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CENTRAL MACULAR THICKNESS IN DIABETIC MACULAR EDEMA

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Abstract

Context. Retinal microvascular dysfunction differs in macular edema lesions in the two eyes of the same patient with diabetic retinopathy.

Objective. To evaluate the relationship between central macular thickness (CMT) and metabolic/systemic factors including anthropometric and laboratory findings, in patients with regressed diabetic retinopathy and a history of pars plana vitrectomy (PPV) combined with internal limiting membrane peeling in one eye.

Subjects and Methods. Forty-two eyes with PPV and the same patients' fellow 42 eyes (without PPV) included this study. Fasting blood samples of these 42 diabetics were collected to study adiponectin levels and other routine parameters.

Results. The average hemoglobinA1c value was 7.3±1.3%. CMT of the vitrectomized eyes were significantly correlated with atherogenic index of plasma, total cholesterol, low density lipoprotein cholesterol and uric acid (UA). On the other hand, CMT of the nonvitrectomized fellow eyes significantly correlated with glucose levels and diabetes duration. Adiponectin, adiponectin/body mass index, adiponectin/fibrinogen were found significantly higher in the subgroup with CMT≥300μm in the vitrectomized eyes ($P<0.05$). UA levels were higher in the subgroup with CMT≥300μm in the fellow (nonvitrectomized) eyes ($P<0.05$).

Conclusions. Although there was no relationship between CMT and hemoglobinA1c values, CMT seemed to be affected by atherogenicity, prooxidant chemical alterations in the course of inflammation, so determination of adiponectin and UA levels may be suggested before surgery to predict the atherosclerotic damage and the postoperative CMT value. Vitrectomy performed at the proper time may be helpful in metabolic remodeling process of the retinal tissue along with life style changes, well control of diabetes, and intraocular treatments.

Keywords: Adiponectin, uric acid, diabetic retinopathy, metabolism, central macular thickness.

INTRODUCTION

Diabetic macular edema (DME) develops due to retinal microvascular dysfunction and blood-retinal barrier (BRB) breakdown with consequent increase in vascular permeability that allows plasma compounds to leak into the retina (1). Longstanding hyperglycemia causes oxidative stress, non-enzymatic glycation of proteins, epigenetic changes, and chronic subclinical inflammation that have been considered to play an important role in the development of metabolic memory (2). Chronic hyperglycemia also promotes apoptosis and vascular changes such as increased vascular permeability, vascular occlusion, atherogenesis, BRB dysfunction and dysregulated angiogenesis. Various interacting pathways result in neurodegeneration, apoptosis, pericyte loss, acellular capillaries, vascular endothelial growth factor (VEGF) increase and endothelial dysfunction (3). Disease duration, genetic predisposition, hypertension (HTN), obesity, pregnancy, puberty, smoking, disturbances of lipid metabolism, systemic inflammatory mediators are among the risk factors for diabetic retinopathy (DR). In brief, inflammation, vascular leakage, tight junction breakdown, endothelial cell apoptosis and DME are the biological events in the development of DR.

A significant relationship between retinopathy and serum triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) was found in DR (4). The cohort studies and meta-analysis of the case-control studies suggested a strong relationship between lipid levels and DME, but this relation was not emphasized by the meta-analysis of prospective randomized controlled trials (5). Dyslipidemia induced DR and DME are thought to have different pathologies. It is thought that DME was the result of BRB breakdown and leakage of serum lipids (6) into the intercellular

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spaces as a result of ischaemic or inflammatory process (7) and DR is caused by dyslipidemia induced atherosclerotic changes (8).

