Serum chemerin and diabetic retinopathy in type 2 diabetic patients
Alaaeldin Abdelsalam Dawooda, Osama Abdalah Elmorsyb, Hala Mourad Demerdashc

aAssistant Professor in Internal Medicine Department, Faculty of Medicine, Menoufia University, bLecturer in Ophthalmology Department, Faculty of Medicine, Menoufia University, cAssistant Prof Clinical Pathology, Pharmacology and Toxicology Department, Faculty of Pharmacy and Drug Manufacturing, Pharos University, Alexandria

Correspondence to Alaaeldin Abdelsalam Dawood, MD, 5 Fatma Elyosef Street, Sporting, Alexandria; Tel: 01223525385; e-mail: aiaadawood2000@yahoo.com

Received 8 May 2017 Accepted 18 July 2017

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

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 fractional 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 $\chi^2$-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,
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 cholesterol, 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.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.213</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>0.815</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Duration of DM</td>
<td>0.523</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.771</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP</td>
<td>0.877</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum creatine</td>
<td>0.155</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.702</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.681</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL</td>
<td>0.859</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL</td>
<td>−0.710</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio</td>
<td>0.129</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; DM, diabetes mellitus; HbA1c, glycosylated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride.
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-κB 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
Serum chemerin and DR in type 2 diabetic patients

Dawood et al.


