ISSN: 03875547
Volume 44, Issue 06, December, 2021

Evaluation of Chemerin level in Iraqi Chronic Kidney Disease with Diabetic Mellitus and without Diabetic Mellitus Patients

Walaa Ahmed AL Jedda[1*], RAGHD A. Y. ALKHADER[2], Maryam Qusay Isaa[3]

Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, Baghdad – Iraq[1,2]
Middle Technical University, Institute of Medical Technology AL-Mansur, Baghdad – Iraq[3]

Corresponding Author: 1*

Keywords:
Chemerin, Type 2 diabetes mellitus, chronic kidney disease.

ABSTRACT

Chronic kidney disease (CKD) is generally a progressive condition that is characterized by significant changes in the structure and function of the kidney as a result of different causes. Chemerin, a novel chemokine and adipokine, is principally produced in adipocytes and liver. It is mainly involved in lipid and carbohydrates metabolism. The present paper aims to evaluate chemerin levels in Iraqi CKD subjects, and to compare serum concentrations of chemerin in CKD subjects with and without diabetes mellitus. Thus, sixty CKD patients compared with thirty normal control group were investigated. The age of the subjects ranged from 30-55 years. The CKD patients have been also subdivided into 2 groups: thirty CKD patients with T2D and thirty CKD patients without T2D. Blood samples have been collected and analyzed for fasting blood glucose, postprandial blood glucose, hemoglobin A_{1c}, urea, creatinine, high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol. The estimation of serum fasting insulin and chemerin levels have been made by ELISA kits. Moreover, calculations of the HOMA-IR, and eGFR have been made. Serum levels of chemerin were highly significantly elevated in CKD patients compared with normal controls. Moreover, serum chemerin concentrations were highly significantly elevated in the CKD group with diabetes compared with CKD group without diabetes. These results would seem to suggest that serum concentrations of chemerin are likely to become a possible marker for assessment of T2D in CKD patients.

1. INTRODUCTION

Chronic kidney disease (CKD) is generally a progressive condition that is characterized by significant changes in the structure and function of the kidney as a result of different causes. CKD is classically defined as a decline in renal function, "an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m²", or markers of renal damage, for example haematuria, albuminuria, or abnormalities detected by laboratory or imaging tests and which are present for three or more months [1]. The pathophysiology of

chronic kidney disease is very complex and its clinical course depending on a wide-spectrum of various etiologies that all leading towards renal failure. The most common causes of chronic kidney disease in all middle- and high-income countries are hypertension and diabetes mellitus (DM). In 2017, the prevalence of CKD was 9.1 percent, and about 1.2 million individuals died from this disease throughout the world [2]. By 2040, CKD is anticipated to be the fifth most important cause of death throughout the world [1]. Type II diabetes mellitus (T2D) is principally a progressive metabolic disorder resulting from genetic factors along with environmental factors [3]. T2D is a chronic condition essentially caused by an impairment in insulin secretion, and/or its action [4], that causes increased blood glucose concentrations, that is considered as the chief cause of CKD [5]. Kidney disease caused by DM (diabetic kidney disease) that is considered one of the most prevalent diabetes complications as it affects nearly forty percent of T2D subjects. It may eventually cause end-stage renal disease (ESRD) in addition it is accompanied by higher risk of cardiovascular diseases and death. Furthermore, subjects having DM can as well develop CKD as a result of etiologies besides DM and several may possibly have a combination of nondiabetic CKD and diabetic kidney disease. Prevalence of T2D is rising throughout the world and subsequently DM -associated CKD is a leading contributor to global disease burden [6].

