Cilostazol, a Potent Phosphodiesterase Type III Inhibitor, Selectively Increases Antiatherogenic High-Density Lipoprotein Subclass LpA-I and Improves Postprandial Lipemia in Patients With Type 2 Diabetes Mellitus

Katsunori Ikewaki, Keiko Mochizuki, Masafumi Iwasaki, Ryoichi Nishide, Seibu Mochizuki, and Norio Tada

Low levels of high-density lipoproteins cholesterol (HDL-C) as well as impaired postprandial lipemia are known to be associated with the increased risk for coronary artery disease (CAD) in patients with type 2 diabetes mellitus (type 2 DM). HDL are heterogeneous in size and apolipoprotein composition. Recent evidence indicates that among the 2 major HDL subclasses, those without apolipoprotein A-II (LpA-I) are more antiatherogenic compared with those with apoA-II (LpA-I:A-II). Cilostazol, a novel selective phosphodiesterase type III inhibitor, has been shown to inhibit platelet activation and is also a potent vasodilator. Additionally, cilostazol has been shown to modulate lipoprotein profiles by raising HDL-C and lowering plasma triglyceride (TG) levels. The present study investigated the effect of cilostazol on HDL composition (LpA-I and LpA-I:A-II levels) and postprandial lipemia in patients with type 2 DM. Seventeen patients were given cilostazol 200 mg twice daily for 12 weeks. At weeks 0 and 12, fat tolerance tests (30 g/m^2) were performed to assess postprandial lipemia. Plasma TG and remnant-like lipoprotein particles cholesterol (RLP-C) were significantly decreased by 17% and 26%, respectively ($P < .05$), and HDL-C was significantly increased by 14% ($P < .01$). LpA-I was significantly increased by 23% ($P < .01$) from the mean value of 45 mg/dL to 55 mg/dL. In contrast, LpA-I:A-II remained unchanged, resulting in significantly increased %LpA-I (apoA-I on LpA-I/total apoA-I × 100) from 35% to 40% ($P < .01$). Areas under the curve for TG and RLP-C after the fat meal were both nonsignificantly decreased by 17%. Patients with higher plasma TG levels had a greater benefit from the treatment with cilostazol as revealed by fasting TG levels and fat tolerance tests. HDL-C responses to cilostazol were independent of baseline plasma TG levels or percentage changes in TG, indicating that the underlying mechanisms for raising HDL and reducing TG levels are distinct. In conclusion, cilostazol selectively increased LpA-I, thus favorably altering HDL towards a more antiatherogenic composition. This finding, together with the improved postprandial lipemia, indicates that cilostazol has a potent antiatherogenic function by modulating HDL and remnant metabolism in patients with type 2 DM.
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LOW LEVELS OF high-density lipoproteins cholesterol (HDL-C) as well as impaired postprandial lipemia are characteristic lipid abnormalities in patients with type 2 diabetes mellitus (type 2 DM) who are at increased risk for coronary artery disease (CAD).[1,2] Plasma concentrations of HDL-C have been shown to be inversely associated with the incidence of CAD.[3] Although the mechanism by which HDL may exert a direct protective effect against development of atherosclerosis is not yet well understood, HDL has been postulated to facilitate the efflux of cholesterol from peripheral tissues and transport it back to the liver in a process termed reverse cholesterol transport.[4] Two major proteins in HDL are apolipoprotein (apo) A-I and apoA-II. Many epidemiologic studies have demonstrated that plasma apoA-I concentration correlates inversely with the incidence of CAD,[5,6] while the correlation of apoA-II levels with the incidence of CAD is unconfirmed and the role of apoA-II in HDL metabolism remains unclear.[5,7] However, recent evidence suggests that apoA-II may even be proatherogenic. A mouse strain with high apoA-II production was more prone to atherogenesis.[8] Similarly, transgenic mice overexpressing mouse apoA-II develop atherosclerosis even on a normal chow diet.[9] Further, coexpression of human apoA-II in transgenic mice overexpressing apoA-I counteracts the beneficial effect of apoA-I against atherosclerosis development.[10]

