Original Article

Association of the serum chemerin level with the development of diabetic retinopathy in patients with type 1 diabetes mellitus

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ABSTRACT

Background: In patients with type 2 diabetes mellitus, the development of diabetic retinopathy (DR) correlates positively with elevated serum chemerin levels. This study was aimed at investigating the probable association between the serum chemerin level and the development of DR in patients with type 1 diabetes mellitus (T1DM).

Methods: In this cross-sectional study, we included Egyptians and classified them into four groups: group 1, including healthy individuals; group 2, including patients with T1DM without DR; group 3, including patients with T1DM with non-proliferative DR (NPDR); and group 4, including patients with T1DM with proliferative DR (PDR). The assessment included best-corrected distance visual acuity assessment, slit-lamp biomicroscopy, funduscopy, fundus fluorescein angiography, and macular ocular coherence tomography. Fasting blood samples were obtained from all participants to measure serum chemerin, glycated hemoglobin (HbA1c), total cholesterol, triglyceride, and creatinine levels. Serum chemerin levels were compared among the groups, and their correlations with age, duration of diabetes, HbA1c, total cholesterol, triglyceride, and creatinine levels were analyzed.

Results: We recruited 209 participants, including 46 healthy individuals in group 1, 52 patients (T1DM and no DR) in group 2, 61 patients (T1DM and NPDR) in group 3, and 50 patients (T1DM and PDR) in group 4, with comparable mean ages and sex ratios among groups. The diabetes duration, body mass index, HbA1c, total cholesterol, triglyceride, and serum chemerin levels differed significantly among the groups (all $P < 0.001$), whereas the creatinine level did not ($P > 0.05$). The serum chemerin level was significantly higher in group 4 than in groups 3 and 2, in group 3 than in group 2, and in groups 3 and 4 than in group 1 (all $P < 0.001$). However, it was comparable between groups 1 and 2 ($P > 0.05$). It correlated with the duration of T1DM and HbA1c, total cholesterol, triglyceride, and creatinine levels but not with age.

Conclusions: Patients with T1DM with DR showed higher serum chemerin levels than those with T1DM without DR or healthy individuals. Serum chemerin levels were higher in those with PDR than in those with NPDR. Thus, serum chemerin levels are a potential biomarker of the development and severity of DR in patients with T1DM. Nevertheless, future diagnostic accuracy studies are required to confirm these potential applications.

KEYWORDS
chemerin protein, human, adipokine, diabetic retinopathies, type 1 diabetes, IDDM

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INTRODUCTION

Diabetes mellitus (DM) is a global health burden, affecting populations in both developing and developed countries. Diabetic retinopathy (DR), a major ocular complication of DM, is the main cause of vision loss in working, middle-aged individuals [1, 2]. It represents a highly specific retinal neovascular disease affecting patients with type 1 and type 2 DM (T1DM and T2DM, respectively). The duration of DM and the level of glycemic control are major factors determining the severity of DR [3].

The International Clinical Disease Severity Scale for DR defines non-proliferative DR (NPDR) as mild DR with a low number of microaneurysms or moderate DR with a high number of microaneurysms and dot-blot hemorrhages. NPDR might be associated with hard exudates and cotton wool patches. PDR is characterized by neovascularization at the disc or elsewhere (NVD or NVE, respectively) and divided into two risk categories: high-risk, with NVD occupying >1/4th to 1/3rd of the disc area, NVD associated with vitreous or panretinal hemorrhage, or NVE associated with vitreous or panretinal hemorrhage; and low-risk PDR [4]. Patients with PDR may have severe visual impairment due to bleeding from new vessels causing vitreous or preretinal hemorrhage or due to tractional retinal detachment. Diabetic macular edema is another major risk for visual impairment [5].

