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Study of relation between Serum C1Q / TNF-Related Protein 9 (CTRP9) and Diabetic Retinopathy in a Sample of Egyptian Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Background: C1q/TNF-Related Protein (CTRP) family members are novel adipokines that have immunomodulatory, anti-inflammatory, glucose regulating, and vascular effects. However, their microvascular effects in diabetic patients remain unclear**.**

Objective: To evaluate the relation between serum CTRP9 and diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM).

Patients and Methods: This cross-sectional study was conducted on 90 subjects with their ages ranging from 35-70 years, selected from diabetes and ophthalmology outpatient clinics of Ain shams University Hospitals for 6 months in a period from May 2019 to November 2019. They were divided into 3 groups: Group (I): 35 Patients with T2DM with diabetic retinopathy. Group (II): 35 Patients with T2DM without diabetic retinopathy. Group (III): 20 Apparently healthy individuals.

Results: there is a highly statistically significant difference between the studied groups as regards S. CTRP9 being highest in Group II Patients with T2DM without diabetic retinopathy followed by Group III Apparently healthy individuals then Group I Patients with T2DM with diabetic retinopathy (P-value <0.001). Also, there is a negative correlation between serum CTRP9 level and Duration of DM, HbA1C FBS, and 2hpp. On performing multiple linear stepwise regression analysis to the statistically significant factors using CTRP9 as a dependent variable with other independent variables, only HbA1C and Duration of DM remained significantly associated with CTRP9.

Conclusion: T2DM patients with diabetic retinopathy have decreased CTRP9 levels regardless of the grade of retinopathy. Loss of protective role of CTRP9 may attribute to DR in patients with long-standing Diabetes.

Keywords: Serum CTRP9, Diabetic retinopathy, T2DM.

INTRODUCTION

Diabetes mellitus is a group of metabolic illnesses marked by chronic hyperglycemia caused by a lack of insulin action, secretion, or both, all of which result in long-term damage and malfunction of several organs, including the eyes, kidneys, nerves, heart, and blood vessels [(1)].

Diabetic retinopathy is the most common and dangerous microvascular consequence of diabetes, with an alarmingly high global prevalence [(2)]. It is the leading cause of vision loss and blindness [(3)].

Diabetic macular edema and proliferative retinopathy sequelae such as vitreous hemorrhage, neovascular glaucoma, and tractional retinal detachment are the most common causes of visual loss in diabetic individuals. Appropriate blood sugar and blood pressure control can considerably prevent the development or progression of these potentially blinding consequences, emphasizing the need for early DR recognition and treatment beginning [(4)].

In the past decade, the CTRP super-family has been discovered as novel anti-inflammatory adipokines with important metabolic effects **(5)**. The CTRP family is composed of 16 members all of which were thought to contribute to energy homeostasis, through altering insulin sensitivity specifically in the muscles and liver **(6)**.

The CTRP superfamily has been found as a new anti-inflammatory adipokine with major metabolic effects [(5)]. The CTRP family contains 16 members, all of which are hypothesized to play a role in energy balance via affecting insulin sensitivity in the muscles and liver [(6)].

CTRP 9 is A member of the CTRP family which shows the highest degree of amino acid identity to adiponectin (approximately 54%) in its globular C1q domain with a potent anti-diabetic, cardioprotective and anti-inflammatory adipokine [(7,8,9)]**.**

CTRP9 has been proven to improve insulin sensitivity and lipid metabolism, both of which help to reduce blood sugar levels [(8)]. Furthermore, because CTRP9's vasoactive potency is nearly three times that of adiponectin, it has a significant vaso-relaxing action and may have substantial therapeutic relevance in the therapy of endothelial dysfunction [(10)].

In addition, the anti-inflammatory effect of CTRP9 was explained by inhibition of TNFα-induced monocytes adhesion to human aortic endothelial cell and inhibits TNFα-induced NF-κB (nuclear factor-κB) activation [(9)]**.** However, the role of CTRP9 in the development of microvascular complications in diabetic patients remains unclear. To the best of our knowledge, this is the first study evaluating the relationship between CTRP 9 and Diabetic Retinopathy in Patients with T2DM.

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This work aimed to study the correlation between serum CTRP9 and diabetic retinopathy in patients with T2DM.