HDL is heterogeneous in apoprotein composition; the major HDL subclasses are those containing only apoA-I (LpA-I) and those containing both apoA-I and apoA-II (LpA-I:A-II.[11] Substantial evidence suggests that these subclasses differ with respect to metabolism and their effects on atherosclerosis. Kinetic studies in normolipidemic subjects[12] and in patients with a genetic deficiency of lecithin: cholesterol acryltransferase[13] indicate distinct metabolic pathways for these 2 HDL subclasses. Most but not all clinical studies support the concept that LpA-I may be a more antiatherogenic lipoprotein than LpA-I:A-II.[14-17]

Impaired postprandial lipemia is commonly present in diabetic patients with normal fasting plasma triglyceride (TG) concentrations.[18] Recent studies have demonstrated evidence that postprandial lipemia is an independent risk factor for CAD.[19,20] In the postprandial phase, newly synthesized TG-rich lipoproteins derived from both the intestine (chylomicron [CM]) and the liver (very–low-density lipoprotein [VLDL]) increase in the plasma, leading to an accumulation of remnant lipoproteins (remnants), which are metabolites of TG-rich lipoproteins and arise from partial metabolism of CM and VLDL by lipoprotein lipase. Remnants are enriched in cholesteryl esters as well as apoE and can be taken up by macrophages to form foam cells.[21]

Cilostazol, a potent phosphodiesterase type III inhibitor, has platelet aggregation inhibitor[22] and vasodilator actions.[23] In addition, early studies performed in Japan[24-32] and recently in

From the Division of Cardiology, Department of Internal Medicine, the Department of Internal Medicine, Aoto Hospital, and the Department of General Medicine, Kashiwa Hospital, Jikei University School of Medicine, Tokyo, Japan.

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Address reprint requests to Katsunori Ikewaki, MD, PhD, Division of Cardiology, Department of Internal Medicine, Jikei University School of Medicine, 3-25-8 Nishi-Shinbashi, Minato-ku, Tokyo, Japan 105-8461.

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the United States[33,34] and Taiwan[35] have demonstrated a beneficial effect by cilostazol on lipoprotein metabolism, characterized by an increase in HDL-C and a reduction of plasma TG level. In the light of these understandings, we wished to test the hypothesis that cilostazol increases antiatherogenic LpA-I and improves postprandial lipemia in hypertriglyceridemic patients with type 2 DM.

MATERIALS AND METHODS

Study Subjects

At the end of 4 to 8 week run-in period to ensure the stability of body weight and diabetic control, 18 patients with type 2 DM were recruited. None of the study subjects had poorly controlled diabetes or evidence of thyroid, liver, or renal dysfunction (creatinine $>$ 2 mg/dL) and none were taking antiplatelet, anticoagulant, or lipid-modifying medications. Medication for diabetes (insulin n = 1, glibenclamide n = 5) and β-blockers (n = 2) were unchanged throughout the study period. All subjects were instructed to maintain their diet, exercise, and alcohol intake throughout the study period, including the run-in period. As the result, the mean body weight and hemoglobin A_{1c} HbA_{1c} did not change during the study period (mean body weight, 67.1 to 67.3kg; HbA_{1c}, 6.8% to 6.8%). Study subjects gave written informed consent to the study protocol.

Study Protocol

Cilostazol administration was started at half-dose (50 mg twice daily) for 2 weeks to prevent possible adverse effects, including headache, flash, and palpitations, after which the dose was increased to 100 mg twice daily. At week 0 and week 12, an oral fat tolerance test was performed as described below.

Oral Fat Tolerance Test

After a 12-hour fast, subjects were given an oral fat meal (30 g/m^2) in liquid formula. The average contents of fat, carbohydrate, and protein were 92%, 5%, and 3%, respectively. The average cholesterol content was 116 mg/1,000 kcal and the ratios of polyunsaturated, monounsaturated, and saturated fatty acids were 3.5%, 32.2%, and 64.3%, respectively. Blood samples were obtained prior to the fat load and at 2, 4, and 6 hours thereafter to monitor plasma total cholesterol, TG, HDL-C, remnant-like particles cholesterol (RLP-C), and RLP-TG levels. Blood samples were drawn into tubes containing EDTA at a final concentration of 0.1%. Blood samples were kept at 4°C; plasma was separated by centrifugation of fresh blood samples at 2,500 rpm for 20 minutes at 4°C. Postprandial lipemia was evaluated by the area under the curve (AUC) of plasma TG, RLP-C, and RLP-TG. Plasma total cholesterol and HDL-C remained constant (variation $<$ 5%) during 6 hours.