White adipose tissue behaves as an active endocrine organ, producing multiple active molecules, or adipokines. Adipokines influence glucose metabolism, affecting the total energy balance. They also act as an organizer of adipose tissue [6]. Altered formation or release of adipokines may directly affect insulin sensitivity, insulin secretion, and glucose metabolism [7]. Chemerin is an adipokine that plays important roles in adipose tissue synthesis, energy metabolism, and inflammatory reactions [8]. It is a 16-kD adipokine involved in the organization of natural and adaptive immunity and the differentiation and metabolism of adipocytes. It can also act as a chemoattractant mediator, directing immune cells to sites of tissue injury and lymphoid organs [8]. In addition, serum chemerin levels correlate positively with other inflammatory markers, such as interleukin 6, tumor necrosis factor-alpha, and C-reactive protein [9].

Serum chemerin levels are elevated in patients with obesity or T2DM compared to healthy individuals [10]. In addition, they are independent cardiovascular risk factors for atherosclerosis and coronary artery disease [11]. In T2DM, the development of multiple microangiopathic disorders, such as nephropathy and retinopathy, correlates positively with elevated chemerin levels. Furthermore, serum chemerin levels are elevated in progressive diabetic nephropathy [12]. Glycated hemoglobin (HbA1c) and serum chemerin levels are elevated in children with T1DM [13].

To the best of our knowledge, no previous study has investigated the possible correlation between serum chemerin levels and the development of DR in patients with T1DM. Therefore, the present study aimed to investigate the potential correlation between the chemerin level and the development of DR in patients with T1DM.

METHODS

This cross-sectional study was conducted from May 2020 to June 2021 at the Al-Azhar University Hospital, Cairo, Egypt, involving Egyptian patients with T1DM referred from the diabetes outpatient clinic of the hospital. T1DM was diagnosed based on the criteria laid down by the American Diabetes Association in 2020 [14]. The Faculty of Medicine Ethics Committee, Al-Azhar University, Cairo, Egypt, approved the study protocol (reference number: DM1-0000051). Study procedures were performed in compliance with the tenets of the Declaration of Helsinki. The participants provided written informed consent for participation in this study. A detailed history was taken, including the duration of DM, the presence of ocular and systemic comorbidities and complications of DM, and any medications used.

All participants underwent a full ophthalmic assessment, including an assessment of the best-corrected distance visual acuity using a Snellen chart (Topcon ACP-8R automatic chart projector, Topcon Corporation, Tokyo, Japan), a detailed anterior-segment slit-lamp examination [15] (Photo-Slit Lamp BX 900; Haag-Streit, Koeniz, Switzerland), and funduscopy with a +90-D lens (Volk Optical Inc., Mentor, OH, USA). Imaging examination of patients with T1DM included fundus photography, fundus fluorescein angiography (Topcon TRC 50IX fundus camera, Topcon, Tokyo, Japan), and macular assessment using a DRI Triton swept-source optical coherence tomography device (Topcon Corp., Tokyo, Japan). The retinopathy stage was determined according to the International Clinical Disease Severity Scale for DR [4].

Inclusion criteria for patients in groups 2 – 4 were age ≥18 years and diagnosis of T1DM. Group 2 included patients with T1DM without DR (Figure 1A-D). Group 3 included patients with T1DM and NPDR (Figure 1E-L). Group 4 included patients with T1DM and PDR (Figure 1M-T). Group 1, or the control group, included age-matched healthy individuals, with no history of DM, impaired glucose tolerance, or other systemic diseases.

Exclusion criteria were the diagnosis of T2DM; the occurrence of infection, diabetic ketoacidosis, diabetic neuropathy, diabetic nephropathy, diabetic angiopathy, or diabetic foot disease in patients with T1DM; pregnancy or lactation; chronic hepatic disease; systemic psychological or neurological disorder; pigmentary degeneration; autoimmune conditions that may affect the test results, such as systemic lupus erythematosus, rheumatoid arthritis, Hashimoto thyroiditis, hypothyroidism or hyperthyroidism; overweight or obesity (body mass index ≥ 24 kg/m^2); and a history of ocular surgery, glaucoma, uveitis, retinal vascular occlusive accidents, or other retinal or choroidal neovascular diseases.

