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Research Article

Effect of Cilostazol as an Antiplatelet Agent on Diabetic Nephropathy with Macroalbuminuria: A Randomized, Double-Blind, Placebo-Controlled Trial (ATP-DN)

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Abstract

Aims: In diabetic nephropathy, the effects of antiplatelet agents in addition to standard care are not clear. The aim of this study (the ATP-DN trial) was to examine the effect of cilostazol on diabetic nephropathy with macroalbuminuria.

Method: The ATP-DN trial is a prospective, randomized, double-blind, placebo-controlled, multicentered clinical trial in Japanese type 2 diabetes with macroalbuminuria. Patients were randomly assigned to receive cilostazol 100 mg or 200 mg or placebo for 14 weeks. The primary endpoint was the change in urinary Albumin-Creatinine Ratio (ACR). The secondary endpoints were changes in Estimated Glomerular Filtration Rate (eGFR), cystatin C, and High Molecular Weight (HMW) adiponectin.

Results: A total of 69 patients were treated. For the primary endpoint, cilostazol decreased the increase of urinary ACR dose-dependently, but not significantly. For the secondary endpoints, cilostazol also decreased the change of eGFR dose-dependently, but not significantly; and did not change cystatin C and HMW adiponectin. In post-hoc analysis, the percentage increase of urinary ACR was significantly lower after treatment with cilostazol compared with placebo (3.2 ± 46.7% vs. 28.5 ± 54.2%, $p<0.05$).

Conclusion: Our results suggest that an antiplatelet agent, cilostazol, might have the effect of reducing albuminuria in diabetic nephropathy with macroalbuminuria.

Keywords: Diabetic Nephropathy; Antiplatelet Agent; Albuminuria; Hyperfiltration; Renoprotective Effect

Abbreviations: Chronic Kidney Disease (CKD); End Stage Renal Disease (ESRD); Renin Angiotensin System (RAS); National Hospital Organization (NHO); Albumin-Creatinine Ratio (ACR); Estimated Glomerular Filtration Rate (eGFR); High Molecular Weight (HMW); Phosphodiesterase (PDE); Cyclic Adenosine Monophosphate (cAMP)

Introduction

Diabetic nephropathy is an inducer of Chronic Kidney Disease (CKD), which progresses to End Stage Renal Disease (ESRD), and a major cause of dialysis and a risk factor for cardiovascular events and death. Interventions for diabetic nephropathy in the microalbuminuric stage may result in remission, and this stage has been shown to be reversible in many clinical studies [1-3]. In contrast, the macroalbuminuric stage may be irreversible and gradually progresses to ESRD over several years. Therefore, it is important to examine interventions in the macroalbuminuric stage that may prevent progression of diabetic nephropathy.

Control of blood glucose, blood pressure, use of renin angiotensin system (RAS) inhibitors, and a low protein diet are recommended as treatment in the macroalbuminuric stage. However, control of risk factors is often difficult clinically [3] and the effects of a low protein diet are uncertain [4]. Use of a RAS inhibitor for prevention of diabetic nephropathy with macroalbuminuria has been examined in many clinical studies [5,6]. The direct renoprotective effect of RAS inhibitors may compensate for the difficulty of control of risk factors and diet therapy.

Antiplatelet agents may also be effective for diabetic nephropathy with macroalbuminuria [7,8]. Cilostazol, an antiplatelet agent that inhibits aggregation of platelets and dilates peripheral vessels, has been shown to have an effect on diabetic nephropathy in animals [9,10] and humans [11-13], but the details were not investigated. To examine the effect of antiplatelet agents on proteinuria in diabetic nephropathy with macroalbuminuria, we planned a prospective clinical trial using cilostazol. In addition, we investigated the effect of cilostazol on adiponectin, which is an adipocytokine that is associated with the prognosis of diabetes and its complications, and is thought to have a renoprotective effect on diabetic nephropathy [14].

