Chemerin is associated with diabetic retinopathy in type 2 diabetes

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Background
Chemerin is a novel adipokine, which is suggested to play a role in the development of type 2 diabetes mellitus (T2DM) and its chronic complications. Diabetic retinopathy (DR) is a common complication of diabetes, caused by diabetic microvascular lesions.
Objective
To investigate the relationship between serum chemerin level and DR in T2DM.
Study design
Eighty participants were enrolled in the study and were divided into three groups: group I included 40 patients with T2DM complicated with DR, and this group was further subdivided to proliferative diabetic retinopathy (PDR) and nonproliferative diabetic retinopathy (NPDR); group II included 20 patients with T2DM not complicated with DR; and group III included 20 apparently healthy patients representing control group. Anthropometric and laboratory measurements including serum chemerin levels were assessed, and values were analyzed to compare the differences among the groups.
Results
Chemerin level was significantly higher in group I than that in both group II and group III (158.4±25.7 vs. 127.4±20.1 and 116.6±20.3 ng/dl, respectively; $P<0.01$). Moreover, chemerin level was significantly higher in the PDR group than that in NPDR group (167.7±28.4 vs. 152.2±22.2 ng/dl; $P<0.05$). Otherwise, no significant difference of chemerin level between group II and group III was found ($P=0.135$).
Conclusion
Serum chemerin levels were elevated in patients with T2DM with DR than those without DR and were elevated in patients with PDR than NPDR, suggesting that chemerin may be involved in the development of PDR.

Keywords:
chemerin, nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, type 2 diabetes mellitus

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Introduction

Diabetic retinopathy (DR) is one of the leading causes of blindness in working-age population [1,2]. It is a serious microvascular complication of DM. Pathological retinal neovascularization is one of the characteristics of proliferative diabetic retinopathy (PDR), which appears at an advanced stage of DR. It results in subsequent intravitreal hemorrhage and tractional retinal detachment, and finally, blindness occurs [3]. In recent years, mounting evidences have emerged about the role of cytokines, inflammatory cells, growth factors, and angiogenic factors in the pathogenesis of DR [4–7].

Chemerin is a cytokine involved in both metabolic and immune dysregulation. Chemerin, also known as retinoic acid receptor responder protein 2 [2] or tazarotene-induced gene 2, is a protein that in humans is encoded by the retinoic acid receptor responder protein 2 gene [8]. Chemerin is expressed at the highest levels in liver and white adipose tissue [9]. It is initially translated as preprochemerin, a 163-amino acid protein that undergoes N-terminal cleavage and C-terminal processing by extracellular proteases cascade to produce an active 16-kDa form [10–13].

Chemerin participates in glucose and lipid homeostasis, and angiogenesis, as well as in the initiation and resolution of inflammation [11,14,15]. Several studies demonstrated that chemerin is potentially involved in diabetes mellitus [9,16].

In addition, chemerin was suggested to be correlated with diabetic peripheral vascular disease [17], ischemic heart disease, and coronary artery disease in patients with type 2 diabetes mellitus (T2DM) [18,19]. Chemerin was also reported to be correlated with inflammation in obese patients with T2DM [20].

Moreover, serum chemerin levels significantly increased in patients with diabetic nephropathy compared with those in the controls. The levels of chemerin and its receptor, chemerin receptor 23, were significantly elevated in the kidney tissues of diabetic rats [21,22]. These findings suggest that chemerin is involved in the pathology of diabetic nephropathy. Chemerin may also be involved in the development of DR, considering that diabetic nephropathy and DR are both microvascular complications of diabetes mellitus.

Taking together, we presumed chemerin would play a role in the development of DR. Therefore, we conducted this study to investigate the association between serum chemerin and DR in T2DM.

Patients and methods

Study population

This case–control study was conducted at Endocrinology Outpatient Clinic, Faculty of Medicine, Ain Shams University Hospitals. Eighty participants were enrolled in the study. Patients were divided into the following three groups: group I included 40 patients with T2DM complicated with DR, and this group was further subdivided to PDR and nonproliferative diabetic retinopathy (NPDR); group II included 20 patients with T2DM not complicated with DR; and group III included 20 apparently healthy patients matched for age and sex, representing control group.