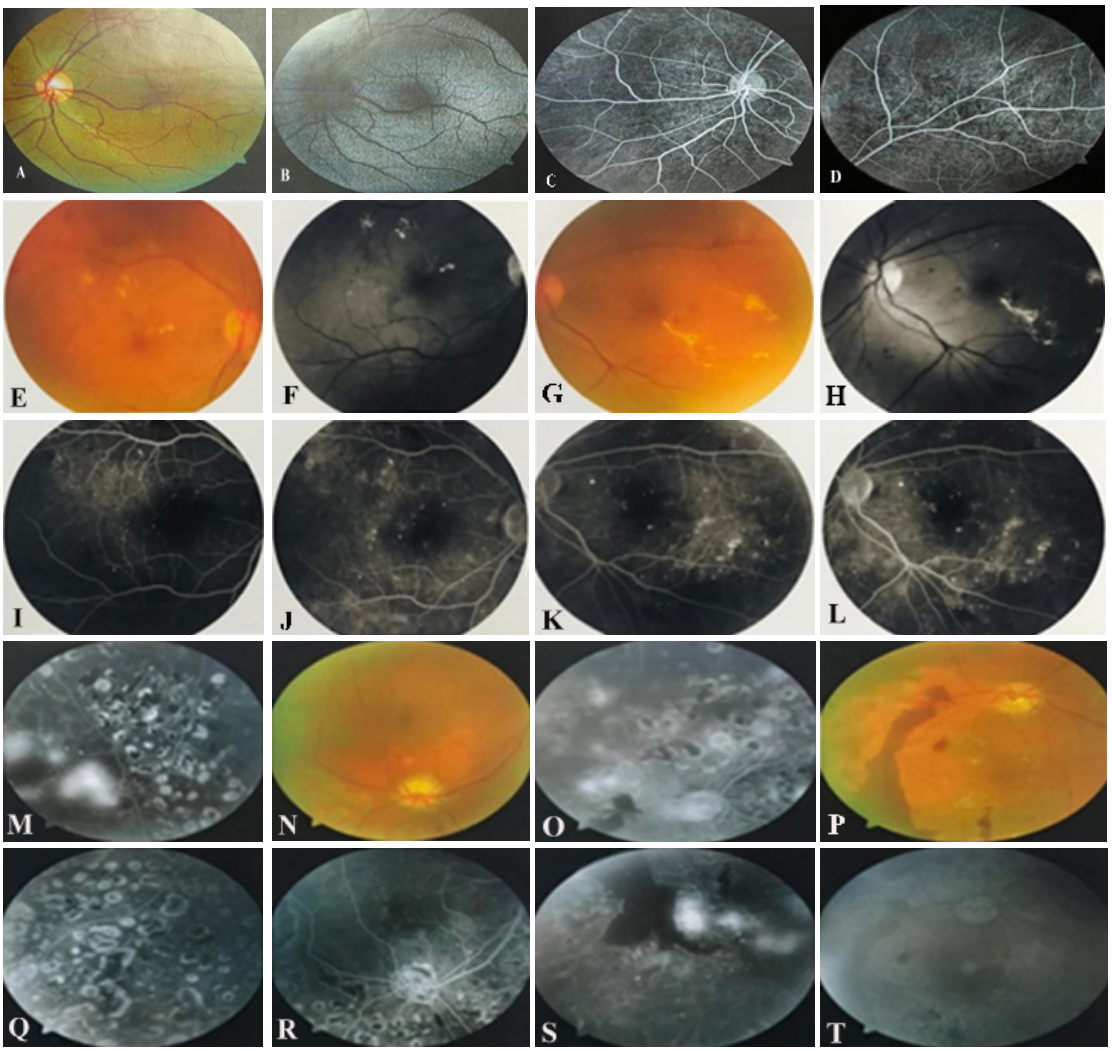

Figure 1. Representative fundus photographs and fluorescein angiographic images acquired with the Topcon TRC 50IX retinal camera (Topcon Corp., Tokyo, Japan) in sample cases from each study group of patients with type 1 diabetes mellitus. (A-D) A patient without diabetic retinopathy (DR) in group 2 with a serum chemerin level of 100.7 ng/mL. (E-L) A patient with non-proliferative DR in the form of microaneurysms, dot or blot hemorrhages, and hard exudates from group 3 with a serum chemerin level of 127.3 ng/mL. (M-T) A patient with proliferative DR in the form of neovascularization elsewhere and subhyaloid hemorrhage with laser marks from group 4 has a serum chemerin level of 193.7 ng/mL.