Participants and Method

Research design: The study is a prospective, randomized, double-blind, placebo-controlled, multicentered clinical trial (the ATP-DN trial) of the effect of cilostazol as an antiplatelet agent on diabetic nephropathy with macroalbuminuria. The participants were treated at 16 centers of the National Hospital Organization (NHO) in Japan. The study was approved by the appropriate ethics committees and conducted in a accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants before study commencement. This study is registered with the University Hospital Medical Information Network (Number: UMIN000007718). There were no changes to methods after trial commencement in this study.

Participants: The participants were Japanese outpatients with type 2 diabetes with macroalbuminuria. All participants met the following criteria: i) 20-75 years old, ii) urinary albumin-creatinine ratio (ACR) >300 mg/g creatinine, iii) serum creatinine <2.5 mg/dl, iv) HbA1c <9.4%, v) blood pressure <160/100

mmHg, iv) treated with a RAS inhibitor for at least 6 months, and vii) not treated with dipyridamole; and did not meet any exclusion criteria: i) hypersensitivity to cilostazol, ii) contraindication for cilostazol (bleeding and congestive heart failure), iii) previous treatment with cilostazol, (v) heart rate >100 /min, (vi) severe liver dysfunction, (vii) Hb <9.0 g/dl, viii) pregnancy, ix) malignancy, x) history or treatment of bleeding or hemorrhagic diseases, including active diabetic retinopathy, xi) a disease with proteinuria except diabetic nephropathy, such as urinary tract infection and nephritis, xii) treatment with CYP3A4 inhibitors, and xiii) use of an investigational drug within the past 30 days. During the follow-up period, changes of dosage and usage of hypotensive drugs including RAS inhibitors, antiplatelet agents except cilostazol, spherical adsorptive carbon beads, thiazolidinediones, statins, and fibrates were not permitted. During this period, participants received low-protein diet therapy (0.8 g/kg/day) and other background therapy remained unchanged.

Randomization and masking: The participants were randomly assigned (1:1:1) to receive cilostazol 100 mg or 200 mg or placebo twice daily for 14 weeks. Randomization was done using a computer-generated random sequence and was stratified according to urinary ACR, blood pressure, estimated glomerular filtration rate (eGFR), HbA1c, and age. The assigned treatment was masked from the patents and investigators.

Physical examination and laboratory tests: Blood pressure was measured in the sitting position. HbA1c levels are expressed in accordance with the National Glycohemoglobin Standardization Program, as recommended by the Japan Diabetes Society. Urinary albumin was obtained from spot urine samples and assayed by turbidimetric immunoassay. The results were corrected for urine creatinine and expressed as the urinary ACR. Two consecutive morning urine samples were collected and the geometric mean of these samples was used for analysis. eGFR was calculated using a formula corrected for Japanese subjects [15]. Serum creatinine was measured by an enzymatic method. Serum cystatin C was assayed using a colloidal gold immunoassay (Alfresa Pharma Corporation, Osaka, Japan). The concentration of high molecular weight (HMW) adiponectin was assessed using a chemiluminescent enzyme immunoassay (Fujirebio, Tokyo, Japan).

Outcomes

The primary endpoint was the change in urinary ACR at 14 weeks from baseline (ΔACR), which was calculated as urinary ACR at 14 weeks – urinary ACR at baseline. The secondary endpoints were changes in eGFR, Cystatin C, and HMW adiponectin at 14 weeks from baseline (ΔeGFR, ΔCystatin C, and ΔHMW adiponectin, respectively). These were calculated using an equation similar to that for ΔACR. For post-hoc analysis, the percentage increase of urinary ACR was calculated as ΔACR / urinary ACR at baseline × 100%.

Statistical analysis

Data in the full analysis set were used. Numeric variables are expressed as mean ± standard deviation. A Student t-test and a Mann-Whitney test were used for comparison of normally and non-normally distributed continuous variables, respectively. A Chi-square test was used to compare categorical variables between groups. Data for three groups (cilostazol 100 mg, 200 mg and placebo) were compared by one-way analysis of variance. Statistical analysis was performed using SPSS v.11 (SPSS, Chicago, IL, USA), with $p < 0.05$ considered to be significant in all analyses. Interim analyses were not performed in this study.