Inclusion criteria

All patients diagnosed as T2DM according to the 2006 WHO standard were included. Ocular examination, including slit-lamp biomicroscopy and ophthalmoscopy, was performed for all patients. According to the 2003 international clinical DR severity scales, patients were divided into T2DM (T2DM with no DR), NPDR and PDR groups. The specific criteria were listed as follows:

T2DM group: no abnormalities.
NPDR group: conforming to one of the following conditions and no signs of proliferative retinopathy, such as microaneurysms, intraretinal hemorrhages, definite venous beading, and prominent intraretinal microvascular abnormalities.
PDR group: one or more of the following: neovascularization and vitreous/preretinal hemorrhage.

Patients with the following ocular diseases were excluded: glaucoma, uveitis, pigmentary degeneration, wet age-related macular degeneration, retinal vein occlusion, and other retina or choroidal neovascular diseases, which may influence the results of the test.

Furthermore, 20 healthy patients who entered the healthy evaluation program were assigned as the control group for this study. They had never been diagnosed with DM, impaired glucose tolerance, or other systemic diseases.

Exclusion criteria

Patients with the following disorders were excluded from this study: type 1 diabetes, T2DM complicated with infection, diabetic ketosis, diabetic neuropathy, diabetic angiopathy, and other systemic diseases that may affect the test results, such as chronic liver disease, systemic lupus erythematosus, rheumatic arthritis, hypothyroidism or hyperthyroidism, pregnancy, and presence of any psychological or neurological disorder (confirmed by history and clinical examination).

Study approval

This study was approved by the ethics committee of hospital, and all of the procedures were performed in accordance with ethical approval institutional guidelines. Each patient gave informed consent to participate in this study.

Study protocol

Detailed information of all patients was recorded, including age, sex, body height, body mass, duration of diabetes, diseases history (ocular diseases and system diseases), and use of medications. BMI was calculated as body weight in kilograms divided by the square of height in meters. Systolic blood pressure and diastolic blood pressure were measured with a mercury sphygmomanometer with the patient in the sitting position.

All enrolled individuals were on an empty stomach for over 12 h, and ~6 ml of blood was collected in sterile dry tubes. Of the collected blood sample, 3-ml was sent immediately to the hospital laboratory was used for testing glycosylated hemoglobin (HbA1c), total cholesterol, triglycerides, and high-density lipoproteins (HDL)-cholesterol. The level of low-density lipoprotein (LDL)-cholesterol was estimated using the formula: total cholesterol-HDL cholesterol-(triglyceride/5).

Another 3 ml blood was immediately centrifuged for 10 min at 4°C at 3500 rpm for serum collection. Then serum was collected and stored at −80°C until further analysis of chemerin level in a biochemistry laboratory.

All reagents and standards were prepared as instructed in the kit. Serum levels of chemerin were determined with commercial human enzyme-linked immunosorbent assay (ELISA) kits used according to the manufacturers' instructions (Human Chemerin ELISA Kit; USCN Life Science & Technology Company, Missouri, Texas, USA).

Standard well, test sample well, and blank well were installed as instructed. Then we added 100 ml of horseradish peroxidase-conjugate reagent to each well covered with an adhesive strip and incubated them for 60 min at 37°C. Then we added chromogen solution A and B to each well and incubated them for 15 min at 37°C. Stop solution was then added to each well to induce a colored reaction product. This product was read using a microplate reader. The intensity of the produced colored product was directly proportional to the concentration of chemerin present in the samples.

Statistical analysis

The data are presented as mean±SD. The values were analyzed by one-way analysis of variance to compare the differences among the groups. Student–Newman–Keuls tests were used to detect the differences among groups. Categorical variables were assessed using χ^2-test. Simple linear regression analysis was performed to evaluate correlation between the parameters.

Then multiple stepwise linear regression analysis was used to determine the contribution of various factors to serum chemerin. All statistical analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, Illinois, USA). The significance of the test was determined according to the *P* value to be nonsignificant if *P* value more than 0.05, significant if *P* value less than 0.05, and highly significant if *P* value less than 0.01.

Results

This study enrolled 80 patients, subdivided into three groups: group I included 40 diabetic patients complicated with DR, of them 16 had PDR and 24 had NPDR; group II included 20 diabetic patients without retinopathy; and group III included 20 apparently healthy patients representing control group. The clinical and biochemical characteristics of the study groups are listed in Table 1.