Laboratory investigations were conducted for all participants using the same protocol. After overnight fasting, two morning blood samples were obtained: one in an ethylenediaminetetraacetic acid tube to assess the HbA1c level [16] and the other in a tube without anticoagulants to assess serum chemerin, creatinine, total cholesterol, and triglyceride levels. The sample was left to coagulate at room temperature for 30 min. The serum samples were further separated into two samples: one to assess creatinine, total cholesterol, and triglyceride levels, and the other stored at - 80°C to assess the chemerin level.

Serum chemerin levels were obtained using human enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's instructions (Human Chemerin ELISA Kit, Catalog No. E-EL-H0698, Elabscience, USA).

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov – Smirnov test was performed for the normality of data distribution. Quantitative data are expressed as the mean (standard deviation [SD]) (range). Qualitative variables are expressed as frequency (percentage). The chi-square test was performed to compare qualitative data among groups. Quantitative data with parametric distribution were compared among more than two groups with the one-way analysis of variance. A post-hoc analysis with Tukey's test was performed for pairwise comparisons of groups at an overall *P*-value < 0.05. The correlation between two numerical parameters was evaluated using Pearson's product-moment correlation. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. Finally, the significance threshold for the *P*-value was set at 0.05.

RESULTS

We recruited 209 participants, including 46 healthy individuals in group 1, 52 patients in group 2, 61 patients in group 3, and 50 patients in group 4. Age and sex ratios were comparable among groups (Table 1). The mean (SD) duration of DM in groups 2, 3, and 4 was 2.92 (1.17), 7.98 (1.79), and 13.23 (2.61) years, respectively (Table 1). The post-hoc analysis with Tukey's test showed that the duration of DM was significantly longer in groups 3 and 4 than in group 2 and in group 4 than in group 3 (all pairwise comparison $P < 0.001$).

The mean HbA1c, total cholesterol, and triglyceride levels differed significantly among groups but not the serum creatinine level (Table 2). Pairwise comparisons revealed that HbA1c levels in groups 2, 3, and 4 differed significantly from those in the control group (all $P < 0.001$). However, HbA1c levels did not differ significantly between groups 2 and 3, 2 and 4, or 3 and 4 (all $P > 0.05$). Similar results were obtained for the total cholesterol level (Table 3).

The mean (range) serum chemerin level was 87.22 (78 – 110.6) ng/mL in group 1, 100.8 (80 – 124.6) ng/mL in group 2, 127.9 (102.8 – 160) ng/mL in group 3, and 179.2 (136.8 – 224.4) ng/mL in group 4, showing significant differences ($P < 0.001$; Table 2).

Pairwise comparisons revealed significantly higher serum chemerin levels in group 4 than in groups 2 and 3, in group 3 than in group 2, and in groups 3 and 4 than in group 1 (all $P < 0.001$). However, serum chemerin levels did not differ significantly between groups 2 and 1 ($P > 0.05$; Table 3).

Among patients with T1DM, the serum chemerin level correlated positively with the duration of DM ($r = + 0.56$, $P < 0.001$) and HbA1c ($r = + 0.69$, $P < 0.001$), total serum cholesterol ($r = + 0.45$, $P < 0.001$), and serum creatinine levels ($r = + 0.15$, $P < 0.05$) but not with age ($r = + 0.13$, $P > 0.05$). Further, the serum chemerin level showed a weak negative correlation with the serum triglyceride level ($r = - 0.28$, $P < 0.001$; Table 4).

