Effect of Circulating Omentin-1 on the Retinal Circulation in Patients With Type 2 Diabetes Mellitus

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Purpose. To identify any significant correlations between retinal circulatory parameters and serum concentrations of omentin-1, a novel adipokine produced by adipocytes, in patients suffering from type 2 diabetes mellitus.

Methods. Eighty-seven patients suffering from type 2 diabetes and incipient diabetic retinopathy (DR) were analyzed and further divided into two groups according to sex. We compared the patients' retinal circulatory parameters measured with laser Doppler velocimetry and serum omentin-1 concentrations.

Results. The plasma omentin-1 concentrations were related positively to the retinal blood flow (RBF) ($r = 0.212$; $P = 0.048$) and primarily with female sex ($r = 0.288$; $P = 0.06$) and negatively to the retinal arterial vascular resistance (RVR) ($r = -0.218$; $P = 0.043$). Moreover, the plasma omentin-1 concentration was modestly but not significantly positively related to the blood velocity. Multiple regression analysis showed that the serum omentin-1 level contributed independently and negatively to the RVR.

Conclusions. Increased concentrations of plasma omentin-1 might be linked to elevated RBF levels probably through elevated blood velocity in patients suffering from type 2 diabetes with incipient DR, especially in female patients, which warrants further investigation.

Keywords: retinal blood flow, omentin, diabetic retinopathy

Diabetic retinopathy (DR) is a leading cause of visual loss in working-age individuals worldwide. In particular, most currently available treatments, including laser photocoagulation and vitrectomy, are invasive and do not completely eliminate the risk of blindness in the advanced stage.[1] Therefore, new treatment strategies are needed for early-stage DR. Because the abnormalities of retinal blood parameters have been described in DR,[2–4] altered retinal hemodynamics were thought to contribute to the development and progression of DR. The endocrine nature of adipose tissue has been widely recognized recently. Adipokines, cytokines primarily generated by adipose tissues, are important regulators of metabolic homeostasis.[5] The literature on adipokines as a possible mechanism in the pathogenesis of DR is contradictory,[6–8] but our recent in vitro[9] and human[10] studies have found that adiponectin, among the adipokines, regulates the retinal circulation. Overall, improvement of the altered retinal microcirculation by adipokines, such as adiponectin, might guard against development and progression of DR.

Omentin is a recently identified adipokine that is preferentially generated by visceral adipose tissue.[11] Moreover, serum adiponectin levels are correlated with circulating levels of omentin-1, the major circulating form of omentin.[12] Omentin-1 also has many beneficial effects that are similar to those of adiponectin.[11,13–15] A clinical study of patients suffering from diabetes mellitus (DM) reported that the serum and vitreous omentin-1 levels were related to the severity of DR,[16] and experimental investigations have shown that omentin has a potent vasodilatory effect on isolated vessels mediated by endothelium-derived nitric oxide (NO),[14] a strong vasodilator of the retinal arterioles.[17] These observations indicated that omentin-1 might affect the retinal vessel parameters in patients with type 2 DM.

Generally, the sex difference in circulating adipokines is related to sex hormones[18] and body fat distribution.[19] Indeed, we found recently that serum adiponectin concentrations were associated positively with the retinal blood flow (RBF) in men suffering from type 2 DM but not in women.[10] However, the adipokines that affect the retinal microcirculation in female patients have not been identified fully. Whereas, reduced serum omentin levels also have been linked to female insulin resistance status, such as in pregnancy[20] and polycystic ovary syndrome.[21] Therefore, omentin might affect the retinal circulation in women suffering from type 2 DM.

However, it has not been clarified fully whether the plasma omentin levels affect the retinal microcirculation in patients suffering from type 2 DM and if sex differences affect the relationship between serum omentin and retinal microcirculation. Therefore, we investigated the relationship between the serum omentin-1 concentrations and retinal circulation in patients suffering from type 2 DM and the effect of sex on the relationship between omentin-1 and retinal vessel parameters in patients suffering from type 2 diabetes.

