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【 ORIGINAL ARTICLE 】

A Study of the Vascular Endothelial Function in Patients with Type 2 Diabetes Mellitus and Rheumatoid Arthritis

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Abstract:

Objective Type 2 diabetes mellitus (T2DM) and rheumatoid arthritis (RA) are both complicated by arteriosclerosis, resulting in increased rates of cardiovascular events. No previous studies have compared the index between RA and T2DM. We assessed the vascular endothelial function in early-stage arteriosclerosis for each disease to determine the influential factors and compared the extent to which these two diseases cause vascular endothelial dysfunction.

Methods This study is a retrospective study based on medical records. Differences in the reactive hyperemia index (RHI) among the groups and factors affecting the RHI in each group was analyzed. The vascular endothelial function was assessed by measuring the RHI using peripheral arterial tonometry.

Patients The study subjects were 114 patients with non-functional thyroid tumors (healthy n=14), T2DM (T2DM n=64), and RA (RA n=36).

Results The RHI was 2.29 in the control, 1.85 in the T2DM, and 1.83 in the RA group, with values lower in the T2DM and RA groups than in the control group (p=0.033) but not markedly different between the two disease groups. The RHI distribution (<1.68/1.68 to <2.10/≥2.1) was as follows: control group: 14.3%/28.6%/57.1%; T2DM group: 42.2%/39.1%/18.8%; and RA group: 36.1%/44.4%/19.4% (p=0.031), respectively. A multivariate analysis identified the triglyceride level and dyslipidemia in the control group and the Disease Activity Score in 28 joints with the erythrocyte sedimentation rate and fasting plasma glucose level in the RA group to influence the RHI.

Conclusion The vascular endothelial function was impaired in approximately 80% of patients with T2DM and RA, with comparable degrees of impairment between the two diseases. No factors affecting the function were identified in the T2DM group, while the function was more impaired in patients with a higher disease activity in the RA group.

Key words: rheumatoid arthritis, type 2 diabetes, Endo-PAT, reactive hyperemia index

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Introduction

Atherosclerosis was previously regarded as a degenerative lesion caused by dyslipidemia, but it is currently considered to be chronic inflammation caused by the infiltration of inflammatory cells, including monocytes and T-cells, in addition to dyslipidemia (1). The mortality rate due to ischemic heart disease and the incidence of myocardial infarction are two to six times higher (2, 3), and the risk of cerebral infarction is two to three times higher (3, 4) in patients with type 2 diabetes mellitus (T2DM) and macroangiopathy than in non-diabetic patients. Clinical studies have revealed impairment of the vascular endothelial function in the early stages of T2DM (5) and an increased risk of cardiovascular disease (CVD) in patients with impaired glucose toler-

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ance (6).

In patients with rheumatoid arthritis (RA), the mortality rate due to CVD is 1.1-5.2 times higher than that in healthy individuals and is associated with the severity of RA (7). Thus, cardiovascular events are considered to be the most important determinants of the survival in patients with RA (8). Clinical observation indicates that patients with RA tend not to suffer from obesity, hypertension, or dyslipidemia, which are common risk factors for atherosclerosis. Accordingly, the pathological processes involved in RA, rather than the above triad, could potentially be involved in the development of atherosclerosis in such patients.

Based on the above background, it seems that T2DM and RA can be complicated by atherosclerosis and therefore are associated with an increased risk of cardiovascular events. It is therefore likely that distinct pathological processes are involved in atherosclerosis in each disease. Studies using a peripheral arterial tonometry (PAT) device (EndoPAT 2000; Itamar Medical, Caesarea, Israel) have shown that the reactive hyperemia index (RHI) can be used as a predictor of the future development of cardiovascular events (9, 10). It is clear that both diseases are associated with a high risk of cardiovascular disease. However, to our knowledge, no studies have so far compared patients with these two conditions relative to nondiabetic individuals using an EndoPAT or shown evidence of a difference in the mechanisms underlying endothelial dysfunction.

