Serum chemerin and diabetic retinopathy in type 2 diabetic patients

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Received 8 May 2017
Accepted 18 July 2017

The Egyptian Journal of Internal Medicine
2017, 29:117–121

Background
Diabetic retinopathy (DR) is one of the microvascular complications of type 2 diabetes mellitus (T2DM). There is a need to find a reliable screening biomarker to help in the early diagnosis of this complication.
The aim of the work was to study the relation between serum chemerin and DR in T2DM patients.
Patients and methods
This study was conducted on 80 T2DM patients in addition to 20 healthy individuals who served as a control group. The participants were grouped into four groups: the T2DM group, the nonproliferative diabetic retinopathy (NPDR) group, the proliferative diabetic retinopathy (PDR) group, and the control group. Laboratory investigations were performed to all participants, which included glycosylated hemoglobin (HbA1c), serum creatinine, lipid profile, urine albumin/creatinine ratio, C-reactive protein (CRP), and serum chemerin. Fundus examination was carried out to all participants by an expert ophthalmologist.
Results
Serum chemerin was significantly higher in the PDR group compared with the other groups, in the NPDR group compared with the T2DM group and controls, and in the T2DM group compared with controls. There was a positive significant correlation between serum chemerin and BMI, HbA1c, diabetes mellitus duration, serum total cholesterol, triglycerides, low density lipoprotein, and CRP and a negative significant correlation between serum chemerin and high density lipoprotein in diabetic patients.
Conclusion
From this study, we can conclude that serum chemerin is significantly higher in patients with DR compared with diabetic patients without retinopathy and in PDR patients compared with NPDR patients. There is a positive correlation between serum chemerin and CRP, BMI, and lipid profile.

Keywords:
chemerin, diabetes mellitus, diabetic retinopathy

Egypt J Intern Med 29:117–121

1110-7782

Introduction

Adipose tissue is an active endocrine organ that produces a different number of adipokines, which can lead to chronic inflammation, oxidative stress, insulin resistance, and type 2 diabetes mellitus (T2DM) [1,2].

Effective treatment of diabetic retinopathy (DR) may delay the onset and progression of this disease, provided early diagnosis is made. An easily accessible, reliable screening biomarker of DR would be of an important benefit in detecting the patients in need of further assessment and treatment. The pathobiology of DR is complex and multifactorial, giving rise to a wide array of potential biomarkers such as advanced glycation end products, inflammatory markers, and vascular endothelial growth factor (VEGF) [3,4].

Chemerin is an adipokine, which may play a role in insulin resistance, glucose metabolism, and lipid metabolism [5]. Chemerin is reported to have a role in neovascularization, which induces endothelial cell proliferation [6,7,8]. We presumed that chemerin may play a role in the development of DR.

The aim of the work was to study the relation between serum chemerin and DR in T2DM patients.

Patients and methods

This study was conducted on 80 T2DM patients without nephropathy (urine albumin <30 mg/day, serum creatinine <1.5 mg/dl) selected from the inpatient department and outpatient clinics of the

Internal Medicine Department, in addition to 20 healthy individuals serving as a control group. The selected patients gave consent for participation in the study before they were exposed to examination and investigations. The study was conducted from January 2016 to September 2016. The protocol of this study was approved by the Ethical Committee of Faculty of Medicine.

The selected participants were grouped into four groups: the T2DM group included 30 T2DM patients without retinopathy; the nonproliferative diabetic retinopathy (NPDR) group included 30 T2DM patients with NPDR; the proliferative diabetic retinopathy (PDR) group included 20 T2DM patients with PDR; and the control group included 20 healthy individuals.

Exclusion criteria

Type 1 DM, diabetic nephropathy, diabetic neuropathy, diabetic angiopathy, history of malignancies, chronic inflammatory diseases (e.g. rheumatoid arthritis), collagen diseases, and chronic infections.

Members of the study group were subjected to thorough history with special emphasis on age, sex, duration of diabetes mellitus (DM), and treatment modalities. Complete physical examination performed to all members. Investigations included glycosylated hemoglobin (HbA1c), lipid profile, serum creatinine, urine albumin/creatinine ratio, and C-reactive protein (CRP).

Serum chemerin level was measured using an enzyme-linked immunosorbent assay (ELISA kit; Quantikin R and D System, Minneapolis, Minnesota, USA), according to the manufacturer's protocol.