Methods

Subjects

We enrolled 143 consecutive native Japanese patients suffering from type 2 DM that were diagnosed based on the criteria of the American Diabetes Association.[22] All patients had visited

our hospital at least once from September 2013 to August 2015. The study adhered to the tenets of the Declaration of Helsinki. The ethics committee of our institution approved the study protocol. All patients provided informed consent before they were included in the study. All patients could be followed. Diabetes was established based on the use of antidiabetes medication or a fasting blood glucose level higher than 140 mg/dL. Patients were considered to be hypertensive when the blood pressure (BP) was over 140/90 mm Hg or they were on drugs for hypertension.[23] Dyslipidemia was diagnosed if the low-density lipoprotein (LDL) cholesterol level was above 140 mg/dL and/or the high-density lipoprotein (HDL) cholesterol level was below 40 mg/dL and/or the triglyceride level was above 140 mg/dL or the patient was being treated with hypolipidemic agents.[24]

The spot urine albumin-to-creatinine ratio (ACR; mg/g creatinine) was used to determine if albumin was excreted in the urine. Based on this ratio, the stage of diabetic nephropathy was classified. Stages I (normo-), II (micro-), and III (macroalbuminuria) were defined as having an ACR below 30, 30 to 300, or above 300, respectively, and an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2. A Hitachi 747 biochemistry analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan) was used to measure the serum creatinine levels within 4 hours of fasting venous blood collection. Renal function also was evaluated based on the eGFR, which was calculated as reported previously.[25] The stages of chronic kidney disease (CKD) were based on the stages established by the National Kidney Foundation Disease Outcomes Quality Initiative Clinical Practice Guidelines.[26]

We excluded patients who had uncontrolled diabetes (hemoglobin [Hb] A1 > 10.0%), uncontrolled hypertension (BP > 140/90 mm Hg), acute renal failure, chronic glomerulonephritis, interstitial nephritis, and cardiovascular diseases, stage 3 CKD, macroalbuminuria, proteinuria, or hemodialysis in proportion to our previous report.[27] Our institutional specialists diagnosed and were masked to the results of the ocular examinations.

A standard ophthalmologic examination was performed in all patients before the RBF was measured. All patients had a visual acuity (VA) of 20/20 or better and an IOP measured with Goldmann applanation tonometry below 20 mm Hg. The VA was evaluated using Snellen equivalents based on the Early Treatment Diabetic Retinopathy Study charts. After pupillary dilation with a 0.5% tropicamide eye drop, a well-trained ophthalmologist, who was masked to the status of the RBF, assessed the DR at each visit. The severity of the DR was determined for each eye based on grading of the seven standard photographic fields[28] once when the patients entered the study; the DR severity was classified none, mild nonproliferative DR (NPDR), moderate-to-severe NPDR, or proliferative DR (PDR).[29] Patients who were classified with the last two and had clinically relevant macular edema were excluded from the study. The severity in the worse eye was used; if both eyes had equally severe DR, one eye was chosen randomly. The ophthalmologic exclusion criteria were a history of previous intravitreal injections, laser photocoagulation, or intraocular surgery, moderate-to-severe cataract, vitreous hemorrhage, tractional retinal detachment, and moderate-to-severe refractive errors (> 3.0 diopters).

RBF Measurements

The RBF was measured after the ocular examination. The subjects were instructed to avoid caffeinated drinks for a minimum of 12 hours before the measurement was performed. A retinal laser Doppler velocimetry (LDV) system (Canon Laser Blood Flowmeter, Model CLBF 100; Canon, Tokyo, Japan) was used to estimate the blood flow in the superior branch of the first-order major temporal retinal artery. The details of the system methodology were reported previously.[30]

Based on the bidirectional LDV, the system facilitates noninvasive measurement of the absolute values of the red blood cells that flow in the centerline of the vessel.[30] The mean retinal blood velocity (V_{mean}) was defined as the velocity of the averaged maximal speed during one cardiac cycle. Computer analysis of the signal produced by the arterial image on the array sensor using the half-height of the transmittance profile to define the vessel edge automatically determined the retinal arterial diameter.[30] There had been no change in medication by the patients with DM for a minimum of 6 months before the RBF was measured.

