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Plasma omentin levels are associated with vascular endothelial function in patients with type 2 diabetes at elevated cardiovascular risk

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ABSTRACT

Aims: Omentin is an adipokine that has protective effects against cardiovascular damage. Previous studies showed an inverse relationship between omentin and obesity, diabetes, and cardiovascular disease. This study aimed to investigate the association between omentin and vascular endothelial function in patients with type 2 diabetes (T2D).

Methods: The subjects were 425 patients with T2D and 223 non-diabetic controls. Fasting plasma omentin levels were measured by enzyme-linked immunosorbent assay, and the endothelium-dependent, flow-mediated dilatation (FMD) was measured by ultrasonography.

Results: Plasma omentin levels were higher, while FMD was lower in participants with T2D than in non-diabetic controls. No significant correlation was found between plasma omentin levels and FMD in either non-diabetic controls or participants with T2D on multivariate analysis. However, stratified analysis in T2D patients revealed that plasma omentin levels were independently and positively associated with FMD in high cardiovascular risk subgroups according to age (≥65 years), estimated glomerular filtration rate (<60 mL/min/1.73 m^2), or preexisting cardiovascular diseases but not in low-risk subgroups.

Conclusions: Plasma omentin levels are independently associated with endothelial function in subgroups of patients with T2D at elevated cardiovascular risk. This study suggests a protective role of omentin against endothelial dysfunction, particularly in high-risk patients.

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1. Introduction

Increased adipose tissue, especially in the abdominal cavity, underlies the development of metabolic disorders and atherosclerotic cardiovascular diseases (CVDs) [1,2]. Accumulating evidence indicates that adipose tissue produces and secretes bioactive mediators termed adipokines, which play a causal role in the link between obesity and metabolic disorders and atherosclerotic CVDs [1–3]. While a large number of adipokines, such as leptin, tumor necrosis factor-α (TNF-α), interleukin-6, and monocyte chemotactic protein-1, exert a pro-inflammatory action to progress obesity-related metabolic and cardiovascular disorders [1,2], several adipokines, including adiponectin, C1q/TNF-related proteins, and omentin, are suggested to exert beneficial effects on these disorders [2,3].

Omentin, first identified as a galactofuranose-binding lectin, or intelectin-1 [4], is abundantly expressed in human visceral adipose tissue and enhances insulin action in human adipocytes *in vitro* [5]. Previous studies in humans showed that circulating omentin levels are decreased in obesity [6,7], metabolic syndrome [8], and type 2 diabetes (T2D) [7,9,10] and are inversely correlated with parameters of obesity, insulin resistance, and metabolic risk factors [6,7,9,11]. Several lines of evidence from animal studies indicate the protective effects of omentin against cardiovascular damage [3,12] through its actions on vascular endothelium [13–15], smooth muscle cells [16], macrophages [17], and cardiomyocytes [18].

Consistent with the experimental evidence, circulating omentin levels were shown to be decreased in patients with coronary artery disease [19–21] and established carotid atherosclerosis [22]. Circulating omentin levels were also inversely correlated with carotid intima-media thickness in healthy subjects [23] and patients with metabolic syndrome [8] and were positively associated with endothelium-dependent, flow-mediated vasodilatation (FMD) in a non-diabetic population [24].

Since omentin levels are dysregulated in obesity, diabetes, and atherosclerosis, the association between omentin and atherosclerosis might be complicated in the T2D population. A recent study showed that serum omentin levels were inversely associated with arterial stiffness and carotid plaque in patients with T2D [10]. However, no other study has examined the relationship between omentin and subclinical atherosclerosis in patients with T2D. Therefore, the present study aimed to investigate the association between plasma omentin levels and vascular endothelial dysfunction, an early surrogate for CVD [25], in Japanese patients with T2D.