Analytical Methods

Plasma total cholesterol and TG levels were determined by automated enzymatic technique using a Toshiba TBA-80FR Auto-analyzer (Tokyo, Japan). HDL-C was measured by heparin-manganese precipitation. Plasma apoA-I, apoA-II, apoB, apoC-II, apoC-III, and apoE concentrations were quantified using immunoturbidometric assays.[36] Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedwald formula. RLP-C and -TG were measured by the method reported by Leary et al.[37] In brief, plasma (5 μL) was added to 300 μL of RLP separation gel, consisting of anti–apoA-I (H-12) and anti–apoB (JI-H) monoclonal antibodies bound to Sepharose 4B gel and then incubated for 2 hours at the room temperature with a vertical magnetic-bead oscillator (RLP Mixer J-100A, Photal, Otsuka Electronics, Tokushima, Japan). The mixture was allowed to settle for 15 minutes. The supernatant was taken for colorimetric measurement of cholesterol and TG (Determiner LTC and Determiner LTG, respectively, Kyowa Medex, Tokyo, Japan).

Plasma LpA-I concentration was measured by an electroimmunoassay method described by Parra et al[38] and expressed as the apoA-I mass (in milligrams) in LpA-I per unit of volume (in deciliters). The apoA-I concentration in LpA-I:A-II was obtained by subtracting the LpA-I value from the total plasma apoA-I concentration.

ApoE phenotype was determined by immunoblot using a specific goat anti-apoE polyclonal antibody using a method reported by Kataoka et al.[39]

Statistical Analysis

Changes in fasting plasma lipids, apolipoproteins, lipoproteins, and AUCs after the fat meal were analyzed by the Wilcoxon signed-rank test. Correlations between baseline plasma lipids and percentage changes in plasma lipids were assessed by the Spearman rank correlation. Difference in response of lipid parameter to cilostazol between high- and low-TG groups was tested by the Mann-Whitney *U* test. The differences were considered significant if the *P* value was less than .05. All statistical procedures were performed using SPSS software (version 9, SPSS Inc, Chicago, IL).

RESULTS

Among 18 patients enrolled in the study, 1 patient discontinued cilostazol treatment due to persistent headache. The data from the remaining 17 (15 men and 2 women) patients were analyzed. The mean age was 64 years (range, 45 to 79 years). As shown in Table 1, the average fasting plasma glucose and HbA_{1c} were 143 mg/dL and 6.8%, respectively; these parameters remained stable throughout the study period (148 mg/dL, 6.8% at week 12, respectively). Mean $\pm$ SE of total-C, HDL-C, and LDL-C were 203 $\pm$ 7, 45 $\pm$ 2, and 124 $\pm$ 6 mg/dL, respectively. Mean plasma TG value was 170 $\pm$ 13 mg/dL, representing a modest hypertriglyceridemic population according to the criteria of the Japanese Atherosclerosis Society (normal fasting TG level $<$ 150 mg/dL). ApoE phenotypes of the study subjects included 11 E3/3, 3 E3/2, 2 E4/3, and 1 E4/4. There was no significant difference in lipid or apolipoprotein levels across apoE phenotypes (data not shown).

Changes in plasma and lipoprotein lipid values after 12 weeks of cilostazol treatment are summarized in Table 1. There were significant increases in HDL-C (14%) and a decrease in plasma TG (−17%), RLP-C (−26%), RLP-TG (−31%), and apoB (−7%). Relative to apoA-I, which showed a modest increase, apoA-II, another major protein constituent of HDL, remained unchanged (mean value, 30 to 31 mg/dL). To assess whether baseline TG and HDL-C associate with percentage change in TG and HDL-C, the correlation between baseline plasma TG, HDL-C levels, and the percentage change in TG, HDL-C are shown in Fig 1. Baseline TG level (r = -0.498, P = .042, Fig 1A), but not HDL-C level (r = .135, P = .605, Fig 1C), was negatively correlated with the percentage change in TG; a higher baseline TG level showed a greater percentage TG reduction. However, HDL-C response to cilostazol was not affected by either baseline TG (Fig 1B) or HDL-C levels (Fig 1D), indicating that the underlying mechanisms which modulate TG and HDL-C by cilostazol are distinct. Indeed, the percentage change in TG was not correlated with the percentage change in HDL-C (r = -0.169, P = .516, data not shown).