It is also known that uric acid (UA) acts as an antioxidant in the early stages of the atherosclerotic process and is the strongest determinant of plasma antioxidant capacity (9). But the levels of serum UA in the advanced stages of the atherosclerotic process rise to 6 mg/dL in women and 6.5-7.0 mg/dL in men, state which paradoxically becomes prooxidant. Studies suggest that increased UA level may be a predictor of vascular impairment in the patients with type 2 diabetes mellitus (T2DM) (10). An elevated UA level is known as a major risk factor for diabetic microvascular diseases (11). In addition a correlation between the intravitreal UA concentrations and the degree of DR was found (12). The existence of a relationship between DME and both serum and intravitreal UA is also known (13).

The adipose tissue is an important source of adipokines which present proinflammatory effects and may be the link between obesity, cardiovascular disease (CVD), diabetes and metabolic syndrome. Adiponectin promotes dilatation of arterioles, increases nitric oxide secretion from endothelial cells and blood flow, and decreases retinal artery resistance. Adiponectin may be transported through the compromised BRB into the aqueous by its receptors (14).

Patients with central macular thickness (CMT) measured as ≥300 μm may undergo intravitreal anti-VEGF (ranibizumab) or steroid injections (15,16). Panretinal photocoagulation (PRP) decreases intraocular promitotic signals and stimulates apoptosis of fibrovascular membranes. PRP is also suggested to have effects to improve DME (17, 18). Intravitreal anti-VEGF injection is less effective in patients with vitreomacular interface (VMI) pathologies compared to patients without VMI. Understanding the cells infiltrating pathologic membranes at the VMI has opened up the possibility of new targets for pharmacotherapy. Vitrectomies for DR remain a vital tool to help relieve tension on the macula by removing membranes, improving edema absorption, and eliminating the scaffold for new membrane formation. Pars plana vitrectomy (PPV) is the choice of surgical intervention to improve anatomical functional results for VMI disorders (19).

In this study our aim was to evaluate the metabolic/systemic factors including serum adiponectin levels (and other laboratory findings) in regressed DR in accordance with CMT values. When we say 'regressed DR', we mention that panretinal laser treatment indication took place, and after completion of the panretinal laser, the existing proliferations regressed, and the eye has no complications of proliferation. We wanted to search if there was a difference between the eyes of a patient whose one of the eyes underwent PPV. In addition, we investigated the relationship between adiponectin lab metabolic profile and CMT.

SUBJECTS AND METHODS

The study included 42 patients aged over 50 years (at a similar rate in both genders) with regressed DR with a minimum follow-up of 6 months at the ophthalmology department between April 2014 and April 2017. In these patients, one of the eyes underwent PPV combined with internal limiting membrane peeling due to VMI disorders with uncomplicated cataract surgery. Following a detailed explanation of the operation and study, written informed consent was obtained from each patient. The cross-sectional observational study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the institutional ethics committee.

Cases with another eye disease that could affect the CMT (such as uveitis, venous thrombosis) and cases with intraocular hemorrhage or previous PPV or optical atrophy that could prevent CMT measurements were all excluded. Patients with thyroid dysfunction, renal diseases (creatinine > 2.0 mg/dL), hepatic failure, heart failure class II or IV NYHA, history of/current use of immunosuppressive agents or systemic steroids and subjects who had hemoglobin <10g/dL were also excluded.

All participants received a complete ophthalmic examination, including an assessment of best corrected visual acuity, biomicroscopic evaluation, intraocular pressure measurement, CMT *via* biomicroscopic fundoscopy and also optical coherence tomography (OCT) at every visit. Forty-two vitrectomized and 42 nonvitrectomized eyes of 42 diabetic patients with regressed DR were included in the study. The mean CMT of the vitrectomized eyes was based on the data of medical records at the 6th month postoperatively. Patients with CMT measured as ≥300 μm underwent intravitreal anti-VEGF ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA) or steroid injections. Patients were examined monthly, intravitreal injections were repeated if they were needed. CMT measurements were acquired through a dilated pupil by an experienced examiner via spectral domain

OCT (Optovue, ARTRue version V 5.1, Optovue Inc. Fremont, CA, USA). The fast macular scanning was used to map macular thickness, and CMT of 1.0 µm was calculated automatically during retinal map analysis.