The calculation of sample size was based on a two sided significant level of 0.05 and a power of 0.90. According to the previous study [11], the required sample size was 38 in each group for a total of 114. Assuming that 20% of patients would not have post-baseline assessment, 150 patients (50 patients per treatment group) were planned to be randomly assigned.

Results

Study participants

A total of 145 participants were enrolled from April 2012 and the last participant completed the 14-week treatment period in August 2013. Of these participants, 62 were excluded mainly due to criteria for HbA1c and blood pressure, 5 withdrew consent, and one patient in each group was randomized but not treated. As a result, 75 participants were randomized at baseline (Figure 1). The baseline characteristics of this population are shown in Table 1. There were no significant differences in metabolic parameters among the three groups. During treatment, two patients were withdrawn from the trial due to adverse effects and one was withdrawn due to non-compliance with medication in the cilostazol 100 mg group; and two patients were withdrawn due to adverse effects and one due to withdrawal of consent in the cilostazol 200 mg group. In the placebo group, no patients dropped out. Thus, final totals of 22, 22 and 25 participants were treated with cilostazol 100 mg, cilostazol 200 mg, and placebo, respectively (Figure 1).

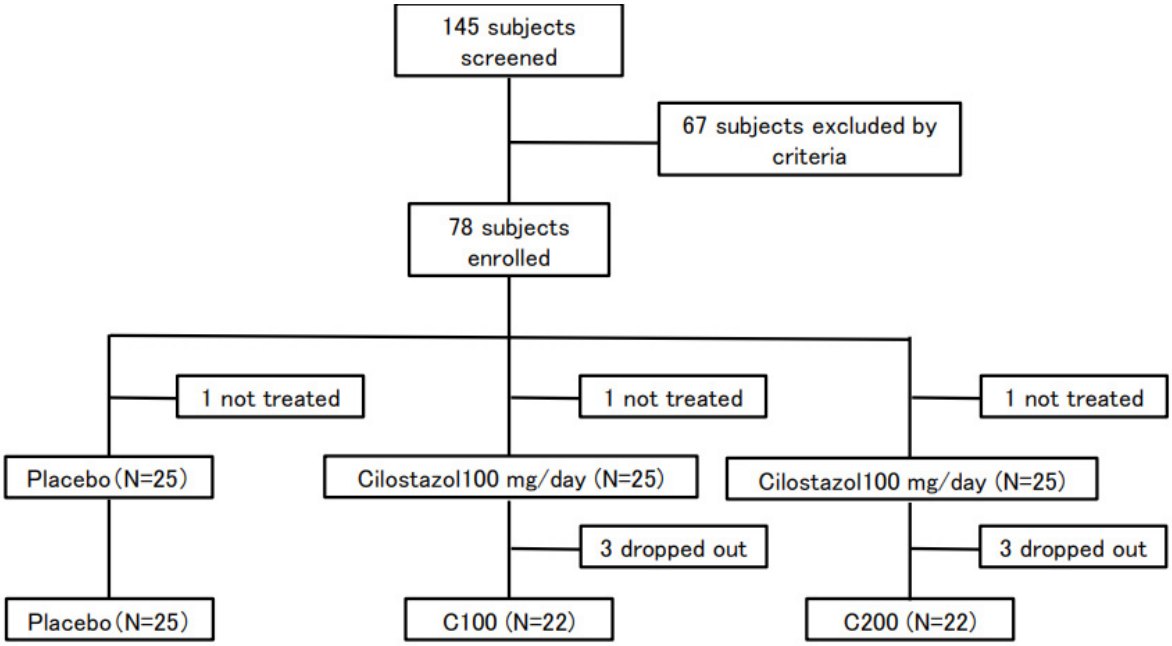

Figure 1: Flow of participants through the main 14-week period of the ATP-DN trial.