PATIENTS AND METHODS

This cross-sectional study was conducted on 90 patients with ages ranging from 35-70 years, selected from diabetes and ophthalmology outpatient clinics of Ain shams University Hospitals for 6 months in a period from May 2019 to November 2019.

They were divided into 3 groups: **Group (I):** 35 patients with T2DM with diabetic retinopathy; **Group (II):** 35 Patients with T2DM without diabetic retinopathy and **Group (III):** 20 apparently healthy individuals as a control group.

Ethical consent:

Ethical approval was obtained from Ain Shams University, Faculty of Medicine, Research Ethics Committee FWA00017858. Informed consent was obtained from all participants included in our study." This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Exclusion criteria: Patients with BMI<30 or ages <35 were excluded from the study, and patients with other ocular diseases: retinal vascular diseases, uveitis, glaucoma, or high myopia

All patients recruited in this study were subjected to full medical history taking emphasizing on the duration of DM, family history of DM, Medication list (metformin, oral hypoglycemic drugs, insulin, and statins), all subjects were physically examined (Body Mass Index (BMI), systolic and diastolic pressure.

Laboratory investigations include FBS, 2hpp, HbA1c, Serum cholesterol, Triglyceride, and Serum CTRP9 measured by ELISA.

The patient's demographics and medical history were obtained from the patient's file or during the patient's visit. BMI was calculated using the standard formula (weight (kg)/height (m^2)).

The selection of diabetic retinopathy and without diabetic retinopathy patients was done by full ophthalmological examination including BCVA, IOP measurement, anterior segment, and posterior segment examination. Ninety patients were enrolled. This included 20 healthy control patients, 35 T2DM patients without diabetic retinopathy, and 35 patients with diabetic retinopathy (23 patients with mild non-proliferative diabetic retinopathy, 6 patients with moderate non-proliferative diabetic retinopathy, 2 patients with severe non-proliferative diabetic retinopathy, 4 patients with proliferative diabetic retinopathy and 27 patients had maculopathy with diabetic macular edema in 6 patients.

Laboratory assessment:

Whole blood samples were collected after an overnight fast from all 90 subjects. Blood collected was split into three portions; the first portion was used to measure fasting blood glucose (FBG) and collected in Na fluoride-containing vacutainer tubes. The second portion was collected on EDTA containing vacutainer tubes to measure glycated hemoglobin (HbA_1c %). The third portion of blood was centrifuged to separate serum for the measurement of insulin and lipid profile (triglycerides (TG) and total cholesterol (TC)) and Isolation of DNA and analysis for HSD11B1(rs846910) gene polymorphism by real-time PCR technique.

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: (fasting blood glucose (mg/dL)) × (fasting blood insulin (μU/mL)/405).

All routine work analyses were measured on the same day of the blood collection, the remaining samples were stored at -80°C till the time of assay for insulin and CTRP 9 using Aviscera biosciences, China ELISA kits SHANGHAI CRYSTAL DAY BIOTECH CO., LTD. Cat. No： E3848Hu.

Statistical analysis

All results were expressed as mean ± standard error of the mean. Analysis of variance (ANOVA) test was used to compare different groups. The correlation between the parameters was done using the Pearson correlation test which is an extended parametric analysis of multiple linear stepwise regression analyses to study the association between CTRP9 and other biochemical parameters. In the multiple linear stepwise regression analysis, the independent variables included demographic factors and other biochemical variables (BMI, age, duration of diabetes, FBG, TC, TG, and HbA1c %, all of which were associated with the examined dependent variable CTRP9 in univariate analysis. All statistical analysis was performed on the STATA statistical Software, release 14.0 (Stata Crop. 2015, College Station, Texas, USA). P-values < 0.05 were considered significant.

RESULTS

There was a highly statistically significant difference between the studied groups as regards **BMI** being highest in **group I** (35.986±3.181) followed by **group II** (35.341±3.657) then **group III** (27.190±0.830), P-value <0.001**.** There was a highly statistically significant difference between group1 and group2 as regards the duration of DM being higher in **group I** (13.486±4.068) than **group II** (8.829±2.584), p-value <0.001, while there was no statistical difference between the studied groups as regard SBP and DBP.