Use of anti-hypertensive drugs [ACE inhibitors, angiotensin II receptor antagonists (ARBs), calcium channel blockers (CCB), alpha blockers, beta blockers, and diuretics], nonsteroidal anti-inflammatory drugs, acetylsalicylic acid (ASA), insulin, oral anti-diabetics, and statins were all recorded. The patients' gender, age, smoking status, alcohol consumption, and self-reported history of CVD (congestive heart failure, coronary heart disease, heart attack, and stent placement or by-pass surgery), HTN, diabetes duration, medication, anthropometric measurements [weight, height, body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR)], systolic blood pressure (SBP) and diastolic blood pressure (DBP) were all recorded during the blood collection. HTN was accepted as having SBP >130 mmHg and/or DBP >85 mmHg or antihypertensive drug usage (20).

Inflammatory markers [complete blood counts (CBC), C-reactive protein (CRP) and fibrinogen], and metabolic parameters [high-density lipoprotein cholesterol (HDL-C), LDL-C, total cholesterol (TC) and triglyceride (TG), glucose, adiponectin, hemoglobin A1c (HbA1c), urea, total protein, albumin, gamma-glutamyl transferase (GGT)] were measured. Atherogenic index of plasma (AIP) was calculated by $\log_{10}$ (TG/HDL-C) (21).

All subjects had at least 12 hours of fasting before blood sampling for biochemical analysis. Blood samples were processed in a centrifuge at 3000 rpm and stored at -80°C until analysis. In addition to the routine biochemistry tests (glucose, HDL-C, TC, TG, urea, creatinine, UA, total protein, albumin, GGT) serum levels of adiponectin were measured using latex enhanced immunoturbidimetric method (Catalog No: AO 2999, Randox Laboratories Ltd., Crumlin, County Antrim, UK) by means of AU2700Plus (Beckman Coulter Mishima K.K., Shizuoka, Japan). The Analytical range of the adiponectin assay was 0.5 – 40.0 µg/mL. The within-day precision (% coefficient of variation) was found as 1.45 at a value of 5.85 µg/mL (N=17), and it was1.00 at a value of 12.05 µg/mL (N=19).

LDL-C was calculated according to Friedewald formula. HbAIc (%) levels were measured using cation-exchange chromatography by means of ADAMS HA-8180V (Arkray Global Business Inc., Kyoto, Japan). CBC was measured by means of BC 6800 (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, Guangdong, China). Serum CRP levels were measured using nephelometric method by means of Immage 800 (Beckman Coulter Inc, Brea, California, USA) and plasma fibrinogen levels were measured using Clauss method (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) by means of BCS XP.

Statistical analysis was performed using statistics software (SPSS version 15.0, SPSS, Chicago, IL, USA). The normality of the distribution of each of the parameters was checked using the Kolmogorov–Smirnov normality test; all our data were non-normally distributed. The data were presented as mean±SD. The averages of anthropometric and systemic factors were compared using Mann Whitney U. The correlations between CMT and systemic factors were evaluated using the Spearman correlation test. Observations from each eye were divided into two groups according to CMT values as follows; one group with CMT <300µm and the other with CMT≥ 300µm. $P<0.05$ was considered as statistically significant.

RESULTS

Demographic and anthropometric characteristics of the subjects were given in Table 1. Postoperative CMT of both vitrectomized and the fellow (nonvitrectomized) eyes, laboratory findings and systemic arterial pressure values were given in Table 2.

The comparisons of the CMT according to gender, surgery side, smoking, systemic drug and diseases in the subgroups of vitrectomized eyes and the fellow eyes are shown in the Table 3. The mean CMT values of the vitrectomized eyes and fellow eyes did not show any significant difference according to the sex, operated site, smoking, any medication or a history of HTN, T2DM, ischemic heart disease, stent or bypass.