Variables	Placebo (n=25)	Cilostazol 100 mg (n=25)	Cilostazol 200 mg (n=25)	*p* value
Age (years)	62.2 ± 7.9	61.2 ± 9.6	61.2 ± 8.9	n.s.
Duration of diabetes (months)	226.6 ± 110.3	159.8 ± 107.8	172.3 ±89.9	n.s.
Gender (n, men / women)	21 / 4	18/ 7	16/ 9	n.s.
BMI (kg/m^2)	26.0 ± 4.6	26.0 ± 3.7	26.2 ± 4.2	n.s.
SBP (mmHg)	135 ± 16	138 ± 16	134 ± 15	n.s.
DBP (mmHg)	74 ± 10	77 ± 11	76 ± 10	n.s
Heart rate (/min)	73 ± 11	78 ± 13	79 ± 14	n.s
HbA1c (%)	7.3 ± 1.0	7.4 ± 0.9	7.5 ± 1.0	n.s
ACR (mg/g CRE)	1056.9 ± 811.9	1369.7 ± 1349.8	1272.0 ± 1117.9	n.s
eGFR (ml/min/1.73 m^2)	47.3 ± 17.9	48.6 ± 19.4	48.3 ± 21.3	n.s.
Cystatin C (mg/l)	1.61 ± 0.55	1.59 ± 0.49	1.66 ± 0.67	n.s.
HMW adiponectin (μg/ml)	5.58 ± 5.26	5.57 ± 4.12	4.15 ± 3.36	n.s.
Diabetic retinopathy (n)				n.s
None	5 (20%)	5 (20.0%)	7 (28%)	
Simple	4 (16%)	8 (32%)	7 (28%)	
Pre-proliferative and proliferative	16 (64%)	12 (48%	11 (44%)	

Table 1: Baseline characteristics of the randomized population.

Changes in metabolic parameters from baseline to 14 weeks

Changes in metabolic parameters from baseline to 14 weeks are shown in Table 2. HbA1c and blood pressure were unchanged by cilostazol treatment, but heart rate significantly increased in participants treated with cilostazol. Urinary ACR increased significantly in the placebo group, but not in the cilostazol 100 mg and 200 mg groups. eGFR decreased significantly with cilostazol 200 mg, but not in the other groups. Cystatin C was unchanged, but HMW adiponectin increased significantly in all three groups.

Variables	Treatment	Week	n		*p* value
SBP (mmHg)	Placebo	0	25	135 ± 16	n.s.
		14	25	136 ± 19	
	Cilostazol 100 mg	0	25	138 ± 16	n.s.
		14	22	137 ± 16	
	Cilostazol 200 mg	0	25	134 ± 15	n.s.
		14	22	136 ± 16	
DBP (mmHg)	Placebo	0	25	74 ± 11	n.s.
		14	25	75 ± 11	
	Cilostazol 100 mg	0	25	77 ± 11	n.s.
		14	22	76 ± 12	
	Cilostazol 200 mg	0	25	76 ± 10	n.s.
		14	22	75 ±10	
Heart rate (/min)	Placebo	0	25	73 ± 12	n.s.
		14	25	74 ± 11	
	Cilostazol 100 mg	0	25	78 ± 13	$p<0.001$
		14	22	89 ±10	
	Cilostazol 200 mg	0	25	79 ±14	$p=0.019$
		14	22	91 ±14	
HbA1c (%)	Placebo	0	25	7.3 ± 1.0	n.s.
		14	25	7.5 ± 1.2	
	Cilostazol 100 mg	0	25	7.4 ± 0.9	n.s.
		14	22	7.3 ±0.9	
	Cilostazol 200 mg	0	25	7.5 ±1.0	n.s.
		14	22	7.6 ±1.2	