Patients underwent detailed eye examinations using the Early Treatment of Diabetic Retinopathy Study protocol of seven-standard-field stereoscopic fundus photography. Retinopathy status was determined through evaluation of fundus photographs and graded according to clinical Early Treatment of Diabetic Retinopathy Study criteria (no retinopathy, NPDR, and PDR). Patients with any disk neovascularization, neovascularization elsewhere, vitreous hemorrhage, fibrovascular proliferation, or tractional retinal detachment were considered to have PDR [9].

Statistical methodology

Data were analyzed using statistical package for the social science (SPSS) software computer program, version 15 (IBM Corp., IBM SPSS Statistics for Windows, Version 15.0, Armonk, NY: IBM Corp. Chicago, USA). Quantitative data were presented as mean and SD. Qualitative data were presented as frequency and percentage. To compare between groups we used the χ^2-test, analysis of variance test, and least significant difference. Correlation between two parameters was made using correlation coefficient. Significance level value was P was less than or equal to 0.05.

Results

There was no significant difference between the studied four groups as regards age and sex. BMI was significantly higher in the diabetic groups compared with the control group. The duration of DM was significantly higher in the PDR and NPDR groups compared with the T2DM group (Table 1).

HbA1c and CRP were significantly higher in the PDR and NPDR groups compared with the T2DM group and controls and in the T2DM group compared with controls. There were no significant differences between the studied groups as regards serum creatinine, urine albumin/creatinine ratio, and lipid profile (Table 1).

Serum chemerin was significantly higher in the PDR group compared with the other groups, in the NPDR group compared with the T2DM group and controls, and in the T2DM group compared with controls (Table 1).

There was a positive significant correlation between serum chemerin and BMI, HbA1c, duration of DM, serum total cholesterol, triglycerides, low density lipoprotein, and CRP and a negative significant correlation between serum chemerin and high density lipoprotein in the studied diabetic patients. There was no correlation between serum chemerin, age, serum creatinine, and urine albumin/creatinine ratio (Table 2).

Discussion

The pathogenesis of DR is multifactorial. Hyperlipidemia, inflammation, insulin resistance, and angiogenesis are the main factors. Therefore, to study the relation between chemerin and DR, we study its relation to BMI, hyperlipidemia, CRP (inflammatory marker), and PDR (angiogenesis indicator).

In the current study, serum chemerin was significantly higher in the diabetic groups compared with controls,

Table 1 Comparison between the studied groups as regards different parameters

Mean±SD	T2DM group (*n*=30)	NPDR group (*n*=30)	PDR group (*n*=20)	Control group (*n*=20)	ANOVA test	*P* value	LSD
Age (years)	55.5±7.1	53.9±6.1	54.5±8.1	55.0±7.8	1.616	>0.05	
BMI (kg/m^2)	27.6±3.5	27.3±3.4	27.6±2.8	26.9±2.8	1.018	>0.05	
Duration of DM (years)	7.3±2.3	9.1±2.9	9.3±2.6		6.159	<0.05	PDR, NPDR vs. T2DM
HbA1c (%)	6.9±0.9	7.8±0.9	8.1±1.0	4.8±0.8	25.3	<0.05	PDR, NPDR vs. T2DM and controls T2DM vs. controls
Serum chemerin (ng/ml)	3102.8±936.6	3519.1±1099.7	4301.8±1126.1	2207.7±667.6	48.2	<0.05	PDR vs. NPDR, T2DM, controls NPDR vs. T2DM, controls T2DM vs. controls
Total cholesterol (mg/dl)	181.3±42.7	192.0±29.1	189.7±36.4	176.5±31.2	0.824	>0.05	
Serum TG (mg/dl)	152.4±32.7	138.9±32.6	151.8±38.3	138.2±33.4	2.141	>0.05	
Serum LDL (mg/dl)	110.2±34.2	124.7±17.2	118.7±30.1	112.8±34.5	1.611	>0.05	
Serum HDL (mg/dl)	42.33±10.1	43.1±9.8	39.9±11.2	42.3±8.6	0.985	>0.05	
Serum CRP (mg/l)	6.1±1.5	9.3±1.3	9.4±1.6	4.8±1.4	17.2	<0.05	PDR and NPDR, vs. T2DM, controls T2DM vs. controls
Urine albumin/ creatinine ratio (mcg/mg creatinine)	23.2±1.3	23.6±1.6	22.1±2.1	19.8±2.3	1.141	>0.05	
Sex [*n* (%)]						>0.05	
Male	13 (43.3)	12 (40)	9 (45)	10 (50)	χ^2=0.169		
Female	17 (56.7)	18 (60)	11 (55)	10 (50)			