CMT values of the vitrectomized eyes were significantly correlated with AIP, TC, LDL-C, UA ($r=0.354$, $P<0.05$; $r=0.385$, $P<0.05$; $r=0.308$, $P<0.01$; $r=0.396$, $P=0.011$, respectively). On the other hand, CMT values of the fellow eyes were significantly correlated with diabetes duration and serum glucose levels ($r=0.431$, $P=0.011$; $r=0.366$, $P<0.05$, respectively) (Table 4). The relation between adiponectin and CMT was weak in both eyes.

Serum adiponectin levels, adiponectin/BMI and adiponectin/fibrinogen ratios were found significantly higher in the subgroup of eyes with

Table 1. Demographic and anthropometric characteristics of the 42 participants

	Mean ± SD	Median	Range
Age (years)	65.9±6.7	65.5	**51-80**
Diabetic age (years)	18.9±4.5	18	**14-37**
Height (cm)	160±8.9	158.5	**146-175**
Weight (kg)	80.5±12.7	79	**60-105**
BMI (kg/m^2)	31.6±5.4	31.8	**22.8-44.4**
WC (cm)	110±13.9	110	**80-134**
WHR	0.7±0.1	0.7	**0.5-0.9**
	Number of patients positive/negative	Percent	
Gender			
Female	20	47.6%	
Male	22	52.4%	
Vitrectomized eye			
Right	23	55%	
Left	19	45%	
Alcohol consumption	0/42	0%	
Smoking status	10/32	23.8%	
Drugs			
ACE inhibitor	7/35	16.7%	
Alfa blockers	1/41	4%	
Beta blockers	9/33	21.4%	
Insulin	27/15	64.3%	
NSAIs	1/41	2.4%	
ASA	12/20	28.6%	
Diuretics	7/35	16.7%	
OAD	23/19	54.8%	
CCB	10/32	23.8%	
Statins	14/28	33.3%	
ARB	12/30	28.6%	
Systemic diseases			
Hypertension	**31/11**	**73.8%**	
T2DM	**42/0**	**100%**	
CAD	**15/27**	**35.7%**	

Abbreviations: SD= Standard deviation; BMI= Body mass index; WC= waist circumference; WHR= waist-to-hip ratio; ACE= Angiotensin converting enzyme; NSAI= Non-steroidal anti-inflammatory drugs; ASA= Acetylsalicylic acid; OAD= Oral anti-diabetics; CCB= calcium channel blockers; ARB= Angiotensin II receptor blockers; HTN= Hypertension; T2DM= Type 2 diabetes mellitus; CAD= Coronary artery disease.

CMT≥300 μm than in the subgroup with CMT<300 μm in the vitrectomized eyes (P<0.05, P<0.05, P<0.01, respectively, Table 5). Also UA levels were higher in the subgroup of eyes with CMT≥300 μm in the fellow (nonvitrectomized) eyes (6.78±1.56 *vs*. 5.47±1.63; P<0.05).

DISCUSSION

This study determined a significant relationship between CMT of vitrectomized 42 eyes of the patients with regressed DR and AIP, TC, LDL-C and UA levels. When the vitrectomized eyes were subanalyzed according to their CMT values (<300 μm or ≥300 μm), a statistically significant difference was found in serum adiponectin, adiponectin/BMI and adiponectin/fibrinogen. In many studies with Type 1 diabetes mellitus and T2DM, it was concluded that the duration of the disease was a significant risk factor for DR independent of the adequacy of glycemic control (4,10). In this study, we found a significant association between instant glycemia level, duration of diabetes and CMT values in the fellow eyes (without PPV) in the same patient. Contradictory with some studies, we did not find a relationship between duration of diabetes and CMT in vitrectomized eyes although this relation was shown in fellow eyes. We suggest this may be due to the inadequacy of VEGF decrease in non-vitrectomized eyes because of insufficiency of anterior retinal photocoagulation and the ongoing inflammation, growth factors, hormones, etc. The biochemical and vascular alterations in the long time