Urinary ACR (mg/g CRE)	Placebo	0	25	1056.9 ± 811.9	*p*=0.04
		14	25	1270.2 ± 982.1	
	Cilostazol 100 mg	0	25	1369.7 ± 1349.7	n.s.
		14	22	1550.5 ± 1703.6	
	Cilostazol 200 mg	0	25	1272.0 ± 1117.9	n.s.
		14	22	1324.2 ± 1214.9	
eGFR (ml/min/1.73 m2)	Placebo	0	25	47.3 ± 17.9	n.s.
		14	25	46.1 ± 17.3	
	Cilostazol 100 mg	0	25	48.2 ± 20.3	n.s.
		14	22	45.5 ± 20.2	
	Cilostazol 200 mg	0	25	48.6 ± 21.3	*p*=0.004
		14	22	43.8 ± 21.7	
Cystatin C (mg/l)	Placebo	0	25	1.61 ± 0.56	n.s.
		14	25	1.66 ± 0.60	
	Cilostazol 100 mg	0	25	1.62 ± 0.50	n.s.
		14	22	1.61 ± 0.57	
	Cilostazol 200 mg	0	25	1.63 ± 0.64	n.s.
		14	22	1.66 ±0.72	
HMW adiponectin (μg/ml)	Placebo	0	25	5.58 ± 5.26	*p*=0.045
		14	25	6.30 ± 5.80	
	Cilostazol 100 mg	0	25	5.91 ± 4.25	*p* <0.001
		14	22	7.10 ± 4.64	
	Cilostazol 200 mg	0	25	4.33 ± 3.55	p=0.011
		14	22	5.32 ± 4.17	

Table 2: Changes in metabolic parameters from baseline to 14 weeks of treatment.

Primary endpoint

Results for the primary endpoint of the change of urinary ACR from baseline to 14 weeks (ΔACR) are shown in Table 3. ΔACR showed a dose-dependent decrease of 214.3 ± 458.7 mg/gCRE for placebo, 100.1 ± 622.8 mg/gCRE for cilostazol 100 mg, and 87.2 ± 416.5 mg/gCRE for cilostazol 200 mg, but the changes were not significant.

Secondary endpoints

Results for secondary endpoints are also shown in Table 3. Cilostazol decreased ΔeGFR dose-dependently (-1.3 ± 8.0 ml/min/1.73 m^2 for placebo, -2.6 ± 6.1 ml/min/1.73 m^2 for cilostazol 100 mg, and -4.8 ± 6.9 ml/min/1.73 m2 for cilostazol 200 mg), but not significantly. Cilostazol did not change ΔCystatin C and ΔHMW adiponectin significantly.

Variables	Placebo (n=25)	Cilostazol 100 mg (n=22)	Cilostazol 200 mg (n=22)	*p* value
Primary endpoint ΔACR (mg/g CRE)	214.3 ± 458.7	100.1 ± 622.8	87.2 ± 416.5	n.s
Secondary endpoints				
ΔeGFR (ml/min/1.73 m^2)	-1.3 ± 8.0	-2.6 ± 6.1	-4.8 ± 6.9	n.s
ΔCystatin C (ml/min/1.73 m^2)	0.05 ±0.15	-0.01 ± 0.23	0.03 ± 0.17	n.s
ΔHMW adiponectin (μg/ml)	0.71 ± 2.71	1.20 ± 1.36	0.99 ± 1.90	n.s

Table 3: Results for primary and secondary endpoints: changes in urinary ACR, eGFR, cystatin C, and HMW adiponectin from baseline to 14 weeks of treatment.

Post-hoc analysis

In post-hoc analysis, the percentage increase of urinary ACR from baseline to 14 weeks was significantly lower in the combined cilostazol 100 mg and 200 mg group (n=44) compared with the placebo group (n=25) (3.2 ± 46.7% vs. 28.5 ± 54.2%, p<0.05) (Figure 2). The percentage increases of eGFR, ΔCystatin C, and ΔHMW adiponectin were not changed by cilostazol.