Thus, the aim of the present study was to determine the differences in the factors that contribute to endothelial dysfunction and the severity of vascular endothelial dysfunction in patients with T2DM and RA relative to nondiabetic subjects.

Materials and Methods

This study is a retrospective study based on medical records. Among the patients who were admitted to the Hospital of the University of Occupational and Environmental Health and its affiliated hospitals between January 2012 and January 2014, we selected those patients with the following conditions who underwent an Endo-PAT evaluation within seven days of admission: patients with a thyroid mass who had a normal glucose tolerance (control group), patients with T2DM who were being treated with oral glucose-lowering drugs alone (T2DM group), and patients with RA who had not been treated with biological drugs and did not have an abnormal glucose tolerance (RA group). The criteria for a normal glucose tolerance were as follows: an HbA1c and fasting blood glucose level that were not consistent with a diagnosis of diabetes or the absence of a prescription for anti-diabetic drugs. The age, sex, or use of glucose-lowering drugs were not considered.

The exclusion criteria were as follows: patients with T1DM, pancreatic diabetes, steroid-induced diabetes, comorbid infection, ketoacidosis, or hyperosmolar nonketotic coma; patients who underwent surgery or had trauma; patients who were on hemodialysis or peritoneal dialysis; patients who had been diagnosed with cardiac arrhythmia or cerebral infarction within the preceding six months; patients with a history of ischemic heart disease, or malignancy; pregnant patients; and patients whose medications for DM, dyslipidemia, or hypertension had been changed in the preceding three months.

The protocol of this study was approved by the Ethics Review Committee of the University of Occupational and Environmental Health. All patients volunteered and gave their informed consent based on the Declaration of Helsinki revised in 2000.

Study design

After admission, the patients were examined with the Endo-PAT 2000 device (Itamar Medical) at rest on an empty stomach in the early morning to measure the RHI and assess the vascular endothelial function. Fasting blood samples were collected on the day after the Endo-PAT evaluation. During the study period, diet and exercise therapies were applied continuously, and any treatment with medications that could affect blood glucose, blood pressure, or lipid levels was to be neither initiated nor changed.

Noninvasive vascular function test

The method used for the digital measurement of the vascular function using PAT has been described in detail previously (11). Based on the circadian variation in the peripheral vascular tone, PAT was performed in all patients between 7:00 and 8:00 am in a quiet, temperature-controlled room (21-24℃). All subjects were examined after an overnight fast and 30-minute rest in the supine position. The baseline pulse amplitude was recorded during a period of 5 minutes before the induction of ischemia. Ischemia was induced by placing the blood pressure cuff on the upper arm, while the opposite arm served as the control. The PAT probes were placed on one finger of each hand. After 5 minutes, the blood pressure cuff was inflated to 60 mmHg above the systolic pressure or 200 mmHg for 5 minutes and then deflated to induce reactive hyperemia. As a measure of reactive hyperemia, the RHI was calculated as the ratio of the average amplitude of the PAT signal over 1 minute beginning 1.5 minutes after cuff deflation (control arm, A; occluded arm, C) divided by the average amplitude of the PAT signal over the 2.5-minute time period before cuff inflation (baseline) (control arm, B; occluded arm, D). Thus, the RHI = (C/D) / (A/B) × baseline correction.

Assessment of disease activity in RA patients

The RA disease activity was assessed by the Disease Activity Score in 28 joints with the erythrocyte sedimentation rate (ESR) (12), the simplified disease activity index (13), and the clinical disease activity index (14). Serological assessments were performed for the ESR, C-reactive protein (CRP), anti-cyclic citrullinated peptide antibody, rheumatoid factor, matrix metalloproteinase-3, and pentraxin-3.