Assay

An enzyme-linked immunosorbent assay kit (BioVendor, Brno, Czech Republic) was used to measure the plasma omentin-1 concentrations.

Calculations

We used the following formula to calculate the RBF:

$$RBF = V_{mean} \times \text{area} \quad (1)$$

where V_{mean} is the mean velocity of the averaged maximal speed/2, and area is the cross-sectional area of the retinal artery at the LDV measurement site.[30] We also used the following formulas: mean arterial BP (MABP) = diastolic BP + (systolic BP–diastolic BP)/3[30]; ocular perfusion pressure (OPP) = 2/3(MABP) − IOP[31]; retinal arterial vascular resistance (RVR) = OPP/RBF[17]; and wall shear rate (WSR), as an index of shear stress, was calculated with a Poiseuillean parabolic model of velocity distribution across the arterial = $8 \times V_{mean}/D$,[30] where D indicates diameter.

Statistical Analysis

The data are expressed as the mean ± SD. The normal distribution of the data was controlled with the Kolomogorov-Smirnov test. The Mann-Whitney *U* test (for continuous data) or the χ^2 statistics (for categoric data) was adopted for comparisons between two groups. To assess how omentin-1 affected the retinal circulation, the correlations between plasma omentin-1 and the retinal circulatory parameters were evaluated using Pearson's statistics. If significant relationships of plasma omentin-1 for the retinal circulatory parameters were found by correlation analysis, further regression analyses were conducted. Standardized regression coefficients from multiple regression analysis of the retinal circulatory parameters in relation to various factors including omentin-1 were analyzed. To investigate this analysis, according to our previous studies,[31,32] we entered age, HbA_{1C}, duration of diabetes, plasma glucose, body mass index (BMI), BP, heart rate (HR), IOP, OPP, LDL, eGFR, and omentin-1. The variables with a *P* less than 0.2 determined by Pearson's statistics then were entered into the multiple regression analysis.[33] We also checked any correlations among variables to eliminate any possible complications resulting from multicollinearity. In the event of a high correlation ($r > 0.7$) among two variables, we chose one of two variables. Statistical significance was considered to be *P* less than 0.05.

Results

There were 87 consecutive native Japanese patients (45 men, 42 women; mean age ± SD, 59.0 ± 10.1 years) suffering from type 2 DM enrolled.

Table 1. Characteristics of Patients Suffering From Type 2 Diabetes With Incipient Diabetic Retinopathy