Table 1. Comparison of demographic and baseline data among study groups

Variables	Group 1 (n = 46)	Group 2 (n = 52)	Group 3 (n = 61)	Group 4 (n = 50)	*P*
Age (y), Mean ± SD	30.81 ± 4.36	29.32 ± 3.45	29.42 ± 4.26	30.34 ± 5.24	0.247
Sex (Male/Female), n (%)	23 (50.0) / 23 (50.0)	22 (42.3) / 30 (57.7)	37 (60.7) / 24 (39.3)	22 (44.0) / 28 (56.0)	0.194
DM (y), Mean ± SD	-	2.92 ± 1.17	7.98 ± 1.79	13.23 ± 2.61	**< 0.001**
BMI (kg/m²), Mean ± SD	23.65 ± 1.25	29.66 ± 2.65	28.74 ± 1.41	29.12 ± 2.41	**< 0.001**

Abbreviations: n, number of participants; y, years; SD, standard deviation; %, percentage; DM, duration of diabetes mellitus; BMI, body mass index; kg/m²; kilograms per square meter. Note: *P, P*-values < 0.05 are shown in bold; Group 1, or the control group, includes age-matched healthy individuals; Group 2, including patients with type 1 diabetes mellitus (T1DM) without diabetic retinopathy (DR); Group 3, including patients with T1DM and non-proliferative DR; Group 4, including patients with T1DM and proliferative DR.

Table 2. Comparison of laboratory data among study groups

Variables	Group 1 (n = 46)	Group 2 (n = 52)	Group 3 (n = 61)	Group 4 (n = 50)	*P*-value
HbA1c (%), Mean ± SD (Range)	5.68 ± 0.85 (4.2 to 6.8)	7.68 ± 0.31 (6.8 to 7.9)	7.77 ± 0.38 (7.3 to 8.4)	8.01 ± 0.31 (7.9 to 9.2)	**< 0.001**
Total cholesterol (mg/dL), Mean ± SD (Range)	163.35 ± 23.74 (121 to 190)	234.34 ± 13.29 (198 to 245)	242.44 ± 18.80 (212 to 268)	245.72 ± 13.73 (242 to 312)	**< 0.001**
Triglycerides (mg/dL), Mean ± SD (Range)	182.15 ± 55.18 (110 to 237)	224.04 ± 53.06 (119 to 276)	185.06 ± 36.92 (115 to 221)	183.70 ± 62.69 (117 to 257)	**< 0.001**
Creatinine (mg/dL), Mean ± SD (Range)	1.43 ± 0.21 (1.09 to 1.75)	1.44 ± 0.23 (1.1 to 1.8)	1.51 ± 0.20 (1.2 to 1.8)	1.51 ± 0.23 (1.2 to 1.85)	0.140
Chemerin (ng/mL), Mean ± SD (Range)	87.22 ± 10.38 (78 to 110.6)	100.8 ± 15.1 (80 to 124.6)	127.9 ± 26.6 (102.8 to 160)	179.2 ± 33.7 (136.8 to 224.4)	**< 0.001**

Abbreviations: n, number of participants; HbA1c, glycated hemoglobin; %, percentage; SD, standard deviation; mg/dL, milligrams per deciliter; ng/mL, nanogram per milliliter. Note: *P*-values < 0.05 are shown in bold. Group 1, or the control group, includes age-matched healthy individuals; Group 2, including patients with type 1 diabetes mellitus (T1DM) without diabetic retinopathy (DR); Group 3, including patients with T1DM and non-proliferative DR; Group 4, including patients with T1DM and proliferative DR.

Table 3. Pairwise comparisons of laboratory parameters with post-hoc Tukey's test

Variables	*P*-value for pair-wise comparison					
	P_1	P_2	P_3	P_4	P_5	P_6
HbA1c (%)	**< 0.001**	**< 0.001**	**< 0.001**	0.738	0.072	0.141
Total cholesterol (mg/dL)	**< 0.001**	**< 0.001**	**< 0.001**	0.191	0.053	0.522
Chemerin (ng/mL)	0.073	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**

Abbreviations: HbA1c, glycated hemoglobin; %, percentage; mg/dL, milligrams per deciliter; ng/mL, nanogram per milliliter. Note: *P*-values < 0.05 are shown in bold; P_1, *P*-value for the comparison between groups 1 and 2; P_2, *P*-value for the comparison between groups 1 and 3; P_3, *P*-value for the comparison between groups 1 and 4; P_4, *P*-value for the comparison between groups 2 and 3; P_5, *P*-value for the comparison between groups 2 and 4; and P_6, *P*-value for the comparison between groups 3 and 4. Group 1, or the control group, includes age-matched healthy individuals; Group 2, including patients with type 1 diabetes mellitus (T1DM) without diabetic retinopathy (DR); Group 3, including patients with T1DM and non-proliferative DR; Group 4, including patients with T1DM and proliferative DR.