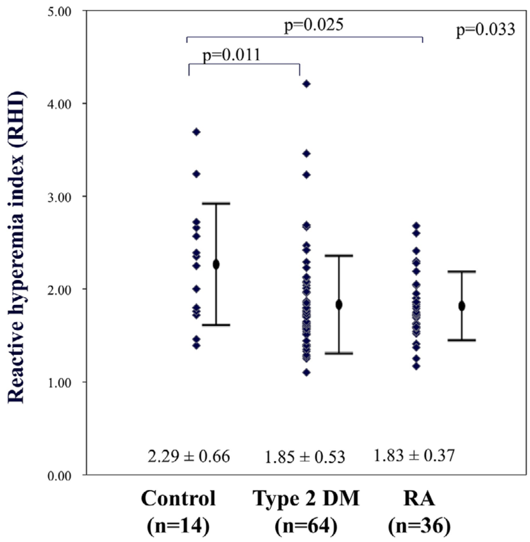

Figure. Scatter plot of the reactive hyperemia index (RHI) by disease type. Data are the RHIs of the control, type 2 diabetes mellitus (T2DM), and rheumatoid arthritis (RA) groups. Data of individual patients with mean and standard deviation values of each group. A one-way analysis of variance (ANOVA) and Kruskal-Wallis test were used to compare the three groups.

Measurements of biochemical variables

Venous blood samples were obtained in the morning following an overnight fast. Serum lipids were measured using a Hitachi 7,350 auto analyzer (Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were determined by the enzymatic method, and LDL-C was determined by the direct method. Fasting plasma glucose levels were measured using a standard enzymatic method. Hemoglobin A1c (HbA1c) (%) was measured by high-performance liquid chromatography using a Tosoh HLC-723 G8 (Tosoh, Kyoto, Japan) and expressed as National Glycohemoglobin Standardization Program (NGSP) values by adding 0.4% to the HbA1c values, which were expressed as conventional Japanese standard substance (JDS) values (15). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: fasting plasma glucose (FPG) (mg/dL) × fasting plasma insulin (FPI) (μU/mL) / 405. Anti-cyclic citrullinated peptide antibody was measured using a chemiluminescence enzyme immunoassay (CLEIA) (STACIA System; LSI Medience Corporation, Tokyo, Japan). Matrix metalloproteinase-3 was measured using a latex turbidimetric immunoassay (LTIA) (JCA-BM8000 series; JEOL, Tokyo, Japan). Pentraxin-3 was measured using an enzyme-linked immunosorbent assay (ELISA) (human pentraxin-3 ELISA System; Perseus Proteomics, Tokyo, Japan).

Statistical analyses

Data are expressed as mean ± standard deviation (SD). Between-group comparisons were tested by the unpaired Mann-Whitney U test or chi-square test. A one-way analysis of variance (ANOVA) and Kruskal Wallis test were used to compare three groups. The chi-square test was used for categorical data. Factors that influence the RHI were analyzed using a Pearson correlation analysis for normally distributed variables and Spearman rank correlation for variables with a skewed distribution. A multivariate stepwise regression analysis was conducted using the RHI as the dependent variable and several parameters. P values less than 0.05 were considered to reflect significant difference. All analyses were conducted using the PASW statistics analysis software program, ver. 19.0 (SPSS, Chicago, USA).

Results

Patient characteristics

This study included a total of 114 patients (control group, n=14, T2DM group, n=64, RA group, n=36). Although the subjects of the three groups were of comparable age, there were more women than men in the control and RA groups. The body mass index (BMI) was 24.2±4.2 kg/m^2 in the control group, 26.2±4.6 kg/m^2 in the T2DM group, and 22.3±4.2 kg/m^2 in the RA group. Hypertension and dyslipidemia was noted in a large proportion of subjects of the T2DM group (approximately 65%), and oral antihypertensive medications and statins were used by 51.6% and 39.1% of patients of this group, respectively. In contrast, the prevalence of hypertension and dyslipidemia in the RA group was as low as roughly 15%. LDL-C levels were well controlled at 121±27 mg/dL in the control group, 118±30 mg/dL in the T2DM group, and 98.9±23.9 mg/dL in the RA group. The levels of HDL-C were not markedly different among the three groups, although the serum TG level was significantly lower in the RA group than in the other groups. The T2DM group included many patients with poor glycemic control, with a mean HbA1c level of 9.2%±1.7% despite ongoing treatment with dietary control and oral glucose-lowering agents.