Parameter	All Patients $N = 87$	Men $N = 45$ (52%)	Women $N = 42$ (48%)	P Value*
Mean age, y	59.0 ± 10.1	59.6 ± 10.0	58.5 ± 10.2	0.38
Hemoglobin A_{1C}, %	7.2 ± 1.1	7.2 ± 1.3	7.2 ± 0.9	0.39
Duration of diabetes, y	10.1 ± 8.8	10.7 ± 9.8	9.6 ± 7.7	0.92
Plasma glucose, mg/dL	157.8 ± 56.0	157.0 ± 48.8	158.6 ± 63.3	0.70
BMI	26.2 ± 5.8	25.6 ± 4.9	26.9 ± 6.7	0.36
Systolic BP, mm Hg	132.4 ± 15.9	132.2 ± 14.6	132.6 ± 17.9	0.91
Diastolic BP, mm Hg	75.1 ± 10.1	76.2 ± 10.5	74.1 ± 9.6	0.42
Mean BP, mm Hg	94.2 ± 10.7	94.8 ± 10.5	93.6 ± 10.9	0.64
HR, beats/min	72.4 ± 11.8	70.7 ± 12.3	74.3 ± 11.2	0.10
IOP, mm Hg	14.4 ± 2.6	14.5 ± 2.9	14.3 ± 2.3	0.79
OPP, mm Hg	48.4 ± 7.0	48.7 ± 7.2	48.1 ± 6.8	0.66
Total cholesterol, mg/dL	180.4 ± 28.0	176.0 ± 26.0	185.1 ± 29.6	0.18
Triglycerides, mg/dL	131.5 ± 58.8	125.4 ± 54.1	138.0 ± 63.5	0.39
HDL, mg/dL	50.8 ± 11.1	48.5 ± 9.3	53.4 ± 12.3	0.06
LDL, mg/dL	109.7 ± 27.1	109.6 ± 28.3	109.9 ± 26.1	0.80
Blood urea nitrogen, mg/dL	14.4 ± 3.3	14.3 ± 2.9	14.4 ± 3.7	0.72
Creatinine, mg/dL	0.66 ± 0.15	0.77 ± 0.11	0.54 ± 0.08	<0.01
eGFR, mL/min/1.73m^2	86.2 ± 16.8	82.1 ± 13.0	90.6 ± 19.2	0.06
Omentin-1, ng/mL	492.1 ± 147.8	480.5 ± 166.8	504.6 ± 125.2	0.27
Insulin use, *n* (%)	23 (26)	10 (22)	13 (31)	0.36
Oral antidiabetic drug, *n* (%)	81 (93)	37 (82)	38 (90)	0.26
Hypertension, *n* (%)	44 (51)	23 (51)	21 (50)	0.92
Dyslipidemia, *n* (%)	51 (59)	21 (47)	30 (71)	0.02
Medications				
β-antagonist, *n* (%)	5 (6)	3 (7)	2 (5)	0.70
ACE inhibitor, *n* (%)	2 (2)	2 (4)	0 (0)	0.17
Angiotensin II type 1 receptor blocker, *n* (%)	23 (26)	12 (27)	11 (26)	0.96
Calcium channel antagonist, *n* (%)	24 (28)	15 (33)	9 (21)	0.21
Diuretic, *n* (%)	2 (2)	2 (4)	0 (0)	0.17
Statin, *n* (%)	36 (41)	14 (31)	22 (51)	0.04
Thiazolidinediones	16 (18)	7 (16)	9 (21)	0.48
Metformin	35 (40)	19 (42)	16 (38)	0.70
Dipeptidyl peptidase-4 inhibitor	34 (39)	21 (46)	13 (31)	0.13

* P values comparing men and women.

Tables 1 and 2, respectively, show the baseline clinical characteristics and retinal circulatory parameters in patients suffering from type 2 DM. There were no significant differences in any parameters except creatinine between the men and women. Men had higher creatinine values compared with women.

Pearson's correlation analysis showed that the serum omentin-1 concentrations were positively related to the RBF ($r = 0.212$; $P = 0.048$) and negatively to the RVR ($r = -0.218$; $P = 0.043$) (Fig. 1, Table 3). This effect of RBF was associated strongly with female sex, although this result did not reach significance ($r = 0.288$; $P = 0.06$). Moreover, the plasma omentin-1 was modestly but not significantly ($r = 0.201$; $P = 0.06$) positively related to the blood velocity. However, the plasma omentin-1 concentrations were not correlated significantly with the vessel diameter or WSR in all patients with incipient DR (Fig. 1, Table 3). In addition to the serum omentin-1, the RVR remained correlated positively ($P < 0.001$, $P = 0.04$, $P = 0.01$, respectively), with the BP and LDL and negatively with age (Table 4). Multiple regression analysis showed that the RVR was correlated negatively ($P = 0.018$) with the serum omentin-1 concentration and positively ($P = 0.0002$) with the mean BP (MBP) but was not related significantly with age or LDL (Table 5). Correlative statistics were not established among RBF and any independent parameters.