Table 4. Correlation between the serum chemerin level and other factors in patients with type 1 diabetes mellitus

Variables	Chemerin (ng/mL)	
	r	*P*-value
Age (y)	+ 0.13	0.068
Duration of DM (y)	+ 0.56	**< 0.001**
HbA1c (%)	+ 0.69	**< 0.001**
Total cholesterol (mg/dL)	+ 0.45	**< 0.001**
Triglycerides (mg/dL)	- 0.28	**< 0.001**
Creatinine (mg/dL)	+ 0.15	**0.036**

Abbreviations: ng/mL, nanogram per milliliter; y, years; DM, diabetes mellitus; HbA1c, glycated hemoglobin; %, percentage; mg/dL, milligrams per deciliter; r, Pearson correlation coefficients value. Note: *P*-values < 0.05 are shown in bold.

DISCUSSION

In the present study, serum chemerin levels were significantly higher in patients with T1DM with DR than in those with T1DM without DR or healthy individuals, and in patients with T1DM with PDR than in those with T1DM with NPDR. Among patients with T1DM, the serum chemerin level correlated positively with the duration of DM, total serum cholesterol, and creatinine levels but not with age. The serum chemerin level showed a weak negative correlation with the triglyceride level.

T1DM is a common metabolic, chronic disease with long-term, multiorgan damage. Microvascular and macrovascular complications of persistent uncontrolled hyperglycemia can result in DR, diabetic nephropathy, and diabetic neuropathy [17]. DR is the most common microvascular complication of diabetes, with a challenging

treatment [17-20]. The pathophysiology of DR is complex [17-19]. In the present study, chemerin levels were significantly higher in patients with DR than in those without DR or healthy individuals, and in patients with PDR than in those with NPDR. Considering that chemerin promotes secretion of the vascular endothelial growth factor (VEGF) [21], serum chemerin may be considered to contribute to retinal neovascularization as a key characteristic of PDR.

Chemerin levels did not differ significantly between patients with T1DM without DR and healthy individuals. This finding suggests that elevated chemerin levels primarily contribute to microangiopathic complications of DM. The same result was found in patients with T2DM [22]. Similarly, Yasir et al. found that serum chemerin levels correlated positively with the presence and severity of DR in patients with T2DM [23].

Serum chemerin levels in patients with T2DM are correlated with DR [12, 23-27]. Only a few studies have investigated serum chemerin levels in patients with T1DM [13, 28]. Similar to the present study, Elsehmawy et al. [13] found significantly higher serum chemerin, total cholesterol, and triglyceride levels in patients with T1DM than in healthy controls and a significant positive correlation between HbA1c and chemerin levels in patients with T1DM. Similarly, El Dayem et al. found that serum chemerin, total cholesterol, and triglyceride levels were significantly higher in patients with T1DM than in healthy controls [28]. However, these studies [13, 28] failed to evaluate the DR status in patients with T1DM. Among the patients with T1DM in the present study, serum chemerin levels were significantly higher in group 4 than in groups 3 and 2, in group 3 than in group 2, and in groups 3 and 4 than in group 1, but did not differ between groups 1 and 2.

Chen et al. found significantly elevated serum cystatin C and chemerin levels in patients with T2DM with DR than in those with T2DM without DR, and in those with PDR than in those with NPDR [24]. Du et al. found significantly elevated serum chemerin levels in patients with T2DM with PDR than in those with T2DM with NPDR. They also found a significant positive correlation between serum VEGF and chemerin levels [26]. Similarly, in the present study, serum chemerin levels were significantly higher in patients with T1DM with PDR than in those with T1DM without DR or with NPDR. Similar to the present study, Du et al. found a significant positive correlation between the serum chemerin level and the duration of diabetes, HbA1c, and total cholesterol levels but not with age [26]. The serum chemerin and triglyceride levels correlated positively in the previous study [26], but showed a weak negative correlation in the present study.