In the RA group, the ESR was 43.6±28.9 mm/h, indicating a state of chronic inflammation. The disease activity was considered high, based on a Disease Activity Score in 28 joints with an ESR of 5.0±1.2, simplified disease activity index of 24.0±11.5, and clinical disease activity index of 22.4±10.3 (Table 1).

The vascular endothelial function

The RHI was 2.29±0.66 in the control group but higher in the other two groups (T2DM: 1.85±0.53, RA: 1.83±0.37, p=0.033) (Figure), although it was comparable between the T2DM and RA groups (p=0.608). The patients was divided into three RHI categories for the assessment: the vascular endothelial dysfunction group, defined as an RHI of <1.68; borderline dysfunction, defined as an RHI of 1.68 to <2.10, defined as an RHI of ≥2.1, based on the cut-off values used in a previous study (16). The proportions of patients with

Table 1. Clinical Characteristics of Participants.

	Control subjects	Type 2 diabetes mellitus	Rheumatoid arthritis	p
Number	14	64	36	
Age (years)	66.2±12.7	61.7±12.5	56.7±13.5	0.074
Sex (males / females)	2 / 12	37/27	8/28	<0.001
BMI (kg/m^2)	24.2±4.2	26.2±4.6	22.3±4.2	<0.001
Systolic blood pressure (mmHg)	137.9±16.1	134.5±19.0	125.0±20.8	0.031
Diastolic blood pressure (mmHg)	76.2±6.9	83.3±12.6	74.9±14.4	0.011
TG (mg/dL)	140.1±75.9	141.9±89.5	82.0±37.0	<0.001
HDL-C (mg/dL)	57.3±19.7	51.4±13.7	55.5±17.3	0.459
LDL-C (mg/dL)	121.4±26.7	118.5±29.9	98.9±23.9	0.002
Fasting plasma glucose (mg/dL)	96.9±5.1	158.3±39.1	91.8±12.9	<0.001
Fasting plasma insulin (μg/mL)	8.1±4.0	6.9±4.8	6.5±4.1	0.388
HOMA-R	2.0±1.0	2.8±2.5	1.5±1.1	0.001
HbA1c (%)	5.7±0.3	9.2±1.7	5.4±0.4	<0.001
eGFR (mL/min/1.73 m^2)	78.6±17.9	77.7±25.7	93.3±18.5	0.003
Hypertension (%)	8 (57.1)	39 (60.9)	5 (13.9)	<0.001
Hyperlipidemia (%)	4 (28.6)	43 (67.2)	6 (16.7)	<0.001
Antihypertensive drug (%)	2 (14.3)	33 (51.6)	10 (27.8)	0.003
Statin (%)	3 (21.4)	25 (39.1)	2 (5.6)	0.001
Diabetes therapy				
DPP1 / α-glucosidase inhibitor		27 (42.2) / 9 (14.1)		
pioglitazone / metformin		10 (15.6) / 18 (28.1)		
sulfonylurea / glinide		35 (54.7) / 2 (3.1)		
Rheumatoid arthritis activity index				
CRP (mg/dL)			1.6±2.0	
ESR (mm/hr)			43.6±28.9	
anti-cyclic citrullinated peptide antibody (mg/dL)			180.1±281.8	
rheumatoid factor (U/mL)			126.4±294.1	
matrix metalloproteinase -3 (ng/mL)			199.1±207.0	
pentraxin3 (ng/mL)			6.3±22.2	
Disease Activity Score in 28 joints with erythrocyte sedimentation rate			5.0±1.2	
simplified disease activity index			24.0±11.5	
clinical disease activity index			22.4±10.3	

Data are mean±standard deviation (SD) or *n*(%).
Between-group comparisons by chi-square test. ANOVA was used to compare three groups.
BMI: body mass index, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HOMA-R: homeostasis model assessment insulin resistance, eGFR: estimated glomerular filtration rate, DPPI: dipeptidyl peptidase-4 inhibitor, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

apparent vascular endothelial dysfunction were 42.2% in the T2DM group and 36.1% in the RA group, which were higher than the 14.3% in the control group.