2. Materials and methods

2.1. Study design and subjects.

We consecutively enrolled 425 patients with T2D who were admitted to the Diabetes Center of the Osaka City University Hospital for the purpose of glycemic control, education, and/or evaluation of diabetic complications between January 2009 and July 2014. T2D was diagnosed based on the criteria of American Diabetes Association [26] and Japan Diabetes Society [27]. Patients with type 1 diabetes or other types of diabetes were not included in this study. We also sequentially included 250 participants from the MedCity21 Health Examination Registry who underwent comprehensive medical examinations at MedCity21 of the Osaka City University Hospital Advanced Medical Center for Preventive Medicine between June 2015 and November 2017. Among the participants, 192 subjects had normal glucose tolerance, 31 subjects had impaired glucose tolerance, and 27 subjects had diabetes, which was defined according to a 75 g oral glucose tolerance test. We finally enrolled 223 participants as non-diabetic controls in the present study. A smoker was defined as a current smoker or an ex-smoker. Preexisting CVDs, including coronary artery disease, cerebrovascular disease, or peripheral artery disease, were confirmed by medical records. The presence of diabetic microangiopathy, including retinopathy (simple, preproliferative, or proliferative retinopathy), nephropathy (microalbuminuria, macroalbuminuria, or eGFR less than 30 mL/min/1.73 m^2), or neuropathy (peripheral or autonomic neuropathy) was also confirmed by medical records.

This study was performed in accordance with the Declaration of Helsinki (1975, as revised in 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (The Japanese Ministry of Health, Labour and Welfare, 2014). The study protocol was approved by the ethics committee of the institution (number 3909). All study participants provided written informed consent.

2.2. Physical and laboratory measurements

Blood pressure was determined using an automatic sphygmomanometer with a conventional cuff after the subjects had rested for at least 5 min. Blood was drawn after an overnight fast and biochemical parameters were analyzed using a standard laboratory method at the Central Clinical Laboratory of the Osaka City University Hospital [28,29]. Glycated hemoglobin A1c (HbA1c) was assessed as the National Glycohemoglobin Standardization Program equivalent value (NGSP, %) according to the guidelines of Japan Diabetes Society [27]. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese eGFR equation [30]. Immunoreactive insulin levels were measured for all the non-diabetic subjects and T2D patients not receiving insulin therapy (n = 463) by electrochemiluminescence immunoassay [Cobas 8000(502/602), Roche Diagnostics, K.K., Tokyo, Japan]. Homeostasis model assessment of insulin resistance (HOMA-R) was calculated according to the following formula: fasting insulin (μU/mL) × fasting glucose (mg/dL)/405 [31].

Fasting plasma levels of human omentin-1 (BioVendor, Candler, NC, USA) and human total adiponectin (Otsuka, Tokyo, Japan) were measured using an enzyme-linked immunosorbent assay following the manufacturer's instructions. The intra- and interassay coefficients of variation for human omentin were <5% and <5%, respectively, whereas those of adiponectin were <10% and <10%, respectively.

2.3. Assessment of vascular endothelial function.

We assessed vascular endothelial function by FMD of the brachial artery. FMD was measured according to the International Brachial Artery Reactivity Task Force guidelines [32] and the Japanese guidelines of the Vascular Failure Workshop Group [33] using a vascular ultrasound system equipped with an edge-tracking system for 2D imaging and a pulsed Doppler flow velocimeter for automatic measurement (UNEXEF; Unex Co. Ltd,. Nagoya, Japan), as we have previously described [28,34]. In brief, a diameter of the brachial artery at rest was measured in the cubital region, and, subsequently, the cuff was inflated to 50 mmHg above systolic blood pressure for 5 min and deflated. The diameter at the same point of the artery was monitored continuously, and the maximum dilatation from 45 to 60 s after deflation was recorded. FMD was calculated as follows: FMD (%) = (maximum diameter − diameter at rest) × 100/diameter at rest.