Table 2. Central macular thickness, laboratory findings and systemic blood pressure of the 42 participants

Parameters	Mean ± SD	Median	Range
CMT- vitrectomized eye (µm)	315.2±133.2	288	168-874
CMT - fellow eye (µm)	337.9±150.2	286	166-890
Adiponectin (µg/mL)	9.3±5.7	7.4	1.6-23.3
Adiponectin/BMI	0.298±0.187	0.32	0.06-0.92
Adiponectin/fibrinogen	0.023±0.014	0.03	0.00-0.06
CRP (mg/dL)	0.6±0.5	0.4	0.1-2.5
HbA1c (%)	7.3±1.3	7.1	5.5-10.5
AIP (log10)	0.51±0.28	0.51	0.02-1.1
HDL-C (mg/dL)	47.7±11.3	47	28-70
LDL-C (mg/dL)	126.4±40.1	125	35-201
TC (mg/dL)	208.4±47.3	199	100,8-307
TG (mg/dL)	164.2±92.3	119	59-379
Glucose (mg/dL)	148.3±74.5	127	77-387
Urea (mg/dL)	56.3±31.5	44	24-158
Creatinine (mg/dL)	0.91±0.33	1	0.55-2.0
UA (mg/dL)	6.0±1.7	6,2	0.9-10.4
Total protein (g/dL)	7.2±0.3	7,3	6.6-7.8
Albumin (g/dL)	4.2±0.3	4,2	3.5-4.7
GGT (U/L)	22.3±10	20	7-48
HGB (g/dL)	13.4±1.8	13.3	10.8-17.6
HCT (%)	41.7±5.6	41.3	35.2-56.8
PLT (x10^9/L)	228.1±62.9	213	90000-380000
WBC (x10^9/L)	8.0±1.8	7.8	5.4-13.1
Fibrinogen (mg/dL)	420.9±76.8	418.1	264.8-558.3
SBP (mmHg)	134.8±18.5	130	100-190
DBP (mmHg)	76.5±12.5	80	60-110

Abbreviations: SD= Standard deviation; CMT= Central macular thickness; BMI= body mass index; CRP= C-reactive protein; AIP= Atherogenic index of plasma; HDL-C= High-density lipoprotein cholesterol; LDL-C= Low-density lipoprotein cholesterol; TC= Total cholesterol; TG= Triglyceride; UA= Uric acid; GGT= Gamma-glutamyl transferase; HGB= Hemoglobin; HCT= Hematocrit; PLT= Platelet; WBC= White blood cell; SBP= Systolic blood pressure; DBP= Diastolic blood pressure.

period make the difference causing macular thickening with the accumulation of some substances beyond DME.

The adverse effects of diabetes may not be reversed when the high blood glucose is corrected, and some may be permanent because of epigenetic changes (22). Many of the local factors in the eye have been removed by surgery, but the altered metabolic and circulatory (systemic) characteristics, oxidative stress, genomic features, proinflammatory factors remain as factors that affect over the years which were shown to be involved in experimental models of hyperglycemic memory (23). Hyperglycemia induced accumulation of chemokines, cytokines, growth factors accompany the severe DR with inflammation and neovascularization (24-26). After vitrectomy most of these substances are supposed to be removed from the tissue, so we can observe the statistically different results between the eyes in the same organism.

The intensive control of HbA1c during diabetes has been shown to have some effects on 'metabolic memory'. The incidence of DME increases when the HbA1c levels increase (18% increase of DME for HbA1c 6.8-9.7% and 36.4% increase of DME for 13.2-19.2%) while a reduction of HbA1c levels with tight glycemic control decreases the rates of DME and other microvascular complications (27). Patients with diffuse retinal thickening were determined to have significantly higher HbA1c levels (28). This could have been due to an initial breakdown of the inner BRB caused by impaired glycemic control. In our study, there was no relationship between CMT and HbA1c values. Although characteristics of our patients presented a mean diabetic age of 18.9 years (range: 14-37 years), HbA1c values were below 10.5% with an average of 7.3±1.3%. We can explain these findings with our small study population and well glycemic control of the diabetics.

