa (Normoalb) (n=20)	Subgroup IIb (Microalb) (n=20)	Subgroup IIc (Macroalb) (n=20)	Student's t-test	P value
	Mean ± S D	Mean ± S D	Mean ± S D	Mean ± S D		
serum chemerin (ng/ml)	43.7 ± 4.2	85.9 ± 4.06	84.65 ± 7.51	235.95 ± 20.21	X^2= 44.01	<0.001**

There was a highly statistically significant elevation in serum chemerin in patients with macroalbuminuria (subgroup IIc) versus control group (p < 0.001). There was no statistically significant difference in patients with microalbuminuria (subgroup IIb) and normoalbuminuria (subgroup IIa) versus control group as regards seum chemerin.

Table (9): Comparison between subgroups of cases regarding FBS, serum urea and creatinine, urinary microalbumin and creatinine, ACR and eGFR

	Subgroup IIa (Normoalb) (n=20)	Subgroup IIb (Microalb) (n=20)	Subgroup IIc (Macroalb) (n=20)	Student's t-test	p-value
	Mean ± S D	Mean ± S D	Mean ± S D		
serum urea(mg/dl)	38.95 ± 1.43	35.6 ± 1.19	136.85 ± 4.01	92.34	<0.001**
serum creatinine (mg/dl)	0.795 ± 0.10	0.875 ± 0.21	6.11 ± 1.36	97.89	<0.001**
microalbumin in urine (mg/l)	9.84 ± 1.39	78.3 ± 6.56	591.95 ± 17.55	X^2= 27.7	<0.001**
ACR(mg/g)	12.92 ± 2.34	80.0 ± 2.16	1145.45 ± 42.04	X^2= 28.98	<0.001**
eGFR(ml/min)	120.45 ± 2.70	101.8 ± 2.55	19.78 ± 3.6	80.92	<0.001**

There was a highly statistically significant elevation in serum levels of serum urea, creatinine, urinary microalbumin and ACR in patients with macroalbuminurea (subgroup IIc) compared to patients with normoalbuminuria and patients with microalbuminuria (subgroups IIa, IIb; respectively) (p < 0.001). However, eGFR showed a highly statistically significant decrease in patients with macroalbuminuria (subgroup IIc) versus patients with normoalbuminuria and patients with microalbuminuria (subgroups IIa, IIb, respectively) (p < 0.001).

Table (10): Diagnostic performance of serum chemerin in discriminating patients with acroalbuminuria from those without

Cut off	Sensitivity	Specificity	PPV	NPV	AUC
100.0	85.0%	75.0%	63.0%	90.9%	78.3%

The diagnostic performance of chemerin for discriminating patients with macroalbuminuria from those without. The best diagnostic cutoff for chemerin was 100.1 ng/mL. This had a diagnostic sensitivity of 85%, specificity 75%, negative predictive value 63%, positive predictive value 90.9%. The area under the curve (AUC) was 78.3%.

DISCUSSION

For all subjects, fasting blood glucose, serum creatinine, serum urea, urine albumin/creatinine ratio, fasting insulin and serum chemerin levels were measured as well as calculation of glomerular filtration rate (estimated GFR using Cock croft-Gault equation), HOMA-IR index and BMI.

The results of the present study showed that diabetic patients had a significant elevation in serum levels of urea when compared to control group. Our results agree with those of **Aronson et al.** [13] and **Priyanka et al.** [14] who attributed such findings to the presence of hyperglycemia, glomerular hypertension, advanced glycation end products (AGE), activation of polyol pathway and infiltration of kidney glomeruli by inflammatory cells like monocytes and macrophage. They stated that the previous factors resulted in glomerular injury and tubulo-interstitial damage that decreased the

functional capability of kidney to excrete waste products.

In the present study, there was a highly significant increase in serum creatinine and serum urea in diabetic patients with macroalbuminuria compared to patients with microalbuminuria, patients with normoalbuminuria and control group. While no statistically significant difference between microalbuminuric, normoalbuminuric diabetic group and control group as regards serum urea and serum creatinine. These findings are in accordance with **Hu and Fing** [15], **Elsebai et al.** [16] who demonstrated increased serum levels of urea and creatinine in patients with diabetic nephropathy and **Nwankwo et al.** [17] who referred this to the progression of diabetic nephropathy leading to impaired kidney functions by overproduction and impaired degradation of extracellular matrix components that lead to their accumulation in the basement membranes and mesangial regions of the glomerulus.