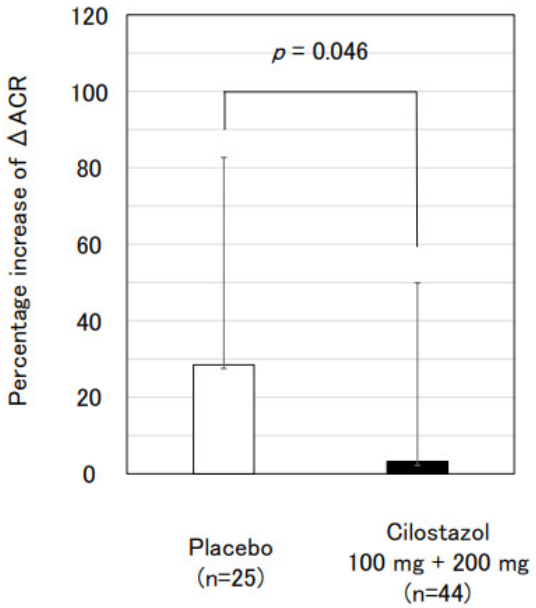

Figure 2: Effect of cilostazol on the percentage increase of urinary ACR in post-hoc analysis.

Adverse events

Palpitation, headache, and tachycardia were reported as main adverse effects: palpitation occurred in 1, 2, and 5; headache in 0, 2, and 2; and tachycardia in 0, 2, and 1 participants in the placebo, cilostazol 100 mg, and cilostazol 200 mg groups, respectively. These adverse effects showed no significant differences among the three groups and there were no deaths in each group.

Discussion

Antiplatelet therapy may be useful for diabetic vascular complications [16], and effects of antiplatelet agents on diabetic nephropathy have been found in animal models [17,18] and humans [7,8]. However, these human studies included relatively few cases, and there are few reports for type 2 diabetes and no randomized, double-blind, placebo-controlled trials. Thus, there is little evidence from large-scale clinical trials for an isolated effect of an antiplatelet agent on diabetic nephropathy. The current study is the first such trial to

examine the effects of cilostazol as an antiplatelet agent in addition to standard care for diabetic nephropathy. Cilostazol is a 2(1H)-quinolinone derivative that is an inhibitor of phosphodiesterase (PDE)-3. By inhibiting PDEs, cilostazol increases cyclic adenosine monophosphate (cAMP) levels, resulting in pleiotropic antiplatelet, anti-inflammatory, and vasodilatory effects. This is the basis for the proposed benefit of cilostazol for treating microvascular complications including diabetic nephropathy [19].

In the current study, cilostazol inhibited the significant increase of albuminuria observed in the placebo group, and decreased ΔACR dose-dependently. In post-hoc analysis, moreover, cilostazol reduced the percentage increase of albuminuria significantly. In contrast, eGFR was reduced by 200 mg cilostazol significantly and cilostazol decreased ΔeGFR dose-dependently. These data suggest a renoprotective effect of cilostazol by decreasing albuminuria through improvement of glomerular hyperfiltration in diabetic nephropathy. Similar results have been reported in an animal model [9]. Proteinuria is a risk factor for progression to ESRD [20,21], indicating the importance of reduction of proteinuria for prevention of kidney disease [22], including diabetic nephropathy [23]. Hyperfiltration is also an important mechanism in diabetic nephropathy [24], and RAS inhibitors, which are established drugs for diabetic nephropathy, exert a renoprotective effect through expanding the efferent artery on renal arterioles and reducing intraglomerular pressure. In contrast, the renoprotective effect of cilostazol has been thought to occur in parallel with regulation of inflammatory biomarkers in animals [9,10] and humans [12,13]. Therefore, regulation of inflammation is assumed to underlie the renoprotective effect of cilostazol, but the hemodynamic mechanism has not been described. For cilostazol in diabetic nephropathy, effects on proteinuria have been shown, but few reports have examined the effect on renal function. In studies showing that cilostazol reduces albuminuria, cilostazol tended to decrease eGFR in the short term until one year [13,25]. These findings are consistent with our results. These data suggest that cilostazol might have a renoprotective effect through a hemodynamic mechanism, similar to RAS inhibitors, but there is no evidence for an effect of cilostazol on the afferent and efferent arterioles of the kidney. It will be interesting and important to investigate the effect of cilostazol on renal arteries in further studies.