Factors affecting the vascular endothelial function

Table 2 shows the correlations between the RHI and various parameters, and Table 3 shows the results of the multivariate analyses with the RHI as the dependent variable. In the control group, the RHI correlated with the age (r=−0.597, p=0.024) and TG (r=0.644, p=0.013). In this group, a multivariate analysis that included the RHI as the dependent variable and age, sex, BMI, antihypertensive drugs, lipid-lowering drugs, LDL-C, HDL-C, TG, systolic blood pressure, hypertension, and hyperlipidemia as the independent variables identified TG (standardized coefficient β=0.749, p=0.003) and dyslipidemia (standardized coefficient β=0.448, p=0.042) as significant factors affecting the RHI (p=0.006, adjusted multiple R^2=0.5333). In the T2DM group, the RHI correlated with the HOMA-R (r=0.250, p=0.046) and the use of metformin (p=0.013). A multivariate analysis performed with the RHI as the dependent variable found no factors that affected the index. In the RA group, the RHI was correlated with the Disease Activity Score in 28 joints with the ESR only (r=−0.339, p=0.043). A multivariate analysis in this group using age, sex, BMI, antihypertensive drugs, lipid-lowering drugs, LDL-C, HDL-C, TG, blood pressure, hypertension, hyperlipidemia, estimated glomerular filtration rate, fasting plasma glucose, fasting plasma insulin, duration of the disease, HOMA-R, HbA1c, Disease Activity Score in 28 joints with the ESR, simplified disease activity

Table 2. Correlation Coefficients between RHI and Markers of Diabetic Control and Various Nonglycemic Metabolic Variables.

	Control group		Type 2 diabetes mellitus		Rheumatoid arthritis	
	r	p value	r	p value	r	p value
Age (years)	-0.597	0.024	0.012	0.922	-0.052	0.764
Sex (male / female)		0.361		0.380		0.413
BMI (kg/m^2)	0.493	0.073	0.035	0.781	-0.062	0.719
Systolic blood pressure (mmHg)	-0.196	0.503	0.108	0.396	-0.039	0.821
Diastolic blood pressure (mmHg)	0.240	0.409	-0.003	0.982	-0.070	0.686
TG (mg/dL)	0.644	0.013	0.095	0.457	-0.021	0.902
HDL-C (mg/dL)	-0.330	0.250	-0.022	0.862	0.206	0.229
LDL-C (mg/dL)	0.097	0.742	0.098	0.440	-0.121	0.483
Fasting plasma glucose (mg/dL)	0.290	0.314	0.123	0.335	-0.236	0.166
Fasting plasma insulin (μg/mL)	0.406	0.190	0.241	0.056	-0.201	0.255
HOMA-R	0.445	0.147	0.250	0.046	-0.216	0.220
HbA1c (%)	0.449	0.107	-0.060	0.636	-0.027	0.875
eGFR (mL/min/1.73m^2)	0.169	0.564	0.097	0.446	-0.034	0.842
Hypertension (%)		0.439		0.563		0.137
Hyperlipidemia (%)		0.258		0.577		0.552
Antihypertensive drug (%)		0.273		0.883		0.314
Statin (%)		0.243		0.655		0.836
Diabetes therapy						
DPPI / α-glucosidase inhibitor				0.629/0.809		
pioglitazone / metformin				0.380/0.013		
sulfonylurea / glinide				0.706/0.247		
Rheumatoid arthritis activity index						
CRP (mg/dL)					-0.012	0.942
ESR (mm/hr)					-0.128	0.458
anti-cyclic citrullinated peptide antibody (mg/dL)					0.268	0.114
rheumatoid factor (U/mL)					0.104	0.546
matrix metalloproteinase -3 (ng/mL)					0.021	0.903
pentraxin3 (ng/mL)					0.042	0.813
Disease Activity Score in 28 joints with erythrocyte sedimentation rate					-0.339	0.043
simplified disease activity index					-0.241	0.156
clinical disease activity index					-0.260	0.126