2.4. Statistical analysis.

Data are expressed as the number (%) or median [interquartile]. For comparisons between non-diabetic and diabetic subjects, the χ^2-test or Wilcoxon rank-sum test was performed as appropriate. Skewed parameters, such as HOMA-R, triglycerides, adiponectin, and omentin levels, were logarithmically transformed before regression analysis. Determinants for log [omentin] or FMD were explored by multiple regression analysis with adjustment for age, sex, log [adiponectin], and possible covariates including drug use in all subjects, non-diabetic controls, and participants with T2D. To assess whether the effect of plasma omentin levels on FMD is modified by age, eGFR, or preexisting CVDs in T2D patients, the interaction term between log [omentin] and age, eGFR, or preexisting CVDs (yes = 1, no = 0) was inserted into the multiple regression analysis model. A p-value of < 0.20 was considered significant for interaction, as has been used in previous studies [35,36], and a p-value of < 0.05 was considered significant for all other analyses. Statistical analyses were performed using the JMP 10 software program (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Clinical characteristics, plasma omentin levels, and FMD of the participants.

The clinical characteristics of the total population, as well as of the non-diabetic controls and participants with T2D are shown in Table 1. The median age, body mass index (BMI), and eGFR of the total population were 62 years, 23.9 kg/m^2, and 71.1 mL/min/1.73 m^2, respectively. Participants with T2D were older than non-diabetic controls and had a median of 11 years of disease duration. As expected, BMI, systolic blood pressure, serum creatinine, fasting glucose, HbA1c, HOMA-R, and triglycerides were higher, while eGFR and high-density lipoprotein (HDL) cholesterol were lower in participants with T2D than in non-diabetic controls. Participants with T2D had lower non-HDL cholesterol with a higher prevalence of subjects treated with statins than non-diabetic controls. The prevalence of history of CVDs, including cerebrovascular disease, coronary artery disease, or peripheral artery disease, was much greater in participants with T2D than in non-diabetic controls. Regarding the antihyperglycemic agents used in the T2D patients, 46 subjects (10.8%) were treated with dietary therapy alone, 153 (36.0%) with sulfonylureas, 131 (30.8%) with biguanides, 128 (30.1%) with dipeptidyl peptidase-4 inhibitors, 46 (10.8%) with thiazolidinediones, and 174 (40.9%) with insulin therapy. In participants with T2D, 128 (30.1%) subjects had diabetic retinopathy, 143 (33.6%) had diabetic nephropathy, 229 (53.9%) had diabetic neuropathy, and 289 (68.0%) had any diabetic microangiopathy.

The median value of the plasma omentin and total adiponectin levels in the total population was 524 ng/mL (range, 209–1961 ng/mL) and 7.0 μg/mL (range, 0.8–46.4 μg/mL), respectively. Plasma omentin levels were significantly higher, while plasma adiponectin levels were lower, in participants with T2D than in non-diabetic controls. The median FMD value in the total population was 6.0% (range, 0–24.6%), with no significant difference between the subjects with and without T2D (Table 1).

3.2. Clinical factors associated with plasma omentin levels

First, we explored the demographic and metabolic factors associated with plasma omentin levels separately in non-diabetic controls and in participants with T2D (Table 2). Multivariate analyses showed that older age, female sex, and lower non-HDL cholesterol levels were independent determinants of higher plasma omentin levels in non-diabetic controls. On the other hand, lower BMI, lower eGFR, higher HbA1c levels, and higher plasma adiponectin levels, in addition to older age and female sex were independent determinants of higher plasma omentin levels in participants with T2D. Further adjustment for HOMA-R did not affect the relationship between omentin and those parameters in each group (data not shown).

3.3. Clinical factors associated with FMD.

To explore the association between plasma omentin levels and FMD, multiple regression analyses were performed with adjustment for age, sex, BMI, systolic blood pressure, smoking, use of renin-angiotensin system (RAS) inhibitors, use of statins, eGFR, HbA1c, log [triglycerides], non-HDL cholesterol, and log [adiponectin] in each group (Table 3). Independent determinants of lower FMD were older age, male sex, and greater BMI in non-diabetic controls, while those of lower FMD were male sex, lower eGFR, higher HbA1c levels, and use of RAS inhibitors in participants with T2D. Notably, no significant association was found between log [omentin] and FMD in all subjects, non-diabetic controls, or participants with T2D.