ANOVA, analysis of variance; CRP, C-reactive protein; DM, diabetes mellitus; HbA1c, glycosylated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; LSD, least significant difference; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Table 2 Correlation between serum chemerin and other parameters in the diabetic patients

	Serum chemerin	
	r	*P*
Age	0.213	>0.05
BMI	0.815	<0.05
Duration of DM	0.523	<0.05
HbA1c	0.771	<0.05
CRP	0.877	<0.05
Serum creatinine	0.155	>0.05
Total cholesterol	0.702	<0.05
Triglycerides	0.681	<0.05
LDL	0.659	<0.05
HDL	–0.710	<0.05
Urine albumin/creatinine ratio	0.129	>0.05

CRP, C-reactive protein; DM, diabetes mellitus; HbA1c, glycosylated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride.

and there was a positive significant correlation between serum chemerin and HbA1c and duration of DM.

This is similar to the finding of Bozaoglu *et al.* [10], who reported that serum chemerin level of patients with T2DM was obviously higher than that of individuals with normal glucose tolerance. T2DM seems to be closely related to the endocrine activity of adipose tissue. The release of adipokines (e.g. chemerin) by adipocytes can lead to a chronic inflammatory state that could play a central role in the development of insulin resistance and T2DM [1].

In the current study, there was a positive significant correlation between serum chemerin and BMI, serum total cholersterol, triglycerides, and low density lipoprotein (and a negative significant correlation between serum chemerin and high density lipoprotein in the studied diabetic patients. This is similar to that reported by Takahashi *et al.* [11] and Hu *et al.* [12].

The positive correlation of serum chemerin with BMI indicates the relation between serum chemerin and obesity. Chemerin can regulate fat metabolism and accelerate the decomposition of fat. It can promote the release of glycerol and free fatty acids from fat cells. In the liver, very low density lipoprotein and triglycerides will be formed from both glycerol and free fatty acids, which will be stored in adipose tissue [13]. This process will promote obesity and exacerbate hyperlipidemia. Previous study found that serum lipid was related with DR [14] and reduction in serum hyperlipidemia will improve the degree of DR and promote the regression of retinal hard exudates

in DR [15]. Therefore, chemerin may play an important role in the development of DR through hyperlipidemia.

In the current study, there was a positive significant correlation between serum chemerin and CRP. Many studies [16–18] reported that chemerin level was significantly higher in patients with elevated CRP in T2DM.

Some researchers have pointed out [19] that inflammatory factors may play an essential role in the pathogenesis of microangiopathy. CRP is considered as one marker of inflammation and has been widely used in clinic for monitoring inflammation. The mechanism for CRP involvement in the diabetic microangiopathy is as follows: [20] insulin resistance induction, complement stimulation, which cause damage to endothelial cells, and suppression of expressions and release of nitric oxide synthase.

Some studies have also shown that chemerin has a relation with inflammatory reaction. Chemerin can share in the initiation and progression of inflammation through the stimulation of macrophage adhesion to extracellular matrix proteins and through stimulation of chemotaxis [21]. Through binding of chemerin receptor 23 (ChemR23), chemerin can activate nuclear factor-kB and mitogen-activated protein kinase pathways in many inflammatory cells such as monocytes, macrophages, and immature dendritic cells [22], which have an essential role in the inflammatory process [17,23]. Chemerin also plays an important role in vascular endothelial cells by regulating the level of expression of ChemR23 in these cells [24]. These indicate that chemerin and ChemR23 system may play a role in the inflammatory state of vascular endothelial cells.

Adamis and others [25–28] support the hypothesis that DR is a low grade, subclinical inflammatory disease, and hence chemerin may take part in DR by promoting inflammation and that there might be synergistic effects between chemerin and CRP.

In the current study, serum chemerin is significantly higher in PDR compared with NPDR. This may point to the role of serum chemerin in pathological retinal neovascularization, which is one of the important characteristics of PDR.