Data are results of Pearson correlation analysis for normally distributed variables and Spearman rank correlation for variables with skewed distribution. Between-group comparisons were tested by unpaired Mann-Whitney U test or Chi-square test.
BMI: body mass index, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HOMA-R: homeostasis model assessment insulin resistance, eGFR: estimated glomerular filtration rate, DPPI: dipeptidyl peptidase-4 inhibitor, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

index, clinical disease activity index, rheumatoid factor, anti-cyclic citrullinated peptide antibody, matrix metalloproteinase-3, CRP, ESR, and pentraxin-3 as the independent variables identified the Disease Activity Score in 28 joints with the ESR (standardized coefficient $\beta=-0.445$, $p=0.012$) and fasting plasma glucose (standardized coefficient $\beta=-0.374$, $p=0.032$) as significant factors that affect the RHI ($p=0.014$, adjusted multiple $R^2=0.202$).

Discussion

In this study, approximately 80% of patients with RA had vascular endothelial dysfunction, the same degree as in the T2DM group, and the prevalence was significantly higher than in the control group. Furthermore, likely due to the involvement of several factors, the same analysis found that the vascular endothelial function was significantly impaired in patients with dyslipidemia in control subjects, while the vascular endothelial function was even more severely impaired in patients with a higher disease activity in the RA group. Thus, our results indicate that the factors associated with vascular endothelial dysfunction depend on the pathological condition.

In control subjects, the vascular endothelium plays an important role in vascular dilatation and constriction, proliferation and anti-proliferation of vascular smooth muscle cells, coagulation and anticoagulation, inflammatory and anti-inflammatory activity, and oxidative and antioxidative activity. Damage of the vascular endothelium alters the balance among these activities, resulting in a loss of vascular tonus

Table 3. Results of Multivariate Analysis with RHI as the Dependent Variable in the Control Group and RA Patients.

Variables	Non-standardized coefficients	Standardized coefficient r	p value	95%CI	
Control subjects					
Intercept	1.190		0.002	0.543	1.837
Triglyceride	0.007	0.748	0.003	0.003	0.010
Hyperlipidemia	0.633	0.448	0.042	0.027	1.240
Adjusted multiple R^2		0.533			
RA patients					
Intercept	3.545		<0.001	2.351	4.738
Disease Activity Score in 28 joints with erythrocyte sedimentation rate	-0.133	-0.445	0.012	-0.235	-0.032
Fasting plasma glucose	-0.012	-0.374	0.032	-0.022	-0.001
Adjusted multiple R^2		0.202			

RHI was the dependent variable in analyses of both groups. The independent variables were age, gender, BMI, use of antihypertensive drugs, use of lipid-lowering drugs, LDL-cholesterol, HDL-cholesterol, triglyceride, systolic blood pressure, hypertension and hyperlipidemia in the control group, and the same variables (excluding hypertension), plus duration of the disease, diastolic blood pressure, eGFR, fasting plasma glucose, fasting plasma insulin, HOMA-R, HbA1c, Disease Activity Score in 28 joints with erythrocyte sedimentation rate, simplified disease activity index, clinical disease activity index, rheumatoid factor, anti-cyclic citrullinated peptide antibody (mg/dL), matrix metalloproteinase-3, CRP, ESR and Pentraxin-3 in the RA group.