Table 2. Retinal Circulatory Parameters

Parameter	All Patients $N = 87$	Men $N = 45$	Women $N = 42$	P Value*
Vessel diameter, μm	111.0 ± 9.2	109.7 ± 10.3	112.3 ± 7.6	0.28
Blood velocity, mm/s	35.2 ± 9.5	34.4 ± 10.5	36.0 ± 8.4	0.22
RBF, μL/min	10.3 ± 3.2	9.9 ± 3.6	10.7 ± 2.7	0.18
RVR, mm Hg min/μL	5.2 ± 2.0	5.6 ± 2.5	4.7 ± 1.3	0.10
WSR, s^{-1}	1277 ± 363	1262 ± 390	1293 ± 337	0.50

* P values comparing men and women.

Discussion

Many reports already have shown that alterations of the retinal circulatory parameters occur in patients with diabetes.[2–4] Actually, the RBF was reported to be significantly lower in patients suffering from type 2 DM with incipient DR compared with nondiabetic control subjects.[31] Thus, the changes in the RBF might be related to the presence of retinopathy. Moreover, a previous study using the blue light entoptic phenomenon reported that the RBF velocity in the capillaries was reduced in

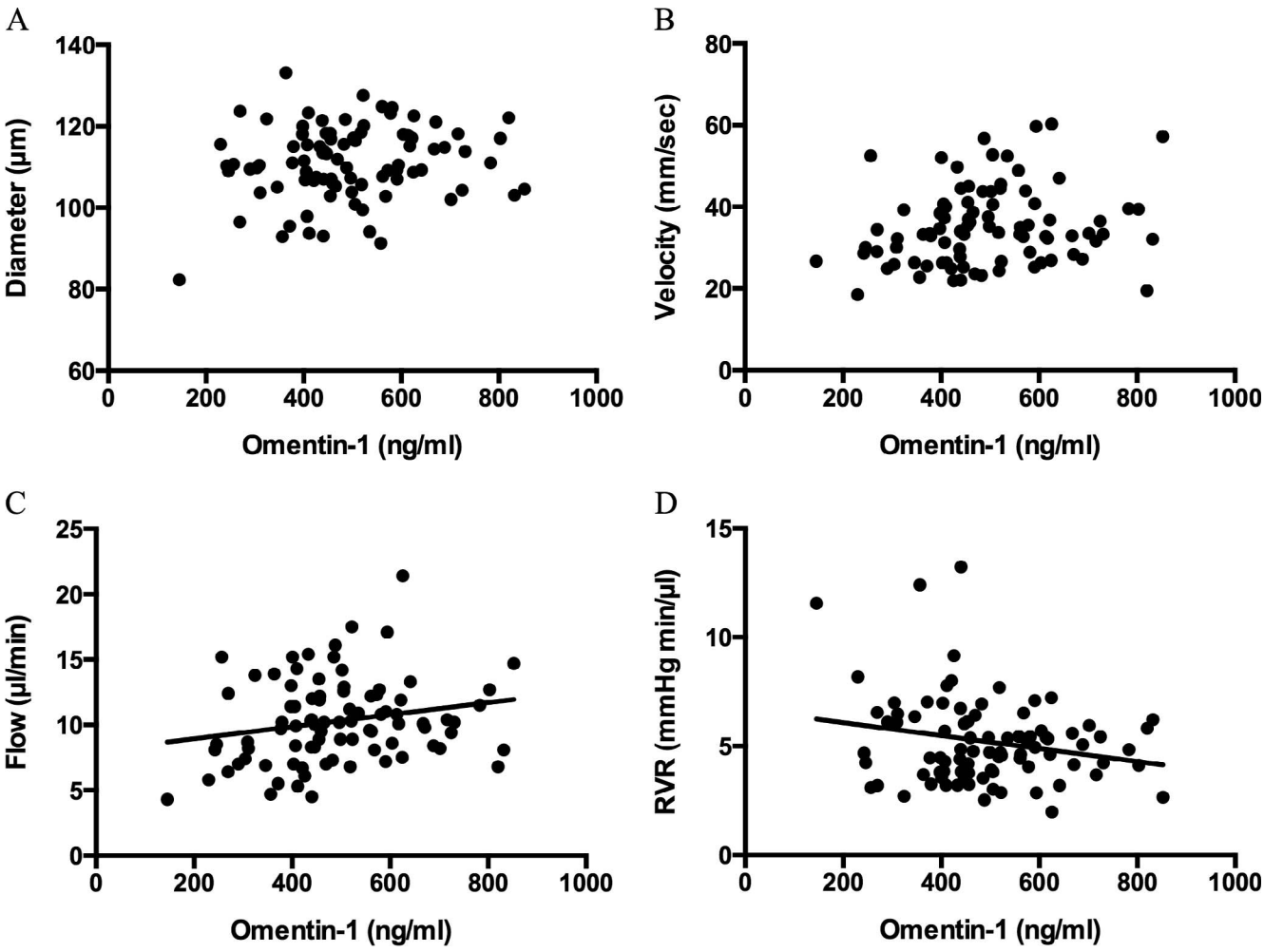

FIGURE. The association between the serum omentin-1 concentrations of the retinal circulatory parameters in patients suffering from type 2 DM with incipient DR. The serum omentin-1 concentration is not significantly related to (**A**) vessel diameter and (**B**) blood velocity, but is significantly positively related to (**C**) retinal blood flow ($r = 0.212$; $P = 0.048$; 95% confidence interval [CI], 0.002–0.405) and negatively to (**D**) retinal arterial vascular resistance (RVR) ($r = -0.218$; $P = 0.043$; 95% CI, −0.410 to −0.008).