Chemerin, a novel chemokine and adipokine, is principally produced in adipocytes and liver and exerts many of its functions e.g. modulating glycolipid metabolism, adipogenesis, inflammation, lipolysis, and insulin resistance (IR) chiefly via it's receptor the chemokine-like receptor-1 (ChemR23) [7]. Chemerin is a 16 k-Da protein that is secreted as an inactive pro-chemerin, which in turn undergoes extracellular serine endopeptidase cleavage of the carboxyl terminus part. It is mainly involved in lipid and carbohydrates metabolism [8]. Chemerin is abundantly expressed in lungs, liver, pituitary gland, white adipocytes; and at lower levels in kidneys, pancreas, skin and adrenal glands. Furthermore, mRNA for pro-chemerin are present in a variety of endothelial cells, chondrocytes, platelets, epithelial cells and fibroblasts [9]. Chemerin has the ability to activate oxidative stress along with the inflammatory response in adipocytes causing IR. Chemerin expression is increased in dyslipidemic, diabetic, and hypertensive subjects who may have metabolic syndrome [10]. Serum chemerin concentrations are elevated in T2D subjects and are positively associated with hypertension, hemoglobin A1c, dyslipidemia, high-levels of inflammatory cytokines, IR and adiposity [11]. In kidneys it was found that elevated serum levels of chemerin is accompanied by renal function deterioration [12].

The present paper aims to evaluate chemerin levels in Iraqi CKD subjects, and to compare serum concentrations of chemerin in CKD subjects with and without diabetes mellitus.

2. Material and Method

The study protocol has been approved by the National Diabetes centre at Mustansiriyah University. The data have been collected from sixty CKD patients compared with thirty normal control group, in the whole period between November 2020 to June 2021. The age of the subjects ranged from 30-55 years. The CKD patients have been also subdivided into 2 groups: thirty CKD patients with T2D and thirty CKD patients without T2D. All individuals have been subjected to physical examinations that include the measurements of: height, weight, body mass index (BMI), systolic blood pressure (SP), and diastolic blood pressure (DP). Blood samples have been collected and analyzed by automated analyzers for: fasting blood glucose (FBG), postprandial blood glucose (PPBG), hemoglobin A1c, urea, creatinine (CREAT), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TGs), total cholesterol (TCs). The estimation of serum fasting insulin (FINS) and chemerin levels have been made by ELISA kits. Moreover, calculations of the homeostasis model assessment-IR (HOMA-IR), and eGFR have been made as described in [13], [14] respectively. The Microsoft Excel 2010 was used to analyze the data. Results are reported as means ±

standard deviation (SD). Significance was defined as a probability value of 0.05.

3. Results

Anthropometric measurements between CKD and normal controls are listed in Table 1. There were no differences between these two groups regarding the: age, height, and body weight. While, there were highly significant elevations in SP and DP (P<0.001), and a significant elevation in BMI (P<0.05) between the CKD patients and normal controls.

Table 1- Anthropometric measurements between CKD patients and normal controls.

Parameters	CKD No (60)	Control No (30)	p-value
	Mean±SD	Mean±SD	
Age (Years)	49.25 ±6.55	42.95 ±3.59	0.120
SP(mmHg)	165±25.45	130.50±5.00	0.001**
DP(mmHg)	90.0±9.50	80.2±10.00	0.001**
Hight (cm)	177.77±2.02	165.93±2.55	0.136
Body Weight (Kg)	88.01±2.19	78.34±2.10	0.06
BMI(Kg/m^2)	27.25 ±2.59	20.20 ±3.11	0.05*
*<0.05: significant; **<0.01: highly significant			

As detailed in Table 2, there were highly significant elevations in FBG, PPBG (P<0.001) and TCs, TGs (P<0.01) in the CKD patients compared with normal controls. In addition, significant elevations in Hemoglobin A1c, HOMA-IR, HDL, LDL, urea and CREAT levels were found in the CKD patients compared with normal controls (P < 0.05). The eGFR was highly significantly lower (P<0.001) in CKD patients compared with normal controls. The CKD patients presented significantly lower FINS and HDL levels (P<0.05) compared with normal controls (Table 2).

Table 2- comparison of the biochemical values between CKD patients and normal controls.