and/or structure. The initial stage of atherosclerosis involves vascular endothelial dysfunction, which is followed later by the development of vascular complications (17). Vascular endothelial dysfunction is an independent predictor of vascular complications (18). Furthermore, vascular endothelial dysfunction is reversible and is recognized as a therapeutic target. Thus, the early diagnosis and therapeutic intervention for vascular endothelial dysfunction are no doubt important to prevent further progression to irreversible atherosclerosis. Although there have been reports of using the RHI to assess patients with RA or T2DM, none of these previous studies compared the index between these two patient groups. Our results showed that while these two diseases typically cause vascular endothelial dysfunction, the severity of the RHI was comparable between the diseases, as was the RHI distribution. A number of previous studies have assessed the RHI in RA patients, but their results were inconsistent (19-21). One study of 107 patients with RA (mean age: 50.2±14.1 years) found that the RHI was comparable between RA patients (2.194±0.810) and control subjects (2.090±0.579) (19). Of note, however: the patients of that study were younger and had lower CRP levels (1.06±2.5 mg/dL) and lower RA activity (DAS28: 4.2±1.4) than the patients of the present study. The observed differences in the RHI between the two studies may thus be due to differences in the background characteristics of the patients. Our study showed that the disease Activity Score in 28 joints with the ESR was an independent and significant factor that affected the RHI in RA patients, and the level of disease activity affected the vascular endothelial dysfunction. In another study, Provan et al. (20) reported that the RHI tended to be lower in patients with active RA than in control patients, a finding that differed from that in our study. In contrast, the RHI values measured by Hjeltnes et al. (21) were comparable to those reported in our study. Taken together, these present and previous findings confirm the impairment of the vascular endothelial function in RA patients, with more severe impairment, as measured by the RHI, in those with a high disease activity. According to these results, the risk of CVD in patients with RA appears to be associated with chronic inflammation and disease activity. Furthermore, these results indirectly support the notion that RA remission helps reduce prevalence of CVD.

The present study has several limitations. First, our clinical study should have been executed after the calculation of the appropriate sample size. A power analysis of the sample size at a power of 95% with a significance level set at 0.05 (σ=0.5) estimated the need for 148 patients with T2DM and RA. Unfortunately, this patient number could not be achieved, thus highlighting the need to interpret the results with caution. Second, while hypoglycemic, antihypertensive, and lipid metabolism-improving medications are known to improve the vascular endothelial function, the present study included many patients who were using these medications, and the proportion of such patients was high, particularly in the T2DM group. This may have contributed to our failure to identify the factors that specifically affected the RHI in this group. Third, in a large, community-based cohort, the factors associated with the RHI were male sex, DM, and the ratio of the total cholesterol to the HDL-C (22). The difference in the RHI between men and women was related to sex-specific determinants of the endothelial function or, alternatively, to the presence of a higher baseline pulse amplitude in men than in women (22). In the present study, there were significantly more women in the control group and RA group than in the T2DM group. The RHI was equivalent in the female-rich RA group and the male-rich T2DM group. If there was no difference between the sexes of both groups, then the RHI of the RA group was lower than that of the T2DM group. Fourth, endothelium-dependent vasodilatation varies according to the menstrual cycle in women, and this variation is associated with changes in the serum estradiol concentrations during the menstrual cycle. The endothelial function is modulated in part by endogenous ovarian hormones, especially estradiol (23). In the present study, vascular endothelial function tests were conducted without taking into consideration the effects of menstruation. Fifth, instead of including normal healthy subjects as the control group, the control group in the present study comprised patients with thyroid tumors. Nevertheless, these patients had a normal hormonal profile, normal glucose metabolism, normal lipid metabolism, and were normotensives and had no smoking history. Finally, because the RHI measurement was performed once only in each patient in this study, the reproducibility of the measurement could not be verified. The vascular endothelial function was assessed only with the Endo-PAT device in the present study. For a better assessment of the vascular function, other diagnostic tools should be used, such as flow-mediated vasodilation. In addition, further longitudinal studies are needed to determine the effect of therapeutic interventions on the RHI.

In conclusion, the results showed the impairment of the vascular endothelial function in approximately 80% of patients with RA, the same degree as in the T2DM group.

Author's disclosure of potential Conflicts of Interest (COI).

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