The dyslipidemia of T2DM is characterized by high TG and decreased HDL-C levels; and low HDL-C is an independent factor for development of both CVD and diabetes (5-7). The key factors for progression of DR and DME are associated with the duration of diabetes, HTN and dyslipidemia (8, 9). It was revealed that the serum TG, TC and LDL-C levels were significantly elevated in DME when compared to

Table 3. The comparisons of the central macular thickness according to gender, surgery side, smoking, systemic drug and diseases in the subgroups of vitrectomized eyes and the fellow eyes

	Vitrectomized eye				Fellow eye			
Parameters	Range	Median	Mean±SD	*P**	Range	Median	Mean±SD	*P**
Gender								
female	168-874	288	338.9±171.4	0.601	166-890	271.5	353±201	**0.328**
male	186-526	272.5	294.7±87.7		185-589	301	325±92.5	
Surgery side								
Right	168-628	288.5	302.9±145.1	0.629	166-890	282.5	327±165.7	**0.330**
Left	176-874	267	327±153.2		185-665	319	349.4±136	
Smoking								
yes	243-526	307	332.1±91.2	0.912	221-589	334	342±116.5	**0.542**
no	168-874	266	309.8±145.1		166-890	286	336.5±160.7	
ACE inhibitors								
yes	246-390	315	319.6±49.7	0.275	246-589	286	328.1±122.5	**0.967**
no	168-874	263	314.3±145.1		166-890	286	340.4±158.2	
Beta blocker								
yes	176-370	256	270.4±67	0.329	166-665	255.5	291.3±158	**0.071**
no	168-874	290.5	327.8±144.9		221-890	298	351.7±148	
Insulin								
yes	168-874	279.5	330.5±152.7	0.440	185-890	286	337.7±161.1	**0.801**
no	176-526	288	288.8±89		166-665	293	338.3±153.8	
ASA								
yes	199-526	266	310.1±95	0.680	185-665	286	336.9±148.2	**0.985**
no	168-874	288.5	317.1±146.1		166-890	286	338.3±153.8	
Diuretics								
yes	168-874	267	388.3±260.4	0.890	166-890	247	441.6±318.4	**0.777**
no	176-526	290.5	300.2±88.4		185-615	286	320.6±101.5	
OAD								
yes	176-503	292	301.6±77.9	0.655	166-615	275	318.5±138.2	**0.182**
no	168-874	258	332.6±182.6		185-890	342	363.9±166.1	
CCB								
yes	199-503	296	306.9±93.6	0.891	218-615	285.5	320.2±121.8	**0.648**
no	168-874	288	317.9±144.9		166-890	298	345±161.9	
Statins								
yes	168-874	290.5	353.4±190.5	0.527	185-890	281	411.5±225.5	**0.531**
no	176-526	266	295.4±89.3		166-460	286	339.2±124.1	
ARB								
yes	168-874	295.5	360±197.3	0.390	166-890	269	33.5±228.7	**0.271**
no	176-526	266	296.7±94.1		185-665	298	339.2±59.7	
HTN								
yes	168-874	290.5	328.7±138.7	0.093	166-890	285.5	342.2±171.6	**0.290**
no	176-526	220	278.5±114.7		258-421	319	325.7±59.7	
T2DM								
yes	168-874	267	308.5±135	0.130	166-890	285	336.3±159.1	**0.177**
no	260-526	361.5	377.3±110.3		286-399	359	350.8±47.8	
IHD								
yes	186-526	289	298.9±111.4	0.729	248-589	280	345.4±127.4	**0.773**
no	168-874	277.5	318.6±138.5		166-890	286	336±157.4	
By-pass								
yes	186-526	332	348±170.6	0.764	253-349	280	294±49.5	**0.814**
no	168-874	277.5	312.6±132.4		166-890	286	342±156.1	
Stent								
yes	186-292	246	246.8±45.2	0.176	248-589	280	363.2±147.7	**0.706**
no	168-874	295.5	324.7±138.9		166-890	286	333.7±152.7	