the preproliferative DR group compared with the background DR group.[34] Another study using video fluorescein angiography found that the RBF was correlated with progressing nonproliferative retinopathy levels.[3] A disrupted RBF in progressing retinopathy might be expected.

The current study showed, for the first time, that the plasma omentin-1 level was positively and significantly correlated with the RBF in patients suffering from type 2 DM with no and mild DR, and this was associated primarily with female sex (Fig. 1, Table 3). But, because cross-sectional study is limited for assessing causal relationships, the result might not reflect the direct effect of omentin-1 on the retinal circulation. Future prospective, longitudinal studies are needed to clarify the relationship between serum omentin-1 and retinal circulation in patients suffering from type 2 diabetes.

The current study also showed that the plasma omentin-1 concentration had a modest but not significantly positive relation to the blood velocity and was not related significantly to the vessel diameter (Fig. 1, Table 3). A previous report showed that omentin caused vasorelaxation of the rat mesenteric artery, which is thought to be the resistance artery.[14] Moreover, omentin-1 increased phosphorylation of

TABLE 3. Pearson's Correlation of Omentin-1 with Retinal Circulatory Parameters in Patients Suffering from Type 2 Diabetes with Incipient Diabetic Retinopathy

	All Patients		Men		Women	
	r	*P* Value	*r*	*P* Value	*r*	*P* Value
Vessel diameter, μm	0.161	0.14	0.136	0.37	0.181	0.25
Blood velocity, mm/s	0.201	0.06	0.177	0.24	0.228	0.15
RBF, μL/min	0.212	0.048	0.162	0.29	0.288	0.06
RVR, mm Hg min/μL	−0.218	0.043	−0.230	0.13	−0.147	0.35
WSR, s^{-1}	0.158	0.14	0.146	0.34	0.170	0.28