The results of the present study showed that there was a highly significant increase in BMI in diabetic patients compared to normal controls. This is in agreement with **Berrington de Gonzalez et al.** [18], **Ganz et al.** [19] and **Menke et al.** [20] who stated that adults who meet or exceed the 25 kg/m^2 BMI threshold were at increased risk of developing type 2 diabetes and other diseases in addition to showing increases in mortality. However, **Hsu et al.** [21] study on Asian Americans illustrated that the Asian Americans have a higher prevalence of type 2 diabetes at relatively lower BMI cut points than whites. This paradox was partly explained by **Araneta and Barrett-Connor** [22] by a difference in body fat distribution where there is a propensity for Asians to develop visceral versus peripheral adiposity, which is more closely associated with insulin resistance and type 2 diabetes than overall adiposity.

The present study demonstrated that there was a significant elevation in serum chemerin levels in diabetic patients compared to normal controls. This is in agreement with **Stejskal et al.** [23], **Yang et al.** [24] and **Coimbra et al.** [25] studies. Chemerin, an adipocytokine, had been shown to regulate adipocyte differentiation and modulate the expression of adipocyte genes involved in glucose and lipid homeostasis, such as glucose transporter 4, adiponectin and leptin. Therefore, several studies suggest that chemerin may play a potential role in obesity-induced insulin resistance and development of type 2 diabetes mellitus [10]. Although a subset of smaller studies did not find differences of chemerin levels between patients with T2DM and individuals with NGT (normal glucose tolerance), **Bozaoglu et al.** [8] and **Weigert et al.** [26] showed that quite probably a proportion of their type 2 diabetic study

subjects might be controlled well by anti-diabetic drugs, that was not the case in the present study.

In addition, a highly significant elevation in serum chemerin levels was detected in patients with macroalbuminuria compared to patients with microalbuminuria, patients with normoalbuminuria and normal controls. Moreover, the present study revealed a highly significant positive correlation between serum chemerin and Alb/Creat ratio in diabetic patient group. These findings are in agreement with and explained by studies done by **Murata et al.** [27], **Hu and Fing** [15] and **Elsebai et al.** [16] who stated that in advanced stages of diabetic nephropathy, there is more glomerular enlargement as a compensatory mechanism to overcome glomerulopathy, leading to more loss of kidney function and more albumin excretion through increased permeability to albumin. This was associated with impaired clearance of chemerin that may lead to the accumulation of chemerin in the blood. This suggesting the possible use of serum chemerin as a predictor for diabetic nephropathy.

Furthermore, results of the present study demonstrated that there were no significant differences in serum chemerin levels between normal controls and diabetic patients with normoalbuminurea and microalbuminurea. This concurs with **Bozaoglu et al.** [8], **Hu and Fing** [15] and **Weigert et al.** [26] who failed to find a significant difference in serum chemerin levels between diabetic patients with microalbuminurea and normal controls.

Concerning HOMA-IR index, the present study showed a significant elevation in HOMA-IR index in patient group compared to control group with a highly significant elevation in macroalbuminuric patients versus controls. Also, a significant elevation was detected in patients with macroalbuminuria compared to patients with microalbuminuria and patients with normoalbuminuria. These findings agree with **Hu and Fing** [15] and **Filippone et al.** [28] who revealed that patients with type 2 DM who develop DN had been shown to be more insulin resistant than those who did not and explained this by the fact that IR can lead to DN; either indirectly through hyperglycemia, hyperinsulinemia, hyperlipidemia, etc., or directly due to renal IR as normal insulin signaling is necessary for proper function of renal bodocytes. Also, **Cohen et al.** [29] and **Catalano et al.** [30] demonstrated that insulin resistance is associated with hemodynamic alteration in the kidney. Hyperinsulinemia has been reported to be able to raise glomerular hydrostatic pressure, increase renal vascular permeability, aggravate glomerular hyperfiltration and enhance renal sodium reabsorption. This could explain underlying mechanisms for the significant elevation in the HOMA-IR score in macroalbuminuria

observed in this study. Moreover, **Hsu et al.** [21] confirmed that type 2 diabetic patients predisposed to higher insulin resistance are more likely to develop microalbuminuria.

In the study at hand, a highly significant positive correlation has been found between serum chemerin levels and FBS. These results are in agreement with **Bozaoglu et al.** [8], **Elsebai et al.** [16] and **Ernst and Sinal** [31]. **Takahashi et al.** [32] demonstrated that chemerin plays a role in the regulation of beta cell function. Chemerin deficient mice showed impaired glucose-stimulated insulin secretion (GSIS) and chemerin transgenic mice revealed enhanced GSIS.