No significant differences were observed regarding age and sex of the study groups. Regarding diabetes duration, there was a significant difference between group I (T2DM with DR) and group II (T2DM without DR) (3.8±2.1 vs. 1.1±0.012 years, respectively; $P<0.01$). Regarding HbA1c, there was a highly significant difference

Table 1 Clinical and biochemical characteristics of the study groups

Parameters	Group I (T2DM with DR) (*n*=40)	Group II (T2DM without DR) (*n*=20)	Group III (control) (*n*=20)	ANOVA	
				f	*P* value
Age (years)	50±5.1	47.2±4.3	44.9±6.5	55.219	0.141
Sex [*n* (%)]					
Male	21 (52.5)	11 (55)	10 (50)	0.100	0.951
Female	19 (47.5)	9 (45)	10 (50)		
Duration of DM (years)	3.8±2.1*,§	1.1±0.012*	–	61.592	0.000
BMI (kg/m^2)	31.8±4.3*	30.5±2.6	29.7±2.8	2.568	0.083
SBP (mmHg)	126.8±14.5	122.3±10.6	122±10.2	1.344	0.267
DBP (mmHg)	82±8.8*	78.3±7.99	75.8±5.9	4.449	0.015
HbA1c (%)	9±1.6*	8.6±0.6*	4.6±0.5	93.707	0.000
Total cholesterol (mg/dl)	208±32.1766*,§	181.7±18.8	180.9±17.9	10.342	0.000
Triglycerides (mg/dl)	175.8±26.4*	168.7±19.7	162.6±16.8	2.343	0.103
HDL-C (mg/dl)	53.5±10.3*,§	64.2±7.6	62.8±10.98	10.189	0.000
LDL-C (mg/dl)	119.3±34.8*,§	84.9±21.3	84.3±20.3	14.545	0.000
Chemerin (ng/dl)	158.4±25.7*,§	127.4±20.1	116.6±20.3	25.741	0.000

The data are presented as mean±SD; ANOVA, analysis of variance; DBP, diastolic blood pressure; DM, diabetes mellitus; DR, diabetic retinopathy; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; $P>0.05$ is not significant; $P<0.05$ is significant; $P<0.01$ is highly significant; *Significant versus control group; §Significant versus T2DM without DR group.

among the studied groups ($P<0.01$), whereas there was no significant difference between group I and group II. Moreover, there was a highly significant difference regarding total cholesterol, HDL-cholesterol, and LDL-cholesterol ($P<0.01$).

Regarding serum chemerin level, there was a highly significant difference among the studied groups ($P<0.01$). It was significantly higher in group I than that in both group II and group III (158.4±25.7 vs. 127.4±20.1 and 116.6±20.3 ng/dl, respectively; $P<0.01$). In spite of being higher in group II than that in group III (127.4±20.1 vs. 116.6±20.3 ng/dl, respectively), the difference of chemerin level was statistically insignificant ($P=0.135$).

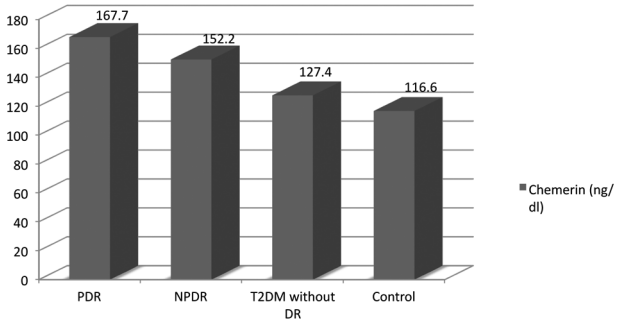
On studying the subgroups of group I (PDR and NPDR groups) in comparison with group II and group III (Table 2), chemerin level was significantly higher in PDR group than that in both group II (T2DM without retinopathy) and group III (control) (167.7±28.4 vs. 127.4±20.1 and 116.6 ±20.3 ng/dl, respectively; $P<0.01$). Likely, chemerin level was higher in NPDR group than that in both group II and group III (152.2±22.2 vs. 127.4±20.1 and 116.6±20.3 ng/dl, respectively; $P<0.01$). Moreover, chemerin level in the PDR group was significantly higher than that in NPDR group (167.7±28.4 vs. 152.2±22.2 ng/dl; $P<0.05$) (Fig. 1).