Abbreviations: SD= Standard deviation; ACE= Angiotensin converting enzyme; ASA= Acetylsalicylic acid; OAD= Oral anti-diabetics; ARB= Angiotensin II receptor blockers; CCB= calcium channel blockers; HTN= hypertension; T2DM= Type 2 diabetes mellitus; IHD= Ischemic heart diseases.
*Mann-Whitney U test.

Table 4. Correlations between imaging (CMT), laboratory and clinical data of vitrectomized or fellow (nonvitrectomized) eyes of 42 diabetics

		Age (years)	Diabetes duration (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	WC (cm)
CMT	r	0.103	0.034	-0.263	0.004	0.220	0.153
vitrectomized eye	*P*	0.531	0.835	0.097	0.982	0.167	0.341
CMT	r	-0.261	***0.431***	0.267	0.104	-0.050	-0.024
fellow eye	*P*	0.142	***0.011****	0.122	0.551	0.777	0.889
		SBP (mmHg)	DBP (mmHg)	Adiponectin (µg/mL)	CRP (mg/dL)	HbA1c (%)	AIP
CMT	r	0.200	0.242	0.277	0.123	-0.106	***0.354***
vitrectomized eye	*P*	0.209	0.128	0.084	0.443	0.511	***0.027****
CMT	r	0.056	-0.0110	0.015	0.036	-0.022	0.152
fellow eye	*P*	0.750	0.531	0.932	0.835	0.900	0.398
		HDL-C (mg/dL)	LDL-C (mg/dL)	TC (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	Urea (mg/dL)
CMT	r	-0.073	**0.308**	***0.385***	0.277	-0.028	-0.013
vitrectomized eye	*P*	0.654	***0.04****	***0.015****	0.084	0.865	0.938
CMT	r	-0.013	0.013	0.191	0.261	***0.366***	0.026
fellow eye	*P*	0.940	0.941	0.287	0.136	***0.033****	0.883
		Creatinine (mg/dL)	UA (mg/dL)	Total protein (g/dL)	Albumin (g/dL)	GGT (U/L)	HGB (g/dL)
CMT	r	0.146	***0.396***	-0.248	-0.263	0.181	-0.037
vitrectomized eye	*P*	0.368	***0.011****	0.123	0.101	0.262	0.819
CMT	r	-0.022	0.276	0.101	0.010	0.056	0.125
fellow eye	*P*	0.903	0.114	0.568	0.956	0.751	0.473
		HCT (%)	PLT (10^9/L)	WBC (10^9/L)	Fibrinogen (mg/dL)	WHR	
CMT	r	-0.097	0.009	-0.039	-0.191	0.223	
vitrectomized eye	*P*	0.544	0.954	0.810	0.231	0.161	
CMT	r	0.116	-0.300	-0.046	0.079	-0.082	
fellow eye	*P*	0.507	0.080	0.794	0.651	0.064	

Abbreviations: BMI= Body mass index; WC= Waist circumference; CMT= Central macular thickness; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; CRP= C-reactive protein; HbA1c= Hemoglobin A1c; AIP= Atherogenic index of plasma; HDL-C= High-density lipoprotein cholesterol; LDL-C= Low-density lipoprotein cholesterol; TC= Total cholesterol; TG= Triglyceride; UA= Uric acid; GGT= Gamma-glutamyl transferase; HGB= Hemoglobin; HCT= Hematocrit; PLT= Platelet; WBC= White blood cell; WHR= Waist-to-hip ratio. *Spearman correlation.