The present study also showed that serum chemerin level was highly significant positively correlated with fasting insulin level supporting a possible role of chemerin on beta cell function. **Sell et al.** [9] attributed this to the fact that chemerin induces insulin resistance in peripheral tissues as skeletal muscle and inhibits glucose uptake. Another explanation was obtained by **Takahashi et al.** [32] who postulated that, in adipocytes, chemerin has the opposite effect, where it increases insulin-stimulated glucose uptake and so, it stimulates insulin sensitivity. Hence, the increase in the levels of circulating chemerin is a compensatory mechanism in patients with insulin resistance.

Moreover, a significant positive correlation has been found between serum chemerin levels and BMI. These results are in agreement with **Bozaoglu et al.** [8], **Hu and Fing** [15], **Ernst and Sinal** [31] and **Bobbert et al.** [33] who detected a strong association between chemerin and obesity. These findings indicated that chemerin may play a role in obesity and the development of obesity comorbidities. **Sell et al.** [9] explained these findings by the fact that human adipocytes express chemerin and chemokine-like receptor 1 (CMKLR1) and secrete chemerin and that adipose tissue explants from obese individuals secrete significantly more chemerin than those isolated from lean individuals and this secretion correlates with increased BMI. Moreover, **Chakaroun et al.** [34] reported that chemerin mRNA expression in adipose tissue increases significantly in obese patients, with expression in omental but not subcutaneous adipose tissue correlating positively with circulating concentrations.

In our study, there was a diagnostic performance of chemerin for discriminating patients with macroalbuminuria from those without. The best diagnostic cutoff for chemerin was 100.1 ng/mL. This had a diagnostic sensitivity of 85%, specificity 75%, negative predictive value 63% and positive predictive value 90.9%. The area under the curve (AUC) was 78.3%.

These findings suggested that serum chemerin can be used as a predictive marker for diabetic nephropathy.

CONCLUSION

In conclusion, this study showed that serum chemerin levels were elevated in diabetic patients especially those with macroalbuminuria versus healthy control. In addition, a cutoff 128.1ng/mL can diagnose patients with diabetic nephropathy. Moreover, serum chemerin levels were significantly correlated with kidney functions as serum creatinine, serum urea and ACR. Therefore, serum chemerin can be considered as an independent predicting marker of diabetic nephropathy as well as an excellent diagnostic marker for patient with clinical diabetic nephropathy.

REFERENCES

1. **Danaei G, Finucane MM, Lu Y et al. (2011):** National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet, 378 (9785): 31–40.
2. **World Health Organization (2016):** Diabetes. Fact sheet N°312. https://www.who.int › Newsroom › Fact sheets ›
3. **Shaw JE, Sicree RA, Zimmet PZ (2010):** Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract., 87 (1): 4-14.
4. **Jones CA, Krolewski AS, Rogus J et al. (2005):** Epidemic of end-stage renal disease in people with diabetes in the United States population: Do we know the cause? Kidney Int., 67: 1684-1691.
5. **De Cosmo S, Minenna A, Ludovico O et al. (2005):** Increased urinary albumin excretion , insulin resistance, and related cardiovascular risk factors in patients with type 2 diabetes: evidence of a sex-specific association. Diabetes care, 28: 910-915.
6. **Goralski, KB, McCarthy, TC, Hanniman, EA et al. (2007):** Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem., 282: 28175-28188.
7. **Banas M, Zabieglo K, Kasetty G et al. (2013):** Chemerin is an antimicrobial agent in human epidermis. PLoS One, 8: e58709.
8. **Bozaoglu K, Bolton K, McMillan J et al. (2007):** Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology, 148: 4687-4694.
9. **Sell H, Laurencikiene J, Taube A et al. (2009):** Chemerin is a novel adipocyte-derived factor inducing insulin resistance in primary human skeletal muscle cells. Diabetes, 58 (12): 2731-2740.
10. **Tan BK, Chen J, Farhatullah S et al. (2009):** Insulin and metformin regulate circulating and adipose tissue chemerin. Diabetes, 58: 1971–1977.
11. **Pfau D, Stepan H, Kratzsch J et al. (2010) a:** Circulating Levels of the Adipokine Chemerin in

Gestational Diabetes Mellitus. Horm Res Paediatr., 79: 101-108.

12. **American Diabetes Association (2014):** Standards of Medical Care in Diabetes. Diabetes Care, 37 (1): s14- s80.

13. **Aronson D, Mittleman MA, Burger AJ (2010):** Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. Am J Med., 116: 466–473.