3.4. Subgroup analysis of the association between omentin and FMD in participants with T2D

We further explored whether elevated risk of CVD might affect the impact of omentin on FMD in participants with T2D. Higher plasma omentin levels and lower FMD were

Table 1 – Clinical characteristics, plasma omentin levels, and FMD in all, non-diabetic, and type 2 diabetic subjects.

	All subjects	Non-diabetes	Type 2 diabetes	*p*
N (male, %)	648 (55.9)	223 (52.0)	425 (57.9)	0.153
Age (year)	62 [50–70]	54 [45–66]	65 [57–72]	<0.001
Diabetes duration (year)	–	–	11 [4–20]	–
BMI (kg/m^2)	23.9 [21.4–26.9]	22.4 [20.8–24.8]	25.0 [22.0–27.8]	<0.001
Systolic blood pressure (mmHg)	125 [113–137]	119 [109–131]	128 [116–143]	<0.001
Diastolic blood pressure (mmHg)	74 [67–81]	74 [66–82]	74 [67–81]	0.928
Cardiovascular diseases (*n*, %)	96 (14.8)	6 (2.7)	90 (21.2)	<0.001
Cerebrovascular disease (*n*, %)	39 (6.0)	3 (1.4)	36 (8.5)	<0.001
Coronary artery disease (*n*, %)	49 (7.6)	3 (1.4)	46 (10.9)	<0.001
Peripheral artery disease (*n*, %)	30 (4.6)	1 (0.5)	29 (6.8)	<0.001
Diabetic microangiopathy (*n*, %)			289 (68.0)	
Retinopathy (*n*, %)	–	–	128 (30.1)	–
Nephropathy (*n*, %)	–	–	143 (33.6)	–
Neuropathy (*n*, %)	–	–	229 (53.9)	–
Smoker (*n*, %)	321 (49.5)	120 (53.8)	201 (47.3)	0.115
RAS inhibitors (*n*, %)	187 (28.9)	17 (7.6)	170 (40.0)	<0.001
Statin (*n*, %)	210 (32.4)	28 (12.6)	182 (42.8)	<0.001
Creatinine (mg/dL)	0.78 [0.65–0.96]	0.73 [0.62–0.85]	0.81 [0.66–1.06]	<0.001
eGFR (mL/min/1.73 m^2)	71.1 [58.2–82.1]	77.2 [66.8–87.3]	67.0 [52.3–78.7]	<0.001
Fasting glucose (mg/dL)	108 [96–129]	99 [94–106]	119 [101–143]	<0.001
HbA1c (%)	7.3 [5.8–9.0]	5.6 [5.5–5.9]	8.3 [7.3–9.7]	<0.001
HOMA-R*	1.70 [1.10–2.56]	1.40 [0.90–2.00]	2.05 [1.34–2.99]	<0.001
Triglycerides (mg/dL)	106 [77–143]	89 [63–125]	116 [89–153]	<0.001
HDL cholesterol (mg/dL)	46 [38–59]	60 [49–71]	41 [36–50]	<0.001
Non-HDL cholesterol (mg/dL)	134 [110–160]	141 [118–160]	129 [106–160]	0.003
Plasma adiponectin (μg/mL)	7.0 [4.6–11.2]	8.5 [6.2–11.8]	6.2 [3.8–11.1]	<0.001
Plasma omentin (ng/mL)	524 [421–681]	464 [374–556]	573 [451–764]	<0.001
FMD (%)	6.0 [4.1–7.9]	6.2 [4.8–7.5]	5.7 [3.6–8.2]	0.083

Data are median [interquartile range] or *n* (%). *P*-values by χ^2-test or Wilcoxon rank-sum test for comparison between the non-diabetic and type 2 diabetic subjects. *, N = 463 for all subjects, n = 240 for diabetic subjects not receiving insulin therapy. FMD, flow mediated dilation; BMI, body mass index; retinopathy, type 2 diabetic subjects with simple, preproliferative, or proliferative retinopathy; nephropathy, type 2 diabetic subjects with microalbuminuria, macroalbuminuria, or eGFR less than 30 mL/min/1.73 m^2; neuropathy, type 2 diabetic subjects with peripheral or autonomic neuropathy; RAS, renin-angiotensin system; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HOMA-R, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein.