Parameters	CKD No (60)	Control No (30)	p-value
	Mean±SD	Mean±SD	
Sex(Males/Females)	(30/30)	(15/15)	/
FBG(mg/dl)	203±11.32	84±5.51	0.001**
PPBS(mg/dl)	289±10.77	148.41±6.12	0.001**
Hemoglobin A_{1c} %	8.45±1.22	4.17±1.33	0.05*
FINS (µU/ml)	12.06±1.77	19.44±1.99	0.05*
HOMA-IR	7.52±1.32	2.28±0.19	0.05*
HDL (mg/dl)	38.19±4.88	56.41±2.13	0.05*
LDL (mg/dl)	140.22±17.32	85.41±11.31	0.05*

TCs(mg/dl)	252.42±13.39	175.15±10.22	0.01**
TGs(mg/dl)	206.25±15.01	110.28±11.67	0.01**
Urea (mg/dl)	56.57 ± 4.12	31.17 ±3.19	0.05*
CREAT (mg/dl)	1.38 ±0.59	0.82 ±0.21	0.05*
eGFR(ml/min)	32.53±5.01	95.92±4.51	0.001**
*<0.05: significant; **<0.01: highly significant			

Table 3 proves that the levels of serum chemerin were highly significantly elevated in CKD patients compared with normal controls(P<0.01).

Table 3- Serum chemerin levels in CKD patients and normal controls.

Parameter	CKD No (60)	Control No (30)	p-value
	Mean±SD	Mean±SD	
Chemerin level (ng/ml)	32.06±4.00	14.92±3.21	0.01**
**<0.01: highly significant			

Comparison of the biochemical values between CKD patients with and without T2D are detailed in Table 4. There were no differences between these two groups regarding: HDL, and CREAT levels. Regarding PPBG, Hemoglobin A1c, FINS, HOMA-IR, LDL, TCs, TGs, urea (all P<0.05) and FBG (P=0.03), there were significant elevations in the CKD group with diabetes compared with CKD group without diabetes. The eGFR level was significantly decreased in CKD group with diabetes compared with CKD group without diabetes (P<0.05).

Table 4- Comparison of the biochemical values between CKD patients with and without T2D.

Parameters	CKD with T2D No (30)	CKD without T2D No (30)	p-value
	Mean±SD	Mean±SD	
Sex(Males/Females)	(13/17)	(16/14)	/
FBG(mg/dl)	210±7.32	105.1±4.12	0.03*
PPBS (mg/dl)	259±7.05	172.52±6.42	0.05*
Hemoglobin A_{1c} %	9.58±2.31	5.67±0.38	0.05*
FINS (µU/ml)	17.10±1.77	13.00±1.45	0.05*
HOMA-IR	6.59±2.04	4.98±1.29	0.05*
HDL (mg/dl)	36.22±2.38	40.61±3.83	0.106

LDL (mg/dl)	145.16±8.18	102.01±7.33	0.05*
TCs(mg/dl)	298.41±20.11	215.15±12.9	0.05*
TGs (mg/dl)	222.05±13.52	151.08±11.64	0.05*
Urea (mg/dl)	76.23 ± 6.52	47.15 ±4.29	0.05*
CREAT (mg/dl)	1.41 ±0.39	1.18 ±0.61	0.184
eGFR(ml/min)	33.84±4.85	63.18±5.73	0.05*
*<0.05: significant; **<0.01: highly significant			

Table 5 proves that serum levels of chemerin were highly significantly elevated in the CKD group with diabetes compared with CKD group without diabetes; (P<0.01).

Table 5- Serum chemerin levels in CKD patients with and without T2D.

Parameter	CKD with T2D No (30)	CKD without T2D No (30)	p-value
	Mean±SD	Mean±SD	
Chemerin level (ng/ml)	27.16±3.09	19.52±4.00	0.01**
**<0.01: highly significant			

4. Discussion

In present study, two studied groups (CKD patients and normal controls) were compared. There was no significant difference in age but a significant increase was found in BMI in CKD patients more than normal controls. This confirms the previous findings of [15] who reported a higher BMI in CKD patients in comparison with controls. They attributed these findings to the increase in water-loading along with obesity in CKD patients. In contrast to earlier findings, [16], revealed that the patients with CKD had significantly lower BMI in comparison to control patients, that caused by the ethnic and environmental difference. El-[17] did not find a difference in BMI. This could be associated with different socioeconomic statuses [17]. In present study, there was a statistical significance regarding FBG, FINS, HOMA-IR, HDL, LDL, TGs and TCs between CKD patients and normal controls. This was reported as well by [15], [16], [18]. In addition, both SP and DP were statistically higher in CKD patients in comparison with normal controls. This confirms the findings of [17].