There was a highly statistically difference between the studied groups as regards CTRP9 being highest in **group II** (269.143±134.183) followed by **group III** (83.000±18.806) then **group I**

(47.286±21.051), P-value <0.001. Regarding the glycemic profile (FBS, 2hPP, HbA1c), it was found to be significantly increased in **group I** and **group II** when compared to **group III**. (p-value<0.001), being the highest in group **I** followed by group **II** then group **III**. Fasting blood sugar in **group I** (176.229±30.007), **group II** (144.343±19.299), and **group III** (93.400±4.684), 2hpp in **group1** (272.086±67.497), **group II** (197.629±25.446) and **group III** (121.650±5.743), While HbA1c in **group I** (9.146±0.613), **group II** (7.820±0.414), and **group III** (4.825±0.215)**.**

As regards the lipid profile (TC, TG) show a high statistically significant difference between the studied groups (p-value<0.001), being the highest in group **I** followed by group **II** then group **III** as follow; T. cholesterol in **group I** (191.600±21.331), **group II** (188.743±17.652), and **group III** (168.900± 2.972), while S. triglyceride in **group I** (146.286±9.584), **group II** (141.457±10.861) and **group III** (92.800±8.871) **(Table 1).**

There was a highly significant negative correlation between S. CTRP9 and duration of DM, FBS, 2 hPP, and HbA1c as regards the total number of patients in **groups (I) and (II)**, P-value <0.001, While There was a non-significant statistical correlation between S. CTRP9 and Age, BMI, SBP, DBP, S. Cholesterol and S.Triglyceride **(Table 2)**.

While applying multiple linear stepwise regression analysis to the statistically significant factors using CTRP9 as a dependent variable with other independent variables, only HbA1C (β = -0.588, P = 0.002) and Duration of DM (β = -0.216, P 0.029), remained significantly associated with CTRP9 **(Table 3)**.

On comparing the value of CTRP9 between groups of patients with different diabetic retinopathy grades using the One-Way ANOVA test, we found no statistically significant difference among them. (P-value equals 1.12) **(Table 4)**.

Table (1): Comparison between the studied groups as regard Clinical and laboratory characteristics

S. CTRP9 (ng/ml)	**Mean ±SD**	47.28	±	2.05	269.14	±	34.18	83.00	±	8.80	65.14	<0.001*
FBS (mg/dl)	**Mean ±SD**	176.22	±	30.00	144.34	±	19.29	93.40	±	4.68	86.99	<0.001*
2hpp(mg/dl)	**Mean ±SD**	272.08	±	67.49	197.62	±	25.44	121.65	±	5.74	72.61	<0.001*
HbA1C%	**Mean ±SD**	9.146	±	0.61	7.82	±	0.41	4.82	±	0.21	533.44	<0.001*
T. C (mg/dl)	**Mean ±SD**	191.60	±	21.33	188.74	±	17.65	168.90	±	2.97	11.90	<0.001*
TG (mg/dl)	**Mean ±SD**	146.28	±	9.58	141.45	±	10.86	92.80	±	8.87	206.59	<0.001*

Table (2): Correlation between CTRP9 and other numerical variables in all patients of groups (I) and (II)

Correlations						
	S. CTRP9					
	With diabetic retinopathy		**Without diabetic Retinopathy**		**Total**	
	R	**P-value**	**R**	**P-value**	**R**	**P-value**
BMI(Kg/m^2)	0.157	0.367	-0.040	0.818	-0.081	0.503
SBP (mm/Hg)	-0.159	0.362	-0.102	0.561	-0.109	0.368
DBP (mm/Hg)	0.029	0.870	-0.014	0.938	-0.022	0.858
Duration of DM (yrs)	0.126	0.472	-0.008	0.965	-0.427	<0.001*
FBS (mg/dl)	0.064	0.713	-0.132	0.451	-0.444	<0.001*
2hpp (mg/dl)	0.211	0.223	-0.169	0.331	-0.467	<0.001*
HbA1C%	-0.103	0.556	-0.263	0.127	-0.664	<0.001*
T. C (mg/dl)	0.199	0.252	0.181	0.297	0.033	0.785
TG (mg/dl)	-0.133	0.446	0.233	0.179	-0.077	0.528

*** Significant**

Table (3): Multivariate regression analysis between S. CTRP9 and other laboratory findings