Table 1. Effect of Cilostazol on Plasma Lipids, Liporoteins, Apolipoproteins Levels, HbA_{1c}, and Postprandial Lipemia

Parameter	Week 0	Week 12	% Change
BMI	25.2 ± 0.8 kg/m^2	25.2 ± 0.8 kg/m^2	0.0%
FPG	143 ± 4.8 mg/dL	148 ± 8.6 mg/dL	3.4%
TC	203 ± 6.6 mg/dL	199 ± 6.5 mg/dL	−1.5%
TG	170 ± 12.5 mg/dL	142 ± 11.1 mg/dL	−16.5%*
HDL-C	44.9 ± 2.3 mg/dL	51.2 ± 2.9 mg/dL	13.9%†
LDL-C	124 ± 6.0 mg/dL	120 ± 6.0 mg/dL	−3.0%
RLP-C	6.2 ± 0.6 mg/dL	4.6 ± 0.6 mg/dL	−25.6%*
RLP-TG	34.3 ± 4.0 mg/dL	23.5 ± 3.3 mg/dL	−31.5%*
ApoA-I	128 ± 4.7 mg/dL	136 ± 4.8 mg/dL	6.3%
ApoA-II	30.0 ± 1.1 mg/dL	30.8 ± 1.0 mg/dL	2.4%
ApoB	114 ± 4.9 mg/dL	106 ± 4.2 mg/dL	−7.5%*
ApoC-II	4.3 ± 0.3 mg/dL	4.2 ± 0.4 mg/dL	−3.4%
ApoC-III	11.6 ± 0.7 mg/dL	11.0 ± 0.7 mg/dL	−5.0%
ApoE	5.0 ± 0.3 mg/dL	4.6 ± 0.3 mg/dL	−7.5%
LpA-I	45.0 ± 3.9 mg/dL	55.2 ± 3.7 mg/dL	22.7%†
LpA-I:A-II	82.6 ± 2.5 mg/dL	80.5 ± 3.1 mg/dL	−2.6%
%LpA-I	34.5% ± 2.1%	40.3% ± 1.9%	16.8%†
HbA_{1c}	6.8% ± 0.3%	6.8% ± 0.3%	−0.2%
AUC			
TG	1347 ± 116 h · mg/dL	1123 ± 90 h · mg/dL	−16.6%
RLP-C	52.4 ± 5.0 h · mg/dL	43.1 ± 4.4 h · mg/dL	−17.8%
RLP-TG	495 ± 65 h · mg/dL	341 ± 40 h · mg/dL	−31.1%*

NOTE. Values are means ± SE.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; %LpA-I, plasma apoA-I/apoA-I on LpA-I × 100; AUC, area under the curve.

*$P < .05$, †$P < .01$ by Wilcoxon signed-rank test.

The effect of cilostazol on HDL subclasses is also shown in Table 1. The mean LpA-I level was significantly increased by 23%, from 45 to 55 mg/dL ($P < .001$), whereas that of LpA-I:A-II remained unchanged. The resulting %LpA-I (apoA-I on LpA-I/total apoA-I × 100) was significantly increased by 17%, thus favorably altering the HDL composition toward antiatherogenic LpA-I predominant. Selective increase in LpA-I was not affected by baseline TG levels as