Table 2 – Multiple regression analysis for the determinants of plasma omentin levels.

	All subjects		Non-diabetes		Type 2 diabetes	
	β	*p*	*β*	*p*	*β*	*p*
Age	0.253	<0.001	0.376	<0.001	0.187	<0.001
Sex (male = 1, female = 0)	−0.081	0.012	−0.155	0.021	−0.078	0.056
BMI	−0.134	<0.001	−0.095	0.168	−0.182	<0.001
eGFR	−0.181	<0.001	−0.032	0.632	−0.180	<0.001
HbA1c	0.275	<0.001	0.068	0.310	0.144	<0.001
Log [triglycerides]	0.031	0.457	−0.024	0.757	0.024	0.643
Non-HDL cholesterol	−0.081	0.032	−0.168	0.012	−0.045	0.376
Log [adiponectin]	0.247	<0.001	0.119	0.132	0.293	<0.001
R^2 (*p*)	0.382 (<0.001)		0.330 (<0.001)		0.345 (<0.001)	

β, standard coefficient by multiple regression analysis. R^2, coefficient of determination. Abbreviations are as in Table 1.

observed in the high-risk subgroups of T2D subjects, such as those with older age (≥65 years), renal dysfunction (eGFR < 60 mL/min/1.73 m^2), or preexisting CVDs, than in the low-risk subgroups (Fig. 1). Therefore, an interaction analysis was performed to assess whether the relationship between omentin and FMD was modified by age, eGFR, or preexisting CVDs. The interaction analysis indicated a potential effect modification by age (*p* for interaction = 0.144), eGFR (*p* for interaction = 0.152), and preexisting CVDs (*p* for interaction = 0.097) on the association between plasma omentin levels and FMD in participants with T2D (Table 4).

Finally, we examined the association between plasma omentin levels and FMD in T2D subjects with and without older age, renal dysfunction, or preexisting CVDs. These strat-

Table 3 – Multiple regression analysis for the determinants of FMD.

	All subjects		Non-diabetes		Type 2 diabetes	
	β	p	β	p	β	p
Age	−0.146	0.003	−0.330	<0.001	−0.110	0.080
Sex (male = 1, female = 0)	−0.127	0.003	−0.226	0.003	−0.105	0.048
BMI	−0.040	0.362	−0.159	0.038	−0.040	0.463
Systolic blood pressure	−0.027	0.517	0.040	0.562	−0.057	0.275
Smoking (yes = 1, no = 0)	−0.077	0.070	−0.080	0.237	−0.060	0.254
RAS inhibitors (yes = 1, no = 0)	−0.088	0.031	0.030	0.650	−0.136	0.006
Statins (yes = 1, no = 0)	0.005	0.901	−0.030	0.639	−0.003	0.953
eGFR	0.103	0.030	0.040	0.567	0.144	0.019
HbA1c	0.005	0.909	0.009	0.898	−0.111	0.030
Log [triglycerides]	−0.019	0.713	−0.043	0.618	−0.020	0.742
Non-HDL cholesterol	−0.057	0.221	−0.057	0.452	−0.015	0.806
Log [adiponectin]	−0.068	0.145	0.015	0.860	−0.051	0.375
Log [omentin]	0.052	0.280	−0.102	0.163	0.062	0.285
R^2 (p)	0.098 (<0.001)		0.271 (<0.001)		0.098 (<0.001)	

β, standard coefficient by multiple regression analysis. R^2, coefficient of determination. Abbreviations are as in Table 1.

ified analyses revealed that plasma omentin levels were independently and positively associated with FMD in subgroups with older age ($\beta = 0.156$, $p = 0.048$), renal dysfunction ($\beta = 0.190$, $p = 0.045$), or preexisting CVDs ($\beta = 0.452$, $p < 0.001$), but not in the subgroups without each CVD risk factor (Table 4).