	Unstandardized Coefficients		**Standardized Coefficients**	**T**	**P-value**
	B	**Std. Error**	**Beta**		
Duration of DM	-7.725	1.463	-0.216	-2.231	0.029*
FBS (mg/dl)	0.054	0.098	0.011	0.068	0.946
2hpp (mg/dl)	-0.021	0.074	-0.009	-0.057	0.955
HbA1C	-102.043	4.591	-0.588	-4.150	<0.001*
Dependent Variable: S. CTRP9					

Table (4): S. CTRP9 and grades of diabetic retinopathy:

	Diabetic retinopathy				Test of Sig.	p-value
	Mild NPDR (n = 23)	Moderate NPDR (n = 6)	Severe NPDR (n = 2)	PDR (n = 4)		
Mean ± SD	54.78 ± 6.21	46.66± 7.22	30 ± 0	42.5± 5.98	0.89	1.12

DISCUSSION

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM) and one of the leading causes of vision loss in persons of working age. Diabetic retinopathy is diagnosed based on clinical symptoms of microvascular retinal abnormalities [(11)].

C1q complement/TNF-related protein 9 (CTRP9) is a novel adipokine that is considered to play a critical role in the pathogenesis of T2DM, dyslipidemia, and coronary artery diseases (CAD), since their expression enhances insulin sensitivity, promote lipid metabolism, and protect against cardiovascular [(7)].

CTRP9 in diabetic mice reduces retinal inflammation and protects the blood-retinal barrier (BRB) through inhibition of the expression of TNF-α, IL-1β, MCP-1, adhesion molecules, and Keeping the balance between the expression of vascular endothelial growth factor and pigment epithelium-derived factor. CTRP9 can prevent the breakdown of BRB and down regulation of tight-junction and consequently, CTRP9 can both quantitatively and qualitatively reduce the vascular leakage in the early stage of diabetic retinas [(12)]. Furthermore, CTRP9 has a crucial vaso-relaxation effect that results in vascular relaxation via the adiponectin receptor-1/AMPK/eNOS/nitric oxide signaling pathway [(7)].

However, CTRP9 has not been investigated in human subjects suffering from diabetic retinopathy. Therefore, the current study was designed to evaluate the relation between serum CTRP9 and diabetic retinopathy in patients with type 2 diabetes mellitus.

In the present study the levels of S. CTRP 9 were significantly higher in **Group II** Patients with T2DM without diabetic retinopathy (269.143±134.183) followed by **Group III** apparently healthy individuals (83.000±18.806) then **Group I** Patients with T2DM with diabetic retinopathy (47.286±21.051) P-value <0.001.This result came in line with **Moradi *et al.*** [(7)] study who found that the circulating CTRP9 levels were elevated in the T2DM group compared to healthy control and **Jia *et al.*** [(8)] who showed elevated CTRP9 levels in individuals with impaired glucose tolerance and newly diagnosed T2DM than in individuals with normal blood sugar. These findings proposed that the elevated CTRP 9 levels in T2DM patients could be a compensatory mechanism developed to reduce the state of hyperglycemia and hyperinsulinemia through enhancing insulin sensitivity or a defensive response against metabolic stress[(8)].

Interestingly, conflicting results were reported by **Ahmed *et al.*** [(13)] who conducted a study to investigate the possible role of CTRP9 in the diagnosis and prognosis of CAD in T2DM postmenopausal female patients and found out that CTRP9 levels were significantly reduced in those individuals with CAD secondary to T2DM, which suggests a compensatory response to insulin resistance, endothelial dysfunction, and inflammatory milieu. These observed disagreements may have resulted from differences in duration of diabetes, characteristics of the study population, and even study design.

The current study found a negative correlation between serum CTRP9 level and duration of DM (P-value <0.001). This matches with **Ahmed *et al.*** [(13)] who found a negative correlation between CTRP9 level and duration of diabetes in patients with T2DM>5 years and patients with CAD secondary to T2DM.

Moreover, the lowest levels of CTRP9 were found in T2DM patients with diabetic retinopathy (**group I**) seem to be due to prolonged DM duration in these patients group (13.48±4.0 years) compared to group II without diabetic retinopathy (8.82±2.58 years), resulting in exhaustion of this beneficial adipokine CTRP9 and loss of its protective role. This could explain our results, the decreased levels of CTRP 9 in T2DM patients with diabetic retinopathy when compared to T2DM alone. Moreover, the state of chronic low-grade inflammation associated with long-standing DM resulted in reduced levels of Adiponectin [(14)], consequently decreased the secretion of CTRP9 as it needs Adiponectin for its production [(15)]. This new finding highlights the possible use of CTRP 9 as a diagnostic and prognostic marker in the development of diabetic retinopathy in patients with long-standing T2DM.