Du *et al.* [29] also showed a significant increase in serum chemerin in patients with PDR and a positive correlation between chemerin and VEGF. Other studies reveal that chemerin is involved in the formation of neovascularization, and accumulating evidences showed that chemerin stimulated the formation of new blood vessels and functional angiogenesis to a similar extent as VEGF in human endothelial cells [30,31].

Kaur *et al.* [6] revealed that chemerin-induced neovascularization in human endothelial cells through stimulation of capillary tube formation, activation of endothelial gelatinase, and activation of phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinases pathways, which is a key mechanism for angiogenesis. Chemerin has been shown to enhance the production of matrix metalloproteinases, which play an important role in the degradation of vascular basement membrane, which is an important step in angiogenesis [6,32,33]. In addition, serum chemerin is associated with epithelial growth factor-like repeats and the discoidin I-like domains 3 (*EDIL3*) gene, which play an important role in angiogenesis. *EDIL3* is an integrin ligand that promotes endothelial cell migration [30,34]. As such, the high level of serum chemerin in the PDR group possibly promotes angiogenesis in the progression of PDR.

From this study, we can conclude that serum chemerin is significantly higher in patients with DR compared with diabetic patients without retinopathy and in PDR compared with NPDR. There is a positive correlation between serum chemerin and CRP, BMI, and lipid profile. Therefore, chemerin may play an important role in the development of DR and it may play this role by promoting inflammation, hyperlipidemia, and neovascularization. Further studies are needed to study whether the inhibition of chemerin could offer new therapeutic opportunities and whether we can use serum chemerin as an early diagnostic marker of PDR.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Antuna-Puente B, Feve B, Fellahi S, Bastard JP. Adipokines: the missing link between insulin resistance and obesity. Diabetes Metab 2008; 34:2–11.

2 Fernández-Sánchez A, Madrigal-Santillán E, Bautista M. Inflammation, oxidative stress, and obesity. Int J Mol Sci 2011; 12:3117–3132.

3 Pusparajah P, Lee L, Abdul Kadir K. Molecular markers of diabetic retinopathy: potential screening tool of the future? Front Physiol 2016; 7:200.

4 Boehm B, Lang G, Volpert O, Jehle PM, Kurkhaus A, Rosinger S, *et al.* Low content of the natural ocular anti-angiogenic agent pigment epithelium-derived factor [PEDF] in aqueous humor predicts progression of diabetic retinopathy. Diabetologia 2003; 46:394–400.

5 Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, *et al.* Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem 2007; 282:28175–28188.

6 Kaur J, Adya R, Tan BK, Chen J, Randeva HS. Identification of chemerin receptor [ChemR23] in human endothelial cells: chemerin-induced endothelial angiogenesis. Biochem Biophys Res Commun 2010; 391:1762–1768.

7 El-Mesallamy HO, El-Derany MO, Hamdy NM. Serum omentin-1 and chemerin levels are interrelated in patients with type 2 diabetes mellitus with or without ischaemic heart disease. Diabet Med 2011; 28:1194–1200.

8 Lin X, Tang X, Jiang Q, Liu Q, Lin Z, Lin J, *et al.* Elevated serum chemerin levels are associated with the presence of coronary artery disease in patients with type 2 diabetes. Clin Lab 2012; 58:539–544.

9 Told R, Baratsits M, Garhöfer G, Schmetterer L. Early treatment diabetic retinopathy study [ETDRS] visual acuity. Ophthalmologe 2013; 110:960–965.

10 Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, *et al.* Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population. J Clin Endocrinol Metab 2009; 94:3085–3088.

11 Takahashi M, Inomata S, Okimura Y, Iguchi G, Fukuoka H, Miyake K, *et al.* Decreased serum chemerin levels in male Japanese patients with type 2 diabetes: sex dimorphism. Endocr J 2013; 60:37–44.

12 Hu W, Feng P. Elevated serum chemerin concentrations are associated with renal dysfunction in type 2 diabetic patients. Diabet Res Clin Pract 2011; 91:159–163.

13 Roh SG, Song SH, Choi KC, Katoh K, Wittamer V, Parmentier M *et al.* Chemerin – a new adipokine that modulates adipogenesis via its own receptor. Biochem Biophys Res Commun 2007; 362:1013–1018.

14 Van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, *et al.* Blood pressure, lipids, and obesity are associated with retinopathy: the hoorn study. Diabetes Care 2002; 25:1320–1325.