Additional subgroup analysis revealed that the relationship between omentin levels and FMD was not different between males and females without effect modification by sex (p for interaction = 0.756) in T2D subjects (Table 4). The presence of diabetic microangioipathy did not affect plasma omentin levels ($\beta = 0.046$, $p = 0.328$) and tended to be negatively associated with FMD ($\beta = -0.096$, $p = 0.080$) in participants with T2D. In subgroup analyses according to the presence of any microangiopathy, no significant association was found between omentin levels and FMD in either subgroup with ($\beta = 0.041$, $p = 0.554$) or without ($\beta = 0.137$, $p = 0.308$) diabetic microangiopathy.

4. Discussion

This study investigated the association between plasma omentin levels and vascular endothelial function, as assessed by FMD, in patients with T2D. Our results demonstrated that plasma omentin levels were positively associated with FMD, a surrogate marker for CVD, in subgroups of patients with T2D at high CVD risk, such as those with older age, renal dysfunction, or preexisting CVDs. Importantly, the association between omentin and FMD was independent of traditional CVD risk factors and adiponectin. On the contrary, no significant association was found between omentin and FMD in low-risk subgroups of patients with T2D or in non-diabetic controls.

To our knowledge, this is the first study to investigate the association between omentin and endothelial function in patients with T2D. Previous studies demonstrated omentin to be a protective factor against atherosclerosis, as it was inversely related to carotid atherosclerosis [8,10,22,23,37] and arterial stiffness [8,10] in a non-diabetic population [8,22,23,37] and in patients with T2D [10]. One prior study evaluated FMD and showed an independent positive correlation between omentin levels and FMD in non-diabetic subjects [24]. In line with that study, our results demonstrated a positive association between omentin and FMD in high-risk patients with T2D, providing additional evidence of the relationship between omentin and endothelial function in T2D.

Of note, in the present study, the relationship between plasma omentin levels and endothelial function was independent of the degree of obesity, adiponectin levels, and traditional risk factors in high-risk patients with T2D. Previous experimental studies have suggested a protective effect of omentin against atherogenesis and vascular damage in rodents through attenuation of the inflammatory response of macrophages and the migration/proliferation of smooth muscle cells [13,15–17,38]. In terms of endothelial function, omentin was shown to stimulate endothelial nitric oxide synthase to promote vasodilatation [13–15]. These experimental studies and our results suggest that omentin directly promotes endothelial function in human subjects with diabetes and CVD risk factors. Adiponectin is also proposed to have beneficial effects on endothelial cells by attenuating inflammation [3] and stimulating nitric oxide production [39]. However, a number of studies, as well as ours, failed to show a significant relationship between adiponectin and endothelial function in both non-diabetic and diabetic subjects [40,41]. Taken together, it can be speculated that the vasodilatory effect of omentin is greater than that of adiponectin and is not complicated by other risk factors. To date, no study has examined whether the beneficial effects of omentin on endothelial cell function are maintained in the context of accumulated risk factors such as hyperglycemia, aging, or uremia.

The present study clearly demonstrated that the association between omentin and FMD varies depending on the risk status for CVD among patients with T2D. A significant association between omentin and FMD was observed in the high-risk patient groups but not in the low-risk counterparts or non-diabetic controls. The association between higher