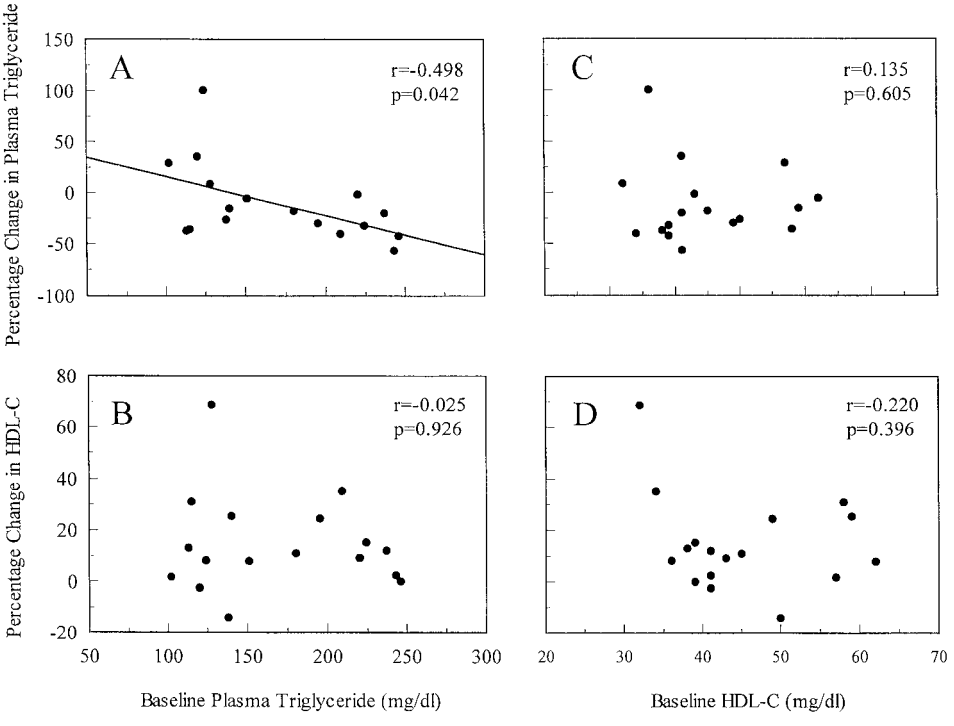

Fig 1. Correlations of baseline plasma triglyceride with % changes in plasma TG (A) and HDL-C (B), and those of HDL-C with % changes in plasma TG (C) and HDL-C (panel D).

Table 2. Effect of Baseline Triglycerides Levels on Plasma Lipids, Lipoproteins, and Apolipoprotein Response to Cilostazol

	Baseline TG ≥ 150 mg/dL (n = 9)			Baseline TG < 150 mg/dL (n = 8)		
Parameter	Week 0	Week 12	% Change	Week 0	Week 12	% Change
TC	206 ± 5.4 mg/dL	199 ± 12.0 mg/dL	−5.3%	199 ± 12.0 mg/dL	204 ± 11.6 mg/dL‡	2.8%
TG	212 ± 9.9 mg/dL	151 ± 10.5 mg/dL	−28.6%†	123 ± 4.2 mg/dL	131 ± 18.9 mg/dL‡	15.1%
HDL-C	43.7 ± 2.5 mg/dL	49.2 ± 2.8 mg/dL	12.7%*	46.4 ± 3.6 mg/dL	53.4 ± 4.9 mg/dL	15.1%
LDL-C	120 ± 4.9 mg/dL	116 ± 6.6 mg/dL	−3.6%	128 ± 10.9 mg/dL	125 ± 9.6 mg/dL	−2.4%
RLP-C	7.6 ± 0.6 mg/dL	4.4 ± 0.3 mg/dL	−41.6%*	4.6 ± 0.5 mg/dL	4.8 ± 0.9 mg/dL‡	4.1%
RLP-TG	45.9 ± 4.3 mg/dL	23.5 ± 2.1 mg/dL	−48.8%	21.3 ± 2.2 mg/dL	23.6 ± 6.3 mg/dL‡	10.4%
ApoA-I	130 ± 3.3 mg/dL	134 ± 3.3 mg/dL	3.4%	125 ± 8.9 mg/dL	137 ± 8.3 mg/dL	9.7%
ApoA-II	30.9 ± 1.4 mg/dL	30.4 ± 1.2 mg/dL	−1.4%	29.1 ± 1.7 mg/dL	31.2 ± 1.5 mg/dL	7.0%
ApoB	120 ± 4.7 mg/dL	105 ± 4.6 mg/dL	−12.6%*	107 ± 7.9 mg/dL	106 ± 7.0 mg/dL	−1.1%
ApoC-II	4.9 ± 0.4 mg/dL	4.0 ± 0.4 mg/dL	−18.4%*	3.7 ± 0.3 mg/dL	4.4 ± 0.6 mg/dL	19.0%
ApoC-III	13.0 ± 0.7 mg/dL	10.9 ± 0.6 mg/dL	−16.0%	10.0 ± 1.0 mg/dL	11.0 ± 1.0 mg/dL	11.0%
ApoE	5.5 ± 0.3 mg/dL	4.4 ± 0.2 mg/dL	−19.7%†	4.3 ± 0.5 mg/dL	4.7 ± 0.6 mg/dL‡	10.2%
LpA-I	45.5 ± 3.7 mg/dL	55.0 ± 3.7 mg/dL	20.9%†	44.3 ± 6.9 mg/dL	55.3 ± 6.3 mg/dL	24.8%*
LpA-I:A-II	84.3 ± 2.2 mg/dL	79.2 ± 3.5 mg/dL	−6.0%	80.8 ± 4.5 mg/dL	81.9 ± 4.9 mg/dL	1.4%
%LpA-I	34.8 ± 2.2%	40.9 ± 2.1%	17.6%†	34.3 ± 3.5%	39.7 ± 3.0%	15.9%
AUC-TG	1,715 ± 103 h · mg/dL	1,231 ± 90 h · mg/dL	−28.2%*	933 ± 55 h · mg/dL	1002 ± 145 h · mg/dL‡	7.3%
AUC-RLP-C	67.4 ± 5.2 h · mg/dL	45.2 ± 4.2 h · mg/dL	−32.9%*	35.5 ± 1.8 h · mg/dL	40.7 ± 7.6 h · mg/dL‡	14.4%
AUC-RLP-TG	671 ± 78 h · mg/dL	363 ± 32 h · mg/dL	−46.0%†	296 ± 35 h · mg/dL	316 ± 73 h · mg/dL‡	6.9%