In present study, serum chemerin concentration was significantly higher in CKD patients in comparison with normal controls. This has been supported by several researches which documented elevated serum chemerin concentration in CKD patients in comparison with controls [12], [15], [17], [19]. Several researches have investigated serum levels of chemerin along with their pathophysiological importance in CKD cohorts [20]. Serum CREAT is significantly as well as independently linked to serum chemerin [19] [21]. Blood chemerin concentration was reported to be dependent on the GFR and negatively related to kidney function. Importantly, a twofold rise in blood chemerin concentration was found in patients undergoing hemodialysis [16]. These findings were strengthened by a research of patients with ESRD undergoing renal transplantation [21], whose high chemerin concentrations returned to baseline chemerin concentrations detected in the healthy controls within 3-months after kidney transplant. There are abundant

amount of data suggesting that plasma/serum chemerin level is positively associated with kidney disease. Nevertheless, numerous groups support the notion that the raised plasma chemerin levels in CKD patients are not due to overproduction of chemerin protein (at least by adipocytes) but as a result of poor kidney elimination [12], [16], [17], [20- 24]. Dialysis directly decreased the plasma level of chemerin [12], supporting this notion.

In present study, serum levels of chemerin were highly significantly elevated in the CKD group with diabetes compared with CKD group without diabetes. On similar lines, [25] also demonstrated that chemerin levels were significantly higher in CKD patients with DM (either on hemodialysis or on predialysis conservative therapy HD) in comparison with those without DM. These findings support the findings of Hu and Feng [19], [26], [27] which confirm the increase in serum chemerin concentration in DM patients with CKD. They documented significantly higher levels of chemerin in T2D subjects with macroalbuminuria in comparison with normal and diabetic subjects with norm- and micro-albuminuria. In addition, they indicated that in the advanced stages of diabetic kidney disease, "there is more glomerular enlargement as a compensatory mechanism to overcome glomerulopathy", causing more loss of renal function along with more urinary albumin excretion via increased permeability to albumin. Importantly, this was accompanied by impaired clearance of chemerin which can cause accumulation of chemerin protein in the blood, implying the potential utilization of serum chemerin as a diagnostic bio-marker for diabetic nephropathy [19], [26], [27].

[28] reported that plasma levels of chemerin were significantly elevated in patients having macro- or microalbuminuria, in comparison with those having normoalbuminuria. Furthermore, subjects having macroalbuminuria had higher circulating chemerin concentrations than those having microalbuminuria. Thus, they implied that chemerin concentrations were independently linked with the progression of albuminurea as well as kidney function in DM. Various mechanisms underlying nephropathy were proposed: chemerin along with ChemR23 (chemerin receptor) are commonly expressed in kidney tissue [29] and elevated in renal tissue of the animals having DM; binding of ChemR23, the protein chemerin attracts the immune cells to sites of inflammation through NF-kB and MAPK signaling pathways, thus promoting their adhesion [30]; the elevation of chemerin level induces alterations in the endothelial activation and junctions associated with soluble CD146, possibly causing leakage of albumin from the blood into the urine; chemerin additionally induces the secretion of fibrotic and inflammatory factors such as TNF-α, TGF-β1, and INF-γ, facilitating renal fibrosis and sclerosis [30].

In summary, serum levels of chemerin are significantly higher in CKD patients than in normal controls. Moreover, serum chemerin concentrations were highly significantly elevated in the CKD group with diabetes compared with CKD group without diabetes. Taken together, these results would seem to suggest that serum concentrations of chemerin are likely to become a possible marker for assessment of T2D in CKD patients.

5. References

[1] K. Kalantar-Zadeh, T. H. Jafar, D. Nitsch, B. L. Neuen, & V. Perkovic. 2021. Chronic kidney disease. Lancet (London, England), p. 1-17.

[2] T. Petreski, N. Piko, R. Ekart, R. Hojs, & S. Bevc. 2021. Review on inflammation markers in chronic kidney disease. Biomedicines, 9(2): 1–16.

[3] R. A. Y. Alkhader, K. A. Wahab Ali, & A. M. Rahmah Al-Kharasani. 2020. Irisin levels related to

glycosylated hemoglobin in type 2 diabetic obese women. Iraqi J. Sci., 61(9): 2150–2155.