Table 5. Comparison of adiponectin, adiponectin/body mass index, adiponectin/fibrinogen in subgroups of vitrectomized eyes according to their central macular thickness

	Vitrectomized eyes		
Parameters	CMT <300 µm n=25 eyes	CMT ≥300 µm n=17 eyes	***P****
Adiponectin (µg/mL)			
Mean ± SD	7.09±4.09	11.27±6.13	***0.016***
Range	1.6-20.4	5.5-23.3	
Adiponectin/ BMI			
Mean ± SD	0.23±0.12	0.37±0.23	***0.037***
Range	0.06-0.53	0.17-0.92	
Adiponectin/ Fibrinogen			
Mean ± SD	0.017±0.011	0.028±0.015	***0.006***
Range	0.01-0.04	0.01-0.06	

SD= Standard deviation; CMT= Central macular thickness; BMI=body mass index.
*Mann-Whitney U test.

those without DME (5, 8, 29). Permeability changes in the retinal microvasculature result in extravascular accumulation of lipoprotein deposits, although the exact role in the pathogenesis of DR and DME remains controversial.

In this study, the relation between the mean of adiponectin value and CMT was weak in both eyes. The mean value of adiponectin in the subgroup with CMT≥300μm was higher than the subgroup with CMT<300 μm in vitrectomized eyes. There are conflicting results about the association of adiponectin levels and DR (30, 31). Increased expression of adiponectin may reduce inflammation, endothelial and vascular damage; however adiponectin may also be a proinflammatory mediator at the same time (32-34).

UA is a potent anti-oxidant and can also act as a pro-oxidant that induces oxidative stress on the vascular endothelial cells, thus mediating progression of diabetes related diseases. The studies showed that increased serum UA levels induce growth factors, chemokines, vascular smooth muscle cell proliferation and stimulate oxidative stress which cause aging of the cells and apoptosis (12, 35, 36). Poor glycemic control in T2DM is associated with an increased serum UA level and dyslipidemia, which could be the initial ongoing biochemical change in the complications of diabetes (37). Also, when there is oxidative stress in the organism, such as atherosclerosis, UA levels increase (38). In our study, the mean AIP value of the cases was higher (0.51 ± 0.28) than 0.24, supporting the high risk of CVD, as AIP has been documented to be related directly to the risk of atherosclerosis (39). The high levels of UA in these cases suggested that the prooxidant properties increased because of atherosclerosis.

Ranibizumab studies showed that VEGF is an important target by reducing foveal thickness and improving visual acuity (16, 39, 40). There was a significant correlation between vitreous UA concentration and vitreous VEGF concentration in non-proliferative DR with diabetic cystoids macular edema (13). In the current study, the greatest limitation of this work is that the association between VEGF and UA concentrations of both plasma and intravitreal fluid could not be investigated because of the design of this study.

In conclusion, CMT was related to dyslipidemia, atherogenicity and serum UA levels in vitrectomized eyes, in regressed DR, while it was associated with diabetes duration and level of glycemia, as essential risk factors, in nonvitrectomized eyes. We think that the association of glycemia and diabetes duration with CMT in nonvitrectomized eyes is originated from both systemic and local tissue changes, the inflammatory markers in vitreous, cytokines, growth factors and vascular structural changes. For CMT values over 300μm, higher values of adiponectin levels were shown in subjects with vitrectomized eyes, and higher values of UA levels were shown in subjects with nonvitrectomized eyes. CMT was affected by atherogenicity, prooxidant chemical alterations and inflammation although there was no relationship between CMT and HbA1c values. We also believe that vitrectomy performed at the proper time may be beneficial along with life style changes, good control of diabetes, and intraocular treatments. Further studies are needed to ensure the importance of the determination of UA and adiponectin levels before surgery to predict the atherosclerotic damage and the postoperative CMT value.

Conflict of interest

The authors declare that they have no conflict of interest.

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