Li et al. [25] discovered that patients with PDR had significantly higher vitreous chemerin protein levels and a significantly higher ratio of the vitreous chemerin level to the serum chemerin level compared to the healthy controls. However, in the present study, we did not assess the vitreous chemerin protein level. Gu et al. also reported that patients with T2DM and elevated chemerin levels showed higher frequencies of DR and diabetic nephropathy but not diabetic neuropathy. In addition, they correlated elevated chemerin levels to microvascular complications of DM [12]. Similar to the present study, they found significantly higher mean (SD) chemerin levels in patients with DM with PDR (119.95 [48.62] ng/mL) or NPDR (112.66 [38.34] ng/mL) than in those with DM without DR (97.69 [40.27] ng/mL) [12].

Many probable mechanisms have been suggested for the role of chemerin in retinal microangiopathy. Promoting inflammation is a probable mechanism for chemerin-induced angiogenesis. Chemerin exhibits induction in the early stages of inflammatory responses [29] and promotes the migration and recruitment of dendritic cells and macrophages [30]. It is involved in the pathophysiology of DR, including inflammatory processes, oxidative stress, neovascularization, and increased vascular permeability [12, 21]. This may explain the elevated chemerin levels in patients with T1DM and DR in the present study and support the possibility of using serum chemerin as a potential biomarker for early screening and prognostication of DR.

Chemerin levels correlate with metabolic disorders [31, 32]. Elevated chemerin levels in patients with obesity could be a causal factor in the development of T2DM and may play a role in mediating obesity and developing T2DM [33]. Fatima et al. suggested a cutoff chemerin level of 13.7 ng/mL, as it could discriminate 73% of new cases of DM among patients with impaired glucose levels with a sensitivity of 91% and specificity of 96% [34]. In the same context, the present study showed a significant positive correlation between the serum chemerin level and the duration of DM and HbA1c, total cholesterol, and triglyceride levels. The association between the serum chemerin level and both the HbA1c level and duration of DM have been well documented in T2DM [22, 35].

To the best of our knowledge, this was the first study investigating the DR status of patients with T1DM who underwent laboratory investigations for the serum chemerin level along with other parameters. However, we did

not test the serum or vitreous VEGF levels for any potential correlation with elevated serum chemerin levels. Further studies are required to discover the network of interactions between chemerin and VEGF in developing PDR in patients with T1DM. Moreover, measuring chemerin levels in the intraocular fluid of the eyes with NPDR or PDR could shed more light on the possibility of using chemerin as a novel biomarker to advance the management of DR in patients with T1DM. We recommend performing diagnostic accuracy studies in the future to confirm the possibility of using the serum chemerin level for early screening and prognostication of DR among patients with T1DM.

CONCLUSIONS

Among patients with T1DM, those with DR, particularly PDR, had significantly elevated serum chemerin levels than those without DR. In addition, the duration of DM and HbA1c, total serum cholesterol, triglyceride, and serum creatinine levels correlated significantly with the serum chemerin level. Thus, chemerin played a crucial role in developing DR, possibly through neovascularization and inflammation. Further research is required to determine if serum chemerin may serve as an early diagnostic marker of DR in patients with T1DM and whether or not lowering the chemerin serum level or hindering chemerin-receptor interaction might provide novel treatment opportunities. Similarly, future diagnostic accuracy studies are required to confirm the possibility of using the serum chemerin level for early screening and prognostication of DR in patients with T1DM.

ETHICAL DECLARATIONS

Ethical approval: The Faculty of Medicine Ethics Committee, Al-Azhar University, Cairo, Egypt, approved the study protocol (reference number: DM1-0000051). Study procedures were performed in compliance with the tenets of the Declaration of Helsinki. The participants provided written informed consent for participation in this study.

Conflict of interest: None.

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