[4] R. A. Y. Alkhader, K. A. W. Ali, & A. M. R. Al-Kharasani. 2019. Betatrophin: It's impact on lipid profile in type two Iraqi obese diabetic women. Indian J. Public Heal. Res. Dev., 10(4): 236–241.

[5] N. H. Cho, J. E Shaw, S. Karuranga, Y. D. Huang, J. D., Ohlrogge, A. W. da Rocha Fernandes, & B Malanda. 2018. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res. Clin. Pract., 138: 271–281.

[6] P. Bramlage, S. Lanzinger, G. van Mark, E. Hess, S. Fahrner, C. H. Heyer, & R. W. Holl. 2019. Patient and disease characteristics of type-2 diabetes patients with or without chronic kidney disease: An analysis of the German DPV and DIVE databases. Cardiovasc. Diabetol., 18(1): 1–12.

[7] X. Lin, X., Yin, L., Qu, J., & Wang. 2021. Decrease of chemerin by aerobic exercise improved glycolipid metabolism of diabetes through increasing key metabolism enzymes and protein mediated by PPAR γ. p.1–24.

[8] A. A. E. W. Elsehmawy, S. E. El-Toukhy, N. M. Ahmed Seliem, R. S. Moustafa, & D. S. Mohammed. 2019. Apelin and chemerin as promising adipokines in children with type 1 diabetes mellitus. Diabetes, Metab. Syndr. Obes. Targets Ther., 12: 383–389.

[9] J. Kaur, H. S. Mattu, K. Chatha, & H. S. Randeva. 2018. Chemerin in human cardiovascular disease. Vascul. Pharmacol., 110: 1–6.

[10] M. A. Dahpy, M. K. Khairallah, N. M. A. Azoz, & G. M. Ezzat. 2020. The associations among RARRES2 rs17173608 gene polymorphism, serum chemerin, and non-traditional lipid profile in patients with metabolic syndrome. Egypt. J. Med. Hum. Genet., 21(1):1-13.

[11] J. Trujillo, I. Chirino Yolanda, N. Martínez-Tagüeña, & J. Pedraza-Chaverri. 2018. Renal damage in the metabolic syndrome (MetSx): Disorders implicated. Eur. J. Pharmacol., 818: 554–568.

[12] J. Blaszak, M. Szolkiewicz, E. Sucajtys-Szulc, M. Konarzewski, S. Lizakowski, J. Swierczynski, & B Rutkowski. 2015. High serum chemerin level in CKD patients is related to kidney function, but not to its adipose tissue overproduction. Ren. Fail., 37(6): 1033–1038.

[13] M. Tara M. Wallace, MD, Jonathan C. Levy, MD & David R. Matthews. 2004. Use and Abuse of HOMA Modeling. Diabetes Care, 27(6): 1487–1495.

[14] C. Burballa, M. Crespo, D. Redondo-Pachón, M. J. Pérez-Sáez, M. Mir, C. Arias-Cabrales, & J. Pascual. 2018. MDRD or CKD-EPI for glomerular filtration rate estimation in living kidney donors. Nefrologia, 38(2): 207–212.

[15] S. A. E. Abd Rabo, N. A. G. Mohamed, N. A. E. Tawfik, & M. M. Hamed. 2016. Serum chemerin level in chronic kidney disease. Egypt. J. Intern. Med., 28(3): 99–107.

[16] D. Pfau, A. Bachmann, U. Lössner, J. Kratzsch, M. Blüher, M. Stumvoll, & M. Fasshauer. 2010. Serum levels of the adipokine chemerin in relation to renal function. Intern. Med., 33(1):171–173.

[17] S. T. El-Khashab, S. O., Gamil, M., Ali, A. Y., El-Khashab, O., El-Khatib, M., Mohamed, K., & Hamed. 2019. Chemerin Level and the Relation to Insulin Resistance in Chronic Kidney Disease," Saudi J. Kidney Dis. Transplant., 30(6): 1381–1388.

[18] R. D. Kilpatrick, C. J. McAllister, C. P. Kovesdy, S. F. Derose, J. D. Kopple, & K. Kalantar-Zadeh. 2007. Association between serum lipids and survival in hemodialysis patients and impact of race. J. Am. Soc. Nephrol., 18(1): 293–303.