15 Cusick M, Chew EY, Chan CC, Kruth HS, Murphy RP, Ferris FR. Histopathology and regression of retinal hard exudates in diabetic retinopathy after reduction of elevated serum lipid levels. Ophthalmology 2003; 110:2126–2133.

16 Yang M, Yang G, Dong J, Liu Y, Zong H, Liu H, *et al.* Elevated plasma levels of chemerin in newly diagnosed type 2 diabetes mellitus with hypertension. J Investig Med 2010; 58:883–886.

17 Lehrke M, Becker A, Greif M, Stark R, Laubender RP, von Ziegler F, *et al.* Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. Eur J Endocrinol 2009; 161:339–344.

18 Weigert J, Neumeier M, Wanninger J, Filarsky M, Bauer S, Wiest R, *et al.* Systemic chemerin is related to inflammation rather than obesity in type 2 diabetes. Clin Endocrinol (Oxf) 2010; 72:342–348.

19 Ying Z, Qian W, Kaiping H. Correlation between type-2 diabetic patient chemerin level changes and lower extremity venous disease. J Shandong Uni Med 2011; 49:9–12.

20 Chunlian C, Yufang Y, Zhicheng W. Study of the correlation between serum chemerin and C-reactive protein levels of type-2 diabetic patients and insulin-resistance and macroangiopathy J Chinese General Practice. 2013; 16:2438–2440.

21 Hart R, Greaves DR. Chemerin contributes to inflammation by promoting macrophage adhesion to VCAM-1 and fibronectin through clustering of VLA-4 and VLA-5. J Immunol. 2010; 185:3728–3739.

22 Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, *et al.* Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 2007; 148:4687–4694.

23 Yamamoto T, Qureshi AR, Anderstam B, Heimburger O, Barany P, Lindholm B, *et al.* Clinical importance of an elevated circulating chemerin level in incident dialysis patients. Nephrol Dial Transplant 2010; 25:4017–4023.

24 Yamawaki H. Vascular effects of novel adipocytokines: focus on vascular contractility and inflammatory responses. Biol Pharm Bull 2011; 34:307–310.

25 Adamis AP. Is diabetic retinopathy an inflammatory disease? Br J Ophthalmol 2002; 86:363–365.

26 Patel JI, Tombran-Tink J, Hykin PG, Gregor ZJ, Cree IA. Vitreous and aqueous concentrations of proangiogenic, antiangiogenic factors and other cytokines in diabetic retinopathy patients with macular edema: implications for structural differences in macular profiles. Exp Eye Res 2006; 82:798–806.

27 Abu EA, Struyf S, Kangave D, Geboes K, van Damme J. Chemokines in proliferative diabetic retinopathy and proliferative vitreoretinopathy. Eur Cytokine Netw 2006; 17:155–165.

28 Hernandez C, Segura RM, Fonollosa A, Carrasco E, Francisco G, Simo R. Interleukin-8, monocyte chemo-attractant protein-1 and IL-10 in the vitreous fluid of patients with proliferative diabetic retinopathy. Diabet Med 2005; 22:719–722.

29 Du J, Li R, Xu L, Ma R, Liu J, Cheng J, Zhang Z, Sun H. Serum chemerin levels in diabetic retinopathy of type 2 diabetic patients. Curr Eye Res 2016; 41:114–120.

30 Bozaoglu K, Curran JE, Stocker CJ, Zaibi MS, Segal D, Konstantopoulos N, *et al.* Chemerin, a novel adipokine in the regulation of angiogenesis. J Clin Endocrinol Metab 2010; 95:2476–2485.

31 Kasai A, Ishimaru Y, Kinjo T, Satooka T, Matsumoto N, Yoshioka Y, *et al.* Apelin is a crucial factor for hypoxiainduced retinal angiogenesis. Arterioscler Thromb Vasc Biol 2010; 30:2182–2187.

32 Rosen LB, Ginty DD, Weber MJ, Greenberg ME. Membrane depolarization and calcium influx stimulate MEK and MAP kinase via activation of Ras. Neuron 1994; 12:1207–1221.

33 Crews CM, Alessandrini A, Erikson RL. The primary structure of MEK, a protein kinase that phosphorylates the ERK gene product. Science 1992; 258:478–480.

34 Aoka Y, Johnson FL, Penta K, Hirata Ki K, Hidai C, Schatzman R, *et al.* The embryonic angiogenic factor Del1 accelerates tumor growth by enhancing vascular formation. Microvasc Res 2002; 64:148–161.