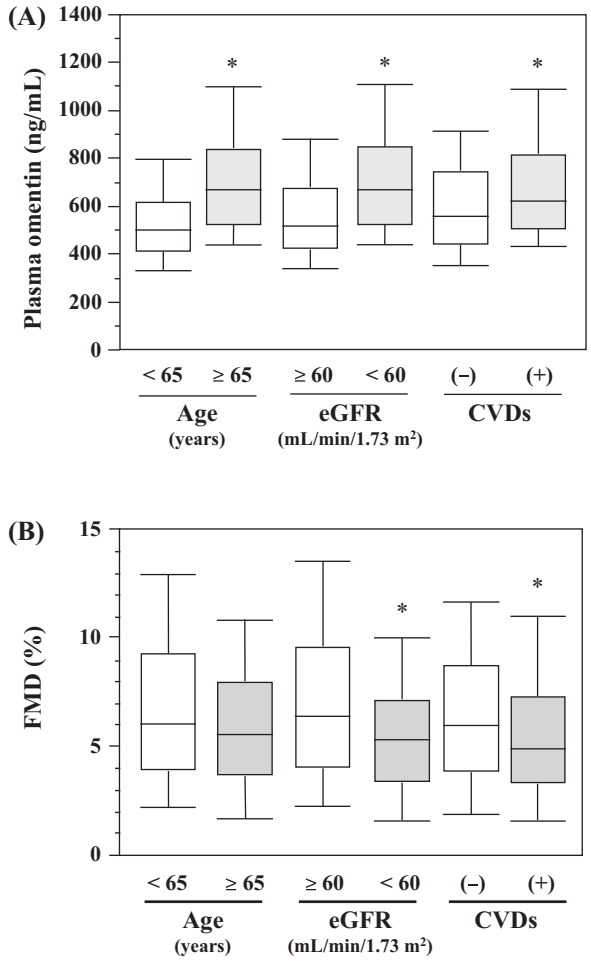

Fig. 1 – Comparison of plasma omentin levels (A) or FMD (B) between low and high cardiovascular risk groups according to age (65 years), eGFR (60 mL/min/1.73 m^2), or preexisting CVDs, among patients with type 2 diabetes. Horizontal bars represent the 10th, 25th, 50th, 75th, and 90th percentile levels. *, $p < 0.05$ vs. low-risk group by Wilcoxon rank-sum test. eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; FMD, flow-mediated dilatation.

omentin and greater FMD observed only in the high-risk subgroups could be explained as a compensatory increase in omentin level in the presence of advanced atherosclerotic vascular damage. While previous studies have indicated the protective role of omentin against atherosclerotic CVDs in humans [19–22], in several recent studies, higher omentin levels were cross-sectionally associated with disease severity in patients with coronary artery disease [38,42]. In a previous study [38], Japanese patients with acute coronary syndrome showed increased omentin levels in plasma and atheromatous plaque compared to control subjects. In a study in Chinese patients with coronary artery disease with ≥90% coronary artery stenosis [42], plasma omentin levels were associated with good coronary collateral circulation, as well as disease severity. Moreover, in several longitudinal studies, high omentin levels were associated with poor CVD outcomes [43,44]. The elevated plasma omentin levels at baseline independently predicted CVD events in patients who underwent coronary angiography [44]. Higher omentin levels at baseline were also associated with increased risk of stroke in a large case-cohort study [43]. Results from these recent studies suggest that while decreased omentin levels are generally associated with atherosclerotic CVDs, omentin levels may be increased to compensate for advanced atherosclerotic vascular damage in patients with established CVDs.

Recent evidence further indicates that omentin level not only serves as a negative risk factor but also increases to counteract the acute phase after the onset of CVDs [45]. In patients with acute myocardial infarction, upregulation of omentin levels with suppression of inflammation were observed at 6 months after onset, despite lower omentin levels at baseline [46]. A one-year follow-up study in patients with T2D demonstrated that an increase in serum omentin levels were associated with an increase in HbA1c levels and pulse wave velocity [47]. In our study, FMD was impaired in subgroups of T2D patients with renal dysfunction or preexisting CVDs, while plasma omentin levels in these subgroups were elevated compared with those in subgroups without renal dysfunction or preexisting CVDs. In addition, reduced eGFR and higher HbA1c levels, as well as older age, were