NOTE. Values are means ± SE.

*$P < .05$, †$P < .01$ by Wilcoxon signed-rank test.

‡Significantly different response ($P < .05$) compared to the group with baseline TG ≥ 150 mg/dL by Mann-Whitney *U* test.

shown in Table 2 or baseline HDL-C levels ($r = -0.261$, $P = .312$, data not shown).

Since baseline TG levels varied among the subjects and were correlated with TG response, the effect of cilostazol was further examined by separating the subjects based on TG level; a high-TG group (TG =150 mg/dL, n = 9) and a low-TG group (TG < 150 mg/dL, n = 8). As shown in Table 2, the responses of TC, TG, RLP-C, RLP-TG, and apoE were significantly different between the 2 groups. In the high-TG group, TG, RLP-C, RLP-TG, apoB, apoC-II, and apoE were all significantly decreased by −29%, −42%, −49%, −13%, −18%, and −20%, respectively. However, in the low-TG group, the response of the aforementioned parameters was not significant, suggesting that hypertriglyceridemic subjects are more likely to benefit from treatment with cilostazol than normotriglyceridemic subjects. In contrast to these TG-associated lipid parameters, responses of HDL-C, LpA-I, and %LpA-I did not differ between the groups, which is consistent with the nonsignificant association between the baseline TG and the percentage change in HDL-C (Fig 1B).

As illustrated in Fig 2, postprandial responses of plasma TG (Fig 2A), RLP-C (Fig 2B), and RLP-TG (Fig 2C) to a fat meal were improved by cilostazol treatment. AUCs of plasma TG and RLP-C were both nonsignificantly decreased by 17% and 18% ($.05 < P < .1$), respectively, and the AUC of RLP-TG was significantly decreased by 31% ($P < .05$, Table 2). In parallel with the response of fasting plasma TG, RLP-C, and RLP-TG, postprandial response to cilostazol varied with baseline plasma TG levels. As shown in Table 2, a significant beneficial response was observed in the high-TG group, in whom the AUCs of plasma TG, RLP-C, and RLP-TG were significantly decreased by 28% to 46%. In contrast, in the low-TG group, these parameters were nonsignificantly increased by 7% to 14%.

DISCUSSION

In the present study, we found that cilostazol, a potent inhibitor of phosphodiesterase type III, favorably modulated lipoprotein profiles in type 2 DM patients. Cilostazol increased HDL-C and reduced fasting plasma TG as well as postprandial lipemia. The observed HDL-C response was not associated with baseline TG levels or TG response. Pooled analysis of previous studies[24-35] showed that plasma TG level was decreased by 22% and HDL increased by 11.8% by cilostazol. Further, baseline TG level was significantly and inversely correlated with percentage change in plasma TG ($r = -0.458$, $P = .049$), while baseline HDL-C level was not correlated with percentage change in HDL-C ($r = -0.410$, $P = .082$), findings consistent with the present study. Taken together, our results are interpreted as indicating that the effects of cilostazol on HDL and TG-rich lipoprotein metabolism may be distinct.