The correlation between chemerin level and different variables (Table 3) revealed a highly significant positive correlation between chemerin level and duration of T2DM ($r=0.678$, $P<0.001$), BMI ($r=0.736$, $P<0.001$), HbA1c ($r=0.443$, $P<0.001$), total cholesterol ($r=0.525$, $P<0.001$), triglycerides ($r=0.316$, $P<0.001$), and LDL-cholesterol ($r=0.538$, $P<0.001$), as well as there was a nonsignificant positive correlation between chemerin level and age ($r=0.476$, $P=0.053$), systolic blood pressure ($r=0.109$, $P=0.336$), and diastolic blood pressure ($r=0.188$, $P=0.094$), whereas there was a highly significant negative correlation between chemerin level and HDL-cholesterol ($r=-0.373$, $P<0.001$).

Discussion

Adipose tissue produces several hormones and cytokines termed 'adipokines', which have widespread metabolic effects in patients with T2DM. Chemerin, one of the recently discovered adipokines, has been shown to

Figure 1



Comparison among study groups regarding serum chemerin level. DM, diabetes mellitus; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T2DM, type 2 diabetes mellitus.

Table 2 Composition between the study groups

Parameters	T2DM with DR		T2DM without DR (n=20)	Control group (n=20)	ANOVA	
	PDR (n=16)	NPDR (n=24)			f	P value
Age (years)	51.6±5.9	48.9±4.4	47.2±4.3	44.9±6.5	38.298	0.187
Sex [n (%)]						
Male	9 (56.3)	12 (50)	11 (55)	10 (50)	0.251	0.969
Female	7 (43.7)	12 (50)	9 (45)	10 (50)		
Duration of DM (years)	6.53±2.23[a,b,c]	3.18±1.69[a,b]	1.1±0.012[a]	–		0.000
BMI (kg/m^2)	32.9±4.1[a]	31.1±4.5	30.5±2.6	29.7±2.8	2.508	0.065
SBP (mmHg)	130.3±16.7	124.4±12.6	122.3±10.6	122±10.2	1.628	0.190
DBP (mmHg)	82.8±8.9[a]	81.5±8.8[a]	78.3±7.99	75.8±5.9	3.030	0.034
HbA1c (%)	9.7±1.7[a,b,c]	8.6±1.4[a]	8.6±0.6[a]	4.6±0.5	71.969	0.000
Total cholesterol (mg/dl)	207.9±33.4[a,b]	208±32[a,b]	181.7±18.8	180.9±17.9	6.805	0.000
Triglycerides (mg/dl)	172.7±21.8	177.8±29.2[a]	168.7±19.7	162.6±16.8	1.715	0.171
HDL-C (mg/dl)	52.9±9.45[a,b]	53.9±11.1[a,b]	64.2±7.6	62.8±10.98	6.744	0.000
LDL-C (mg/dl)	120.4±35.2[a,b]	118.5±35.3[a,b]	84.9±21.3	84.3±20.3	9.589	0.000
Chemerin (ng/dl)	167.7±28.4[a,b,c]	152.2±22.2[a,b]	127.4±20.1	116.6±20.3	19.440	0.000

The data are presented as mean±SD; ANOVA, analysis of variance; DBP, diastolic blood pressure; DM, diabetes mellitus; DR, diabetic retinopathy; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; $P>0.05$ is not significant; $P<0.05$ is significant; $P<0.01$ is highly significant; [a]Significant versus control group; [b]Significant versus T2DM without DR group; [c]Significant versus NPDR group.

Table 3 Correlation between chemerin level and different variables

Parameters	Serum chemerin (ng/dl)	
	r	*P*-value
Age (years)	0.476	0.053
Duration of DM (years)	0.678	0.000
BMI (kg/m^2)	0.736	0.000
SBP (mmHg)	0.109	0.336
DBP (mmHg)	0.188	0.094
HbA1c (%)	0.443	0.000
Total cholesterol (mg/dl)	0.525	0.000
Triglycerides (mg/dl)	0.316	0.004
HDL-C (mg/dl)	–0.373	0.001
LDL-C (mg/dl)	0.538	0.000

DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; $P>0.05$ is not significant; $P<0.05$ is significant; $P<0.01$ is highly significant.

regulate adipocyte differentiation and modulate the expression of adipocyte genes involved in glucose and lipid homeostasis [11].

Our research showed that the serum chemerin levels of patients with NPDR and PDR were significantly higher than the level of serum chemerin in the patients without DR as well as the control group. Moreover, chemerin level in the PDR group was significantly higher than that in NPDR group. This was consistent with the results of Du *et al.* [23] who found a highly significant difference between NPDR and PDR groups regarding chemerin level, which was higher in PDR group.