Additionally, it is well known that adipokines with cardiovascular protective properties (like CTRP9 and CTRP13) are downregulated in diabetic patients. On the contrary, pro-inflammatory adipokines (like resistin, CTRP1, visfatin) are upregulated in T2DM. This disturbed balance between pro-inflammatory and anti-inflammatory adipokines in T2DM can contribute to the development of metabolic and vascular complications [(16)], so lower levels of CTRP 9 in patients with diabetic retinopathy might reflect the imbalance between pro-inflammatory adipokines and anti-inflammatory adipokines in these patients.

Several studies have shown the protective vascular effects of CTRP9 against CVD,

atherosclerosis, and vascular damage, [17-19]. CTRP9 was shown to increase nitric oxide production resulting in endothelium-dependent vasorelaxation through the AMPK/endothelial nitric oxide synthase (eNOS) pathway [10], attenuating neointimal formation after vascular injury **(20),** and protecting against cardiac injury [19]. Therefore, CTRP9 was considered as a vasorelaxant adipocytokine that may have beneficial protective vascular effects. However, the role of CTRP9 in the development of microvascular damage remains unclear. To the best of our knowledge, this study is the first to demonstrate decreased plasma CTRP9 levels in human diabetic patients with diabetic retinopathy compared to those without diabetic retinopathy.

Our results indicated that CTRP9 exhibited a negative correlation with FBS, 2hpp, and HbA1C (P-value <0.001), While There was a non-significant statistical correlation between S. CTRP9 and Age, BMI, SBP, DBP, S. Cholesterol and S.Triglycerides. Interestingly, conflicting results were reported from studies investigating the correlation of serum CTRP9 in T2DM with the glycemic profile. One study found a negative correlation between serum CTRP9 level and FBG, HbA1c% [13], whereas another study showed a positive correlation between CTRP9 and FBS, HbA1c in newly diagnosed T2DM [8].

While on performing multiple linear stepwise regression analysis to the statistically significant factors using CTRP9 as dependent variable with other independent variables, only HbA1C (β = -0.588, P = 0.002) and Duration of DM (β = -0.216, P 0.029), remained significantly associated with CTRP9. In Ahmed *et al*. study [13], multivariate linear regression to the statistically significant factors, it was found FBS (β = -0.262, P > 0.008), BMI (β = -0.243, P > 0.004) and T2D duration (β = -0.277, P > 0.005), remained significantly associated with CTRP9.

CONCLUSION

The present study showed decreased levels of CTRP 9 in T2DM patients with diabetic retinopathy when compared to T2DM alone and these findings could be due to prolonged DM duration in these patients group compared to group II without diabetic retinopathy, resulting in exhaustion of this beneficial adipokine CTRP9 and loss of its protective role.

This novel finding could suggest the possible use of CTRP 9 as a diagnostic and prognostic marker of diabetic retinopathy in patients with a long-standing T2DM although there is no statistically significant difference among different diabetic retinopathy grades.

On doing multiple linear stepwise regression, only HbA1C and Duration of DM remained significantly associated with CTRP9.

List of Abbreviations:

2hPP: 2hour postprandial, AMPK: AMP-activated protein kinase, BMI: body mass index, BRB: blood-retinal barrier, CAD: coronary artery diseases, CTRP9: C1q complement/tumor necrosis factor (TNF)—related protein, DBP: diastolic blood pressure, DR: diabetic retinopathy, eNOS: Endothelial nitric oxide synthase, FBS: fasting blood sugar, HbA1c: hemoglobin A1c, HDL: high-density lipoprotein, HOMA-IR: Homeostasis model assessment insulin resistance, IL-1: interleukin-1, LDL: low-density lipoprotein, MCP1: monocyte chemoattractant protein-1, NF-Kb: nuclear factor-kappab, NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, SBP: systolic blood pressure, T2DM: type 2 diabetes mellitus, TC: total cholesterol (TC), TG: triglycerides, TNF-α: tumor necrosis factor-alpha.

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