To the best of our knowledge, this is the first demonstration that LpA-I, one of the major HDL subclasses, is selectively increased by cilostazol. Collective in vitro and in vivo data demonstrate that LpA-I is more effective in effluxing cholesterol from tissues,[40,41] the initial step of the so-called reverse cholesterol transport, compared with LpA-I:A-II, and that the increased LpA-I exerts a protective effect against diet-induced atherosclerosis in mice[10,42] and in humans.[14] Surprisingly, LpA-I:A-II remained unchanged by cilostazol treatment, resulting in HDL composition being richer in LpA-I. In this context, the selective increase in LpA-I by cilostazol may be considered to be protective against the development of CAD. Several lipid-lowering agents have been reported to modulate LpA-I and LpA-I:A-II levels.[43] Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and cation exchange resins generally raise LpA-I with no effect on LpA-I:A-II, but the LpA-I increase is either small (~7%) or inconsistent.[44-46] In

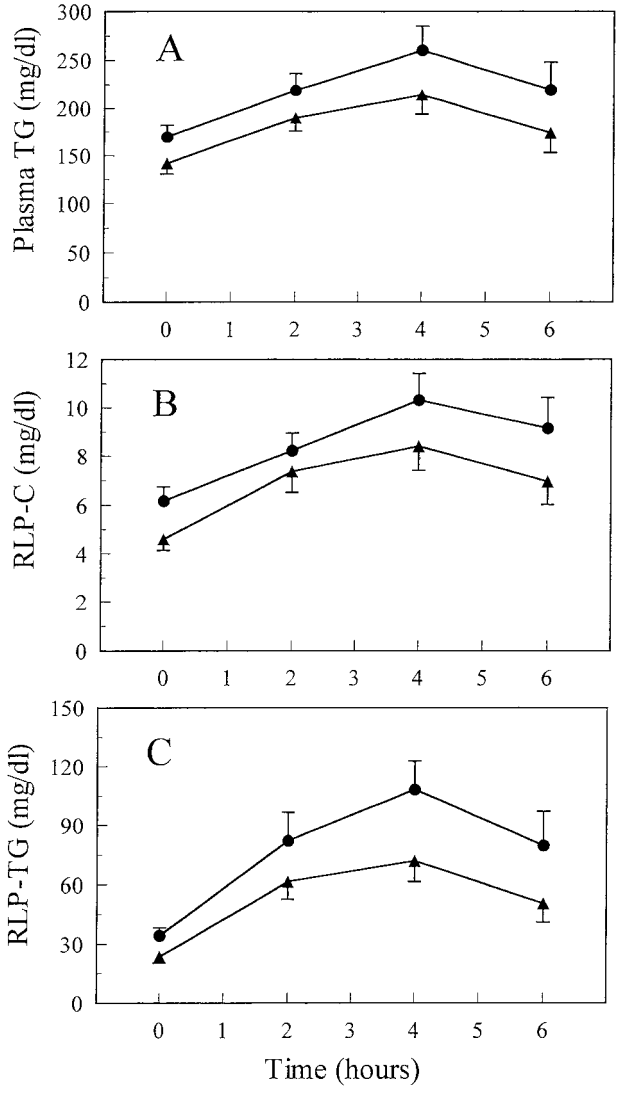

Fig 2. Effect of cilostazol on postprandial changes in plasma TG (A), RLP-C (B), and RLP-TG (C). Values at week 0 (●) and week 12 (▲). Values are expressed as the mean ± SE.

contrast, fibrate derivatives, like cilostazol, lower TG, raise HDL-C, and LpA-I:A-II, but lower LpA-I.[47,48] Therefore, an increase in HDL-C secondary to the improved lipolysis via activation of lipoprotein lipase by the fibrate derivatives results in the elevation of LpA-I:A-II, but not LpA-I. At present, the exact mechanism to increase HDL by cilostazol is unknown. Cilostazol inhibits phosphodiesterase type III, thereby increasing intracellular cyclic adenosine monophosphate (cAMP) levels. Previous studies reported that increased cAMP enhanced cholesterol efflux from cholesterol-loaded human skin fibroblasts[49] and apolipoprotein-mediated HDL generation from murine macrophase cells,[50] therefore indicating a potential mechanism for an HDL-raising effect by cilostazol. Although cilostazol[51] and cAMP[52] have been shown to increase lipoprotein lipase in rats, 3 clinical studies in humans reported that lipoprotein lipase activity was not modulated by cilostazol treatment.[27,31,32] Elam et al[34] also observed that time course of the effect of cilostazol on HDL-C differed from that on TG, and that the change in HDL-C was not correlated with the decrease in TG, supporting our hypothesis that different mechanisms may be responsible for the effect of cilostazol on HDL-C and TG. These findings from clinical studies, together with the different response of HDL subclasses compared to fibrate derivatives, suggest that the increased lipoprotein lipase activity may not be involved as the major underlying mechanism for the increased HDL-C by cilostazol. However, effects of cilostazol on HDL subclasses, apoA-I, or apoA-II have not been documented previously. Thus, this unique effect of cilostazol on HDL, namely, the selective increase in LpA-I, should be confirmed in future studies.