More recently, Li *et al.* [24] determined the presence of chemerin in the human vitreous body. Patients with PDR presented significantly higher vitreous chemerin levels than those in the control group. The ratio of vitreous chemerin to plasma chemerin concentration in patients with PDR was significantly higher than that in the controls. These findings indicate that chemerin is involved in the pathology of DR.

Moreover, our study revealed no significant difference of the chemerin level in T2DM without retinopathy group and control group. This was consistent with some other studies [9,23,25]. On the contrary, Bozaoglu *et al.* [16] found that the serum chemerin level of patients with T2DM was obviously higher than that of individuals with normal glucose tolerance, especially, the serum chemerin level of those overweight and obese individuals was significantly higher than the normal ones. This inconsistency may be caused by the environmental and ethnic differences between the populations or differences in sample collection and storage.

Our results showed a positive correlation between chemerin and HbA1c, as revealed by previous studies which proved that plasma chemerin level was positively correlated to HbA1c and fasting blood glucose [9,12,26,27].

Moreover, we found a highly significant positive correlation between chemerin level and BMI, total cholesterol, triglycerides, and LDL-cholesterol as well as a highly significant negative correlation between chemerin level and HDL-cholesterol. Similarly, chemerin levels have been reported to be associated with components of the metabolic syndrome, including BMI, hypertension, and plasma triglycerides [16,21,23,28,29].

The positive correlation of serum chemerin with BMI indicated that chemerin is related to obesity. Chemerin can regulate fat metabolism and accelerate the decomposition of fat. It can also inhibit the synthesis of cyclic adenosine monophosphate, activate hormone-sensitive lipase, and promote metabolism of fat cells and release of glycerol and free fatty acids. Glycerol and free fatty acid will synthesize triglycerides and very-low density lipoprotein in the liver, which will then be stored in white adipose tissue [30]. This process will promote obesity and exacerbate hyperlipidemia. Previous study found that serum lipid was related with DR [31], and reduction of elevated serum lipid levels will alleviate the degree of DR and promote the regression of retinal hard exudates in DR [32,33]. Thus, chemerin may be involved in the development of DR through promoting hyperlipidemia.

Recent studies reveal that chemerin are involved frequently in the formation of neovascularization [34,35]. Accumulating evidences showed that chemerin mediated the formation of new blood vessels and functional angiogenesis to a similar extent as vascular endothelial growth factor in human endothelial cells [34]. Moreover, it was found that chemerin induced functional angiogenesis in human endothelial cells, by promoting migration, capillary tube formation, activation of endothelial gelatinase (matrix metalloproteinases-2/matrix metalloproteinases-9), and activation of phosphatidylinositol 3-kinase/Akt and MAPKs pathways, which is a key mechanism for angiogenesis and cell survival [36]. So, the high level of serum chemerin possibly promotes the development of retinal neovascularization in the progression of PDR.

Furthermore, chemerin can increase the generation of mitochondrial reactive oxygen species (ROS) in human endothelial cells. Knockdown of chemerin receptor by shRNA or treatment with the mitochondria-targeted antioxidant Mito-TEMPO decreased the chemerin-associated ROS generation [37]. Elevated ROS can increase the level of oxidative stress, which is the important risk factor in DR progress. Another research found that chemerin was correlated with 8-isoprotaglandim F2a, which reflects the process of oxidative stress [20]. Moreover, chemerin was reported to enhance the response to oxidative stress [9]. Furthermore, chemerin was shown to have a negative correlation with the measurement of antioxidant status, characterized by the HDL-linked paraoxonase-1 enzyme [38]. Thus, chemerin may be also involved in the development of DR through promoting oxidative stress.

Conclusion

This study showed that serum chemerin levels were elevated in patients with T2DM with DR than those without DR and were elevated in patients with PDR than NPDR. These findings suggest that chemerin may be involved in the development of PDR by promoting inflammation, hyperlipidemia, oxidative stress, and neovascularization. Further experiments are needed to reveal whether there is a network of cooperation between chemerin and vascular endothelial growth factor in the development of PDR. In addition, the chemerin levels in intraocular fluid, such as vitreous and aqueous humor, in patients with NPDR and those with PDR need to be investigated. The effect of chemerin on retinal vascular endothelial proliferation, migration, and capillary tube formation in-vitro as well as the mechanisms need to be investigated.

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Conflicts of interest

There are no conflicts of interest.

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