14. **Priyanka T, Zenith K, Satyavani K *et al.* (2010):** Clinical significance of urinary Monocyte Chemo-attractant Protein-1 (uMCP-1) in Indian type 2 diabetic patients at different stages of diabetic nephropathy. International Journal of Diabetes Mellitus, 2: 15–19.

15. **Hu W, Fing P (2011):** Elevated serum chemerin concentrations are associated with renal dysfunction in type 2 diabetic patients. Diabetes research and clinical practice, 91 (2): 159- 163.

16. **Elsebai AA, Saad WE, Mahdy MM (2014):** Serum Chemerin and Beta 2-Microglobulin in Type 2 Diabetes: Assessment of Diabetic Nephropathy. Life Science Journal, 11 (8): 992-1000.

17. **Nwankwo EA, Wudiri WW, Gadzama AA (2006):** Serum uric acid correlates with the progression of nephropathy in patients with diabetes mellitus. Pak J Med Sci., 22 (4): 391-395.

18. **Berrington de Gonzalez A, Hartge P, Cerhan, JR *et al.* (2010):** Body-mass index and mortality among 1.46 million white adults. N Engl J Med., 363: 2211–2219.

19. **Ganz ML, Wintfeld N, Li Q *et al.* (2014):** The association of body mass index with the risk of type 2 diabetes: a case–control study nested in an electronic health records system in the United States. Diabetology & Metabolic Syndrome, 6 (1): 50.

20. **Menke A, Rust KF, Fradkin J *et al.* (2014):** Associations between Trends in Race/Ethnicity, Aging, and Body Mass Index With Diabetes Prevalence in the United States: A Series of Cross-sectional Studies Increase in Diabetes Prevalence Over Time. Ann Intern Med., 161 (5): 328-335.

21. **Hsu WC, Araneta MR, Kanaya AM *et al.* (2015):** BMI Cut Points to Identify At-Risk Asian Americans for Type 2 Diabetes Screening. Diabetes Care, 38: 150–158.

22. **Araneta MR, Barrett-Connor E (2005):** Ethnic differences in visceral adipose tissue and type 2 diabetes: Filipino, African-American, and white women. Obes Res., 13: 1458–1465.

23. **Stejskal D, Karpisek M, Hanulova Z *et al.* (2008):** Chemerin is an independent marker of the metabolic syndrome in a Caucasian population – a pilot study. Biomed Pap., 152 (2): 217-221.

24. **Yang M, Yang G, Dong J *et al.* (2010):** Elevated plasma levels of chemerin in newly diagnosed type 2 diabetes mellitus with hypertension. Journal of Investigative Medicine, 58: 883–886.

25. **Coimbra S, Proença JB, Santos-Silva A *et al.* (2014):** Adiponectin, Leptin, and Chemerin in Elderly Patients with Type 2 Diabetes Mellitus: A Close Linkage with Obesity and Length of the Disease. BioMed Research International, 701915: 1-8.

26. **Weigert J, Neumeier M, Wanninger J *et al.* (2010):** Systemic chemerin is related to inflammation rather than obesity in type 2 diabetes. Clinical Endocrinology, 72: 342–348.

27. **Murata M, Saito T, Otani T *et al.* (2009):** An increase in serum retinol-binding protein 4 in the type 2 diabetic subjects with nephropathy. Endocr J., 56: 287–294.

28. **Filippone EJ, Gupta A, Farber JL (2014):** Normoglycemic Diabetic Nephropathy: The Role of Insulin Resistance. Case Rep Nephrol Urol., 4 (2): 137–143.

29. **Cohen AJ, McCarthy DM, Stoff JS (1989):** Direct hemodynamic effect of insulin in the isolated perfused kidney. Am J Physiol., 257: F580–F585.

30. **Catalano C, Muscelli E, Quiñones GA *et al.* (1997):** Effect of insulin on systemic and renal handling of albumin in nondiabetic and NIDDM subjects. Diabetes, 46: 868–875.

31. **Ernst MC, Issa M, Goralski KB *et al.* (2010) a:** Chemerin Exacerbates Glucose Intolerance in Mouse Models of Obesity and Diabetes. Endocrinology, 151 (5): 1998-2007.

32. **Takahashi M, Okimura Y, Iguchi G *et al.* (2011):** Chemerin regulates beta-cell function in mice. Sci Rep., 1: 123.

33. **Bobbert T, Schwarz F, Fischer-Rosinsky A *et al.* (2015):** Chemerin and prediction of Diabetes mellitus type 2. Clinical Endocrinology, 2: 1–6.

34. **Chakaroun R, Raschpichler M, Klöting N *et al.* (2012):** Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. Metabolism: Clinical and Experimental, 61 (5): 706–714.