Recent meta-analysis by Hokanson et al[53] demonstrated that plasma TG is a risk factor independent of HDL-C. Zilversmit was the first to propose that postprandial lipemia contributes to the development of atherosclerosis.[21] Many subsequent studies have confirmed the atherogenecity of postprandial lipemia and further demonstrated that CM and VLDL remnants are proatherogenic lipoproteins of postprandial origin. It has been proposed that type 2 DM patients may have generic defects in postprandial lipemia.[18] Postprandial lipemia, namely, hypertriglyceridemia, along with low levels of HDL put type 2 DM patients at a high risk for CAD. Recent development of RLP-C, an assay to directly determine remnants in plasma, permitted us to evaluate postprandial remnant lipoprotein metabolism.[54] We showed that, using fat tolerance test, postprandial lipemia was improved by the treatment of cilostazol. Given that lipoprotein lipase activities were unchanged by cilostazol, it is possible that the improved postprandial lipemia is attributable to the suppression of hepatic VLDL secretion as previously reported.[27,32,55]

There are some limitations in the present study. First, this study is relatively small in sample size. This small sample size, together with a fact that some study subjects showed greater responses to cilostazol than others (ie, 69% *v* 11% increase in a outlier and the average of the remaining subjects, respectively, for HDL-C; 101% increase *v* 18% decrease in a outlier and the average of the remaining subjects, respectively, for plasma TG) may have a noticeable effect on the results. Although the influence of the outlier on the response of plasma lipid to cilostazol was found to be very little, the results should be interpreted with caution. Responses of TG-associated parameters differed between high- and low-TG groups (Table 2). These parameters tended to deteriorate with cilostazol treatment in low-TG group. Although it is not clear why low-TG subjects responded differently as compared with high-TG counterparts, we speculate that the TG-lowering effect of cilostazol cannot further improve TG metabolism in subjects who are having relatively normal TG metabolism. Second, this study lacks a control group. In order to minimize factors that could obscure or confound the effects of the cilostazol, we did not changed medications and the study subjects were instructed to maintain their diet, exercise, and alcohol intake throughout the study period As the result, body weight or HbA_{1c} did not change significantly. Nonetheless, the definite conclusion deserves a parallel-group clinical trial. Third, we did not measure postheparin lipoprotein lipase and hepatic lipase activities, which did not allow us to propose the exact mechanism for the

TG-lowering effect by cilostazol. However, as described above, several studies have reported that cilostazol did not modulate the lipase activities.[27,31,32] Fourth, most of the study subjects were male patients with type 2 DM. Thus, caution must be exercised to generalize our observations to female counterparts or nondiabetic patients with hyperlipidemia.

Cilostazol was originally marketed in Japan for the treatment of chronic arterial disease with symptom of intermittent claudication. In addition to its vasodilator and antiplatelet properties, studies in Japan[24-32] and those in other countries[33-35] have demonstrated cilostazol's favorable effect on lipoproteins metabolism; increasing HDL-C and lowering TG levels. The present study further characterized the lipid-modifying property as a selective increase in antiatherogenic LpA-I and an improved postprandial lipemia in type 2 DM patients. Recent in vitro studies demonstrate other pharmacologic effects for this substance, suppression of platelet-derived growth factor[56] and proliferation of smooth muscle cells,[57] which are translated to prevent restenosis after percutaneous transluminal coronary angioplasty.[58,59] These effects may offer long-term benefit in patients with high risk for CAD such as dyslipidemic diabetic patients.

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