Table 4. Characteristics of Patients Suffering From Type 2 Diabetes With Early-Stage DR and the Correlation Between Retinal Circulatory Parameters and Various Systemic and Ocular Parameters

	RBF		RVR	
Variable	*r*	*P* Value	*r*	*P* Value
Age	0.151	0.16	−0.266	0.01
Hemoglobin A_{1C}	0.047	0.67	−0.067	0.54
Duration of diabetes	0.137	0.21	−0.127	0.24
Plasma glucose	−0.148	0.17	0.189	0.08
BMI	−0.074	0.49	0.173	0.11
Systolic BP	−0.015	0.89	0.298	0.005
Diastolic BP	−0.037	0.31	0.429	<0.001
Mean BP	−0.030	0.78	0.419	<0.001
HR	−0.069	0.52	0.143	0.18
IOP	−0.046	0.67	0.075	0.49
OPP	−0.014	0.90	0.400	<0.001
LDL	−0.181	0.09	0.217	0.04
eGFR	0.038	0.72	−0.028	0.80
Omentin-1	0.212	0.048	−0.218	0.043

endothelial NO synthase (eNOS) leading to NO production in cultured human umbilical vein endothelial cells.[35] Thus, because it is possible that omentin-1 relaxes the resistance arteriolar vessels, omentin-1 might contribute to increasing upstream blood flow velocity followed by attenuated resistance with vasorelaxation of more peripheral retinal arterioles compared with the first-branch retinal arterioles observed in the current study. In this study, omentin-1 also was associated negatively with the RVR (Fig. 1, Table 3); however, due to the cross-sectional design of our study, further investigation is warranted.

Low-density lipoprotein is particularly susceptible to oxidative modification, and oxidized LDL can impair the vasomotor function of the coronary arterioles,[33] which are considered to be resistance vessels.[36] Because oxidized LDL can reduce eNOS protein expression in human umbilical vein endothelial cells,[37] oxidized LDL might elicit vasoconstriction of the resistance site in the retinal circulation. It is possible that LDL might cause vasoconstriction at the retinal resistance site, but because our study was cross-sectional, future studies should consider a longitudinal or prospective approach to examine the relationship between LDL and the retinal circulation.

Age was associated significantly with the RVR only by univariate analysis and not multivariate analysis (Tables 4, 5). Age was correlated positively with the increased maximal-to-minimal velocity ratio, which can reflect loss of compliance of the retinal vasculature in patients suffering from types 1 and 2 diabetes.[38] Thus, although any causative interpretations derived from this cross-sectional study should be considered with caution, the vessel rigidity of the retinal circulation can increase with aging in patients suffering from type 2 diabetes. However, we reported previously that the RVR in healthy subjects did not differ significantly among young, middle-aged, and elderly patients.[32] Overall, the RVR in response to aging might differ between healthy subjects and patients with DM.

Table 5. Standardized Regression Coefficients From Multiple Linear Regression Analysis of Retinal Circulatory Parameters in Relation to Independent Variables in 87 Patients Suffering From Type 2 Diabetes

Variable	RBF	RVR
Omentin-1	0.186 (0.08)	−0.236 (0.018)
LDL	−0.124 (0.26)	0.108 (0.28)
Plasma glucose	−0.134 (0.21)	0.101 (0.30)
Age	0.095 (0.39)	−0.146 (0.16)
MBP		0.396 (0.0002)
BMI		0.092 (0.36)
HR		−0.055 (0.59)
	$r^2 = 0.096$, $P = 0.08$	$r^2 = 0.306$, $P = 0.0001$

Our experimental research in cats showed that the RVR decreased in response to reduced OPP caused by reduced systemic BP over the lower limit of flow autoregulation.[39] Due to impaired autoregulation of the RBF in patients suffering from type 1 DM,[40] diabetes-induced dysfunction might be connected to the observation that the RVR was positively correlated with the MBP and OPP (Table 5).