Table 4 – Subgroup analysis of the association between omentin and FMD according to sex, age, renal function, or cardiovascular diseases in patients with type 2 diabetes.

	n	FMD		P for interaction
		β	p	
Male	246	0.010	0.897	0.756
Female	179	0.160	0.086	
Age < 65 (years)	208	−0.028	0.716	0.144
Age ≥ 65 (years)	217	0.156	0.048	
eGFR ≥ 60 (mL/min/1.73 m^2)	264	0.007	0.926	0.152
eGFR < 60 (mL/min/1.73 m^2)	161	0.190	0.045	
Cardiovascular diseases (–)	335	−0.010	0.884	0.097
Cardiovascular diseases (+)	90	0.452	<0.001	

Relationship between log [omentin] and FMD was adjusted for age, sex (male = 1, female = 0), BMI, systolic blood pressure, smoking (yes = 1, no = 0), use of RAS inhibitors (yes = 1, no = 0), use of statins (yes = 1, no = 0), eGFR, HbA1c, log [triglycerides], non-HDL cholesterol, and log [adiponectin]. A potential effect modification by age, eGFR, or preexisting cardiovascular diseases (yes = 1, no = 0) on the effect of omentin and FMD was also analyzed. Abbreviations are as in Table 1.

independently associated with increased omentin levels only in participants with T2D. Previous experimental studies indicate that the expression and/or secretion of omentin in human adipose tissue were decreased by glucose/insulin and stimulated by fibroblast growth factor 21 and dexamethasone [45]. A clinical study demonstrated that increase in serum omentin levels was correlated with decrease in high-sensitivity C-reactive protein levels, independently of changes in glucose or HOMA-R, after treatment with metformin for six months in women with polycystic ovary disease [48]. Because omentin levels were not inversely associated with HbA1c or HOMA-R in our results, it can be speculated that omentin is upregulated in response to inflammation or vascular damage due to accumulated risk factors, such as chronic hyperglycemia, aging, and renal dysfunction, in patients with T2D.

This study has several limitations. First, data on neither visceral fat area nor waist circumference were available, which would have served as better adjustment factors than BMI in the multivariate analyses. Second, because this was a cross-sectional study, a causal relationship between omentin and endothelial function could not be clarified. Third, the participants were receiving statins, RAS inhibitors, and/or antihyperglycemic agents, which could have affected omentin levels, FMD, and/or related risk factors. To minimize the effect of at least statins and RAS inhibitors on FMD, the use of these drugs was adjusted for in multivariate analyses. Fourth, because the background characteristics, such as age and eGFR, were quite different between the non-diabetic and diabetic subjects, the absolute values for omentin levels and FMD cannot be simply compared between groups. Lastly, the information on CVDs and diabetic microangiopathy were obtained only from medical records, therefore the effect of the mico- or macrovascular complications on omentin levels or FMD could be underestimated.

In conclusion, this study demonstrated that plasma omentin levels are independently and positively associated with FMD in patients with T2D with older age, renal dysfunction, or preexisting CVDs, but not in those without or non-diabetic controls. Our data indicate that omentin, which possesses vasodilatory properties, has a positive association with endothelial function, even in high-risk T2D patients with impaired endothelial function. This study further proposes that plasma omentin level is a potential biomarker of vascular health in high-risk, but not low-risk, patients with T2D. Further longitudinal or interventional studies are warranted to clarify whether increasing omentin levels, e.g., by weight reduction or anti-diabetic drugs, may be linked with the improvement of FMD in patients with T2D.

Conflict of interest

The authors declare that they have no competing interests related to the present study.

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Author contributions

MHay, TM, and ME conceived the study, participated in its design and coordination, and helped in the drafting of the manuscript. MHay and TM performed the statistical analyses. MHay, MHat, YK, and YY enrolled the patients with T2D and performed vascular examinations. SF, MK, KMot, KMor, AS, TS, and MI contributed to the discussion section and were involved in drafting and revising the manuscript. All authors have read and approved the final version of the manuscript.

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