In this study, cilostazol decreased the increase of ΔACR dose-dependently but not significantly in the 100 mg, 200 mg, and placebo groups. Tang et al. also examined cilostazol attenuation of deterioration of albuminuria in diabetic nephropathy with similar results, but also some differences, since in Tang, et al. ΔACR was significantly reduced by cilostazol compared with the placebo [13]. This discrepancy might be due to the following issues, some of which are also limitations of the current study. The first cause may be the difference in study design: the current double-blind multicenter study in patients with macroalbuminuria, compared to a single-blind single-institute study in patients with micro and macroalbuminuria plus peripheral arterial occlusion disease. The second cause may be the differences in treatment period and dose of cilostazol: we used a 14-week period with 100 mg or 200 mg cilostazol twice daily, whereas Tang et al used treatment for 52 weeks at 200 mg cilostazol per day. The results of both studies suggested that reduction of albuminuria depended on the duration and dose of cilostazol, and it is possible that the treatment period in our study might have been too short and the dose too low to detect significant differences. The third cause might be the number of cases, since we included patients with macroalbuminuria only, which led to difficulty securing a high number of cases compared to that in Tang et al. Moreover, we randomized the patients into three dose groups, leaving ≤25 cases in each group. In contrast, Tang et al. examined 90 cases in two equally sized groups. The last cause might be differences in handling of RAS inhibitors between the two studies. In our protocol, participants had been treated with RAS inhibitors for at least 6 months at baseline, and alteration of dosage and usage were not permitted during the follow-up period. In Tang et al., RAS inhibitors were not administered in all cases at baseline, and there was no rule regarding use of RAS inhibitors in the follow-up period. This difference in the handling of RAS inhibitors may have influenced the results.

Cilostazol regulates inflammatory biomarkers associated with diabetic nephropathy, as mentioned above, and atherosclerosis, such as high-sensitivity C-reactive protein, the soluble CD40 ligand, interleukin-6, tumor necrosis factor-α, and vascular cell adhesion molecule-1 [13, 26, 27]. We focused on adiponectin as an anti-inflammatory factor because adiponectin may have a renoprotective effect [14]. We particularly focused on HMW adiponectin, which is a multimer of adiponectin that is a useful marker for metabolic syndrome and diabetic angiopathy, including diabetic nephropathy [28, 29]. In cellular and diabetic animal models, cilostazol increases adiponectin via activation of peroxisome proliferator-activated receptor-γ [30]. In the current study, HMW adiponectin increased in all three groups, but without a significant difference. In previous studies in patients with diabetes, adiponectin increased or was unchanged after cilostazol administration [26, 27], but these studies did not specify the stage of diabetic nephropathy and amount of proteinuria. The current study is the first report of the effect of cilostazol on HMW adiponectin in diabetic nephropathy with macroalbuminuria.

The main adverse events in the study of headache, palpitation, and tachycardia were expected before administration and can be explained by the pharmacological mechanism of cilostazol. Headache was due to the effect of vasodilatation, while palpitation and tachycardia were due to acceleration of adrenergic receptor stimulation by increasing cAMP through inhibition of PDE. None of the events were severe clinically.

In conclusion, cilostazol may have a renoprotective effect of reducing albuminuria through amelioration of hyperfiltration in diabetic nephropathy with macroalbuminuria. Establishment of antiplatelet therapy for diabetic nephropathy with macroalbuminuria may be important for reduction of ESRD, cardiovascular events, and death due to diabetes.

Disclousure

Clinical trial reg. no. UMIN000007718, www.umin.ac.jp/ctr/index/htm

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Conflict of interest: Disclosures of conflict of interest with regard to the study are as follows. Drugs including placebo were provided by Otsuka Pharmaceutical Co., Ltd. Inspection was performed by Otsuka Pharmaceutical Co., Ltd.

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