Multiple regression analysis showed that the plasma omentin-1 level was independently and negatively related to the RVR (Table 5). The RVR is affected by changes in the OPP and RBF, and the OPP also was calculated from the systemic BP and IOP. Because plasma omentin-1 concentrations were not associated significantly with the IOP (Pearson's correlation, $r = -0.038$, $P = 0.72$; data not shown), omentin-1 can affect the RVR by changes in the systemic BP in addition to the retinal parameters. Indeed, omentin-1 was associated negatively with the systemic BP in patients with the metabolic syndrome.[41] Furthermore, omentin inhibited noradrenaline-induced increases in the mean BP in rats.[42] Although serum omentin-1 levels were not correlated significantly with the mean BP in the current study (Pearson's correlation, $r = 0.116$, $P = 0.28$; data not shown), we speculated that omentin-1 affects the RVR by altering systemic conditions and local ocular factors in the retinal circulation.

The serum omentin-1 concentration was related positively to the RBF, which was largely associated with female sex (Table 3). Indeed, the plasma omentin-1 concentration was associated significantly with the HDL cholesterol, which was primarily associated with male sex.[43] Although the relationship between omentin-1 and HDL cholesterol is unclear, dysregulation of omentin might affect the insulin signal, resulting in altered HDL production.[44,45] Thus, sex differences in the reaction of omentin might depend on tissues and organs. However, a specific omentin receptor has not been identified. Although it is difficult to define sex differences in the expression of the omentin receptor, sexual dimorphism might exist in the sensitivity to omentin-1 in the retinal microcirculation.

The current study had several limitations. First, the results of the cross-sectional design limit inferences about the causality effect of this study. A prospective study should explore the relationship of serum omentin-1 concentrations on the retinal circulatory parameters in type 2 DM. Second, we could not evaluate the effects of systemic medications on the retinal circulation. Clinical studies have shown that several widely used glucose-lowering medications, such as metformin and the thiazolidinediones increase the circulating omentin-1 concentrations.[15,46] Thus, further investigations of systemic medications that can affect the plasma omentin-1 concentrations are needed. Third, we did not assess other adipokines, specifically adiponectin. Although serum brain natriuretic peptide is correlated with the serum adiponectin level[47] but not the serum omentin level in patients with heart failure,[48] omentin-1 has insulin-sensitizing,[11] anti-inflammatory,[13] vasodilative,[14] and cardioprotective effects,[15] similar to those of adiponectin as described by most reports. One study already reported that plasma omentin-1 levels were related positively to the adiponectin levels.[12] Thus, regulation of omentin-1 might depend on adiponectin. However, due to the cross-sectional design of our study, we cannot prove a causal relationship between omentin-1 and adiponectin. Therefore, interventional studies are needed to explore whether there is

any direct interplay or underlying linking mechanism between these two bioactive molecules. Fourth, we did not measure the serum sex hormone levels or check the menopausal status of the female patients. Previous reports have showed that sex hormones affect omentin-1 regulation.[18,49] Indeed, other studies have found that serum omentin-1 levels differed significantly between sexes in various clinical populations.[12,50] Although the current serum omentin-1 concentrations were similar between sexes, the relationships between sex hormones and omentin regulation need further analysis in a larger study. Finally, this study did not include healthy control subjects, because the focus of this study was to assess the relationship between circulating omentin-1 levels and retinal vessel parameters in patients suffering from type 2 diabetes. A healthy control group should be incorporated into the design of future studies.

In summary, the current findings showed that the plasma omentin-1 concentration was correlated positively with the RBF in patients suffering from type 2 DM and was associated predominantly with female sex. These findings suggested that omentin-1 might affect the RBF in early-phase DR, especially in women, which warrants further investigation. The RBF is impaired in early-stage DR in patients suffering from type 2 DM, indicating the importance of appropriately managing serum omentin-1 levels through lifestyle changes and appropriate pharmacotherapy.

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