[19] W. Hu & P. Feng. 2011. Elevated serum chemerin concentrations are associated with renal dysfunction in type 2 diabetic patients. Diabetes Res. Clin. Pract., 91(2): 159–163.

[20] M. Bonomini & A. Pandolfi. 2016. Chemerin in renal dysfunction and cardiovascular disease. Vascul. Pharmacol., 77: 28–34.

[21] P. Rutkowski, T. Sledzinski, H. Zielinska, S. Lizakowski, E. Goyke, S. Szrok-Wojtkiewicz, & B. Rutkowski. 2012. Decrease of serum chemerin concentration in patients with end stage renal disease after successful kidney transplantation. Regul. Pept., 173(1–3): 55–59.

[22] S. Dellepiane, D. Medica, C. Guarena, T. Musso, A. D. Quercia, G. Leonardi, & V. Cantaluppi. 2019. Citrate anion improves chronic dialysis efficacy, reduces systemic inflammation and prevents Chemerin-mediated microvascular injury. Sci. Rep., 9(1):1–10.

[23] Ahmed, M. M. E. (2021). Car-T Cell Therapy: Current Advances and Future Research Possibilities. Journal of Scientific Research in Medical and Biological Sciences, 2(2), 86-116. https://doi.org/10.47631/jsrmbs.v2i2.234

[24] F. E. Salama, Q. A. Anass, A. A. Abdelrahman, & E. B. Saeed. 2016. Chemerin: A biomarker for cardiovascular disease in diabetic chronic kidney disease patients. Saudi J. Kidney Dis. Transpl., 27(5): 977–984.

[25] S. Zylla, R. Rettig, H. Völzke, K. Endlich, M. Nauck, & N. Friedrich. 2018. Serum chemerin levels are inversely associated with renal function in a general population. Clin. Endocrinol. (Oxf)., 88(1): 146–153.

[26] V. Kumar, M., Prajapati, R., Saxena, P., Singh, A., & Misra. 2021. Evaluation of Chemerin in Acute Coronary Syndrome and its Role in Cardiodiabetics. J. Clin. Prev. Cardiol., 10(1): 8–12.

[27] M. M. Elsebai, A. A., Saad, W. E., & Mahdy. 2014. Serum chemerin and beta 2-microglobulin in type 2 diabetes: assessment of diabetic nephropathy. 11(8): 992–1000.

[28] A. M. A.-R. Tahoun, A. Abdou El lawah, M. A. EL dahshan, & A. M. E. sayed Shalaby. 2019. Serum Chemerin Level as Biomarker for Renal Dysfunction in Type II Diabetes. Egypt. J. Hosp. Med., 77(3): 5081–5088.

[29] Dasari, P., M, N., & Thiyagarajan, C. (2021). Hashimoto's Thyroiditis Presenting as Bilateral Ovarian Masses in an Adolescent. Journal of Scientific Research in Medical and Biological Sciences, 2(2), 81-85. https://doi.org/10.47631/jsrmbs.v2i2.253

[30] P. Gu, W. Wang, Y. Yao, Y. Xu, L. Wang, P. Zang, & J. Shao. 2019. Increased Circulating Chemerin in Relation to Chronic Microvascular Complications in Patients with Type 2 Diabetes. Int. J. Endocrinol., p. 1–11.

[31] Zerin, T., Islam, A., Gulnahar, S., Farjana, N. E., Begum, M. A. ., & Sadia, H.-E. (2021). Identification and Antibiotic Susceptibility of Blood Culture Isolates from Rajshahi, Bangladesh. Journal of Scientific Research in Medical and Biological Sciences, 2(2), 1-10. https://doi.org/10.47631/jsrmbs.v2i2.264

[32] W. Hu, Q. Yu, J. Zhang, & D. Liu. 2012. Rosiglitazone ameliorates diabetic nephropathy by reducing the expression of chemerin and chemr23 in the kidney of streptozotocin-induced diabetic rats. Inflammation, 35(4): 1287–1293.

[33] V. Wittamer, J. D. Franssen, M. Vulcano, J. F. Mirjolet, E. Le Poul, I. Migeotte, & D. Communi. 2003. Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. J. Exp. Med., 198(7): 977–985.