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Ezetimibe Monotherapy Reduces Serum Levels of Platelet-Activating Factor Acetylhydrolase in Patients With Dyslipidemia

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Abstract

Background: The combination of ezetimibe with statin therapy reduced cardiovascular events compared to statin monotherapy in IMPROVEIT study, and ezetimibe monotherapy attenuated atherosclerosis in basic study. We previously showed ezetimibe monotherapy was especially effective for metabolic syndrome (MetS) patients. We investigated the effects of ezetimibe monotherapy for high-density lipoprotein cholesterol (HDL-chol) function and platelet-activating factor acetylhydrolase (PAF-AH) activity.

Methods: Forty-two patients who initially received ezetimibe (10 mg/day) without statin treatment for 16 weeks from January 2009 to August 2011 were enrolled. Patients were divided into MetS and non-MetS groups, and serum levels of lipids, PAF-AH, and HDL-chol efflux capacity (HDL-CEC) at baseline and after 16 weeks of treatment were investigated. Serum PAF-AH, HDL-associated PAF-AH (HDL-PAF-AH), and LDL-associated PAF-AH (LDL-PAF-AH) were measured.

Results: In all patients, age, the percentages of males, and body mass index were 61.0 ± 8.8 years, 59.5% and 26.3 ± 3.4 kg/m^2, respectively. Total cholesterol and low-density lipoprotein cholesterol (LDL-chol) were significantly decreased by ezetimibe monotherapy.

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Serum PAF-AH and LDL-PAF-AH were significantly decreased by ezetimibe monotherapy, whereas HDL-PAF-AH and HDL-CEC were not. There was no difference in the results of PAF-AH and HDL-CEC between MetS and non-MetS groups.

Conclusions: Ezetimibe monotherapy might prevent coronary heart disease (CHD) regardless of the presence of MetS, because PAF-AH was independent risk factor for CHD.

Keywords: Metabolic syndrome; Platelet-activating factor acetylhydrolase; Cholesterol efflux capacity

Introduction

Dyslipidemia causes cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall, and is the foremost cause of premature mortality and disability-adjusted life years [1]. Ezetimibe selectively inhibits the intestinal absorption of cholesterol and related phytosterols. In the IMPROVE-IT study, the combination of ezetimibe plus simvastatin therapy in patients with post-acute coronary syndrome significantly reduced cardiovascular events compared to simvastatin monotherapy [2].

Ezetimibe monotherapy has been shown to reduce atherothrombotic complications after superficial plaque erosion [3] and to attenuate atherosclerosis associated with lipid reduction and the inhibition of inflammation [4]. We previously reported that ezetimibe monotherapy for dyslipidemia patients reduced the serum levels of total cholesterol (T-chol), low-density lipoprotein cholesterol (LDL-chol), and non-high-density lipoprotein cholesterol (non-HDL-chol), especially in metabolic syndrome (MetS) (Zenith Trial) [5]. But ezetimibe is not recommended as a fist choice for dyslipidemia.

Platelet-activating factor acetylhydrolase (PAF-AH) activity is a circulating enzymatic biomarker of inflammation that is primarily bound to LDL-chol [6]. We previously reported that PAF-AH activity was associated with paroxysmal atrial fibrillation [6] and HDL-associated PAF-AH activity was associated with diabetes mellitus (DM) and the coronary artery calcification score [7]. PAF-AH activity was also associated with

both unstable and stable coronary heart disease [8] and was an independent predictor of coronary artery disease (CAD) [9].

HDL-chol efflux capacity (HDL-CEC), one of the functions of HDL-chol, has a strong inverse association with atherosclerosis [10]. We previously reported the efficacy of HDL-CEC against atherosclerosis and CAD [11-15].

In this study, we investigated PAF-AH and HDL-CEC in dyslipidemia patients receiving ezetimibe monotherapy.

Materials and Methods

Study design

Kumagai et al previously reported the effects of ezetimibe on dyslipidemia patients with MetS (Zenith Trial) [5]. Each subject signed an informed consent form after the protocol was explained. Patients who were treated with ezetimibe for dyslipidemia from January 2009 to August 2011 at Fukuoka University Hospital and its related hospitals in the Kyushu area of Japan were enrolled. Patients who were pretreated with statin after a 4-week washout period were enrolled. Serum samples were collected at baseline and after 16 weeks of treatment with ezetimibe. The patients were divided into MetS and non-MetS groups. Male, the presence of MetS, and a lower ratio of LDL-chol to HDL-chol were independent factors that predicted a good response to ezetimibe monotherapy. For this investigation, the Zenith Trial including the current investigation was approved by the Independent Review Board (IRB) of Fukuoka University (2017M160) and conducted according to the Declaration of Helsinki regarding investigations in humans. We excluded 16 patients from the Zenith Trial due to insufficient blood sample volumes, and finally analyzed 42 patients.

PAF-AH activity

Serum lipoprotein-associated phospholipase A2 was measured by a spectrophotometric assay using an automatic analyzer (JCA-BM6010, JEOL, Ltd, Tokyo, Japan) [16]. HDL-associated PAF-AH (HDL-PAF-AH) activity was measured in apolipoprotein B-depleted serum, which was separated by precipitation of apo-B using phosphotungstate acid/$MgCl_2$. The value of LDL-associated PAF-AH (LDL-PAF-AH) activity was taken to be the value of PAF-AH activity in whole serum minus the value of HDL-PAF-AH activity, as previously described [6, 7].

HDL-CEC

HDL-CEC was measured by an *ex vivo* technique, as previously described [11-15]. 3H-cholesterol-labeled J774 macrophage cells were incubated with apoB-depleted serum samples for 4 h. Radiolabeled cholesterol counts in macrophage and medium were measured by a liquid scintillation analyzer (Tri-Carb 2900TR, Perkin Elmer Co., Ltd, MA, USA). HDL-CEC was

calculated as HDL-CEC (%) = (radioactivity in the medium/radioactivity in the medium + macrophages) × 100/cholesterol efflux activity in serum-free medium.

Measurements of various parameters

Age, gender, body mass index (BMI), history of hypertension (HT), DM, and CAD were evaluated. BMI was calculated as weight (kg)/height^2 (m^2).

Serum levels of white blood cell (WBC), high-sensitivity C-reactive protein (hs-CRP), blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alkaline phosphatase (ALT), T-chol, TG, LDL-chol, HDL-chol, remnant-like particle-cholesterol (RLP-chol), and adiponectin were evaluated at the Fukuoka University Hospital Laboratory Unit or by SRL Corporation, as reported previously [5].

Statistical analyses

All data analyses were performed using the SAS (Statistical Analysis System) Software Package (Ver. 9.4, SAS Institute Inc., Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Continuous variables with a normal distribution were expressed as mean ± standard deviation and compared between groups by Student's *t*-test. Continuous variables with a non-normal distribution were expressed as median (interquartile range) and compared between groups by the Wilcoxon rank sum test. Categorical variables were compared between groups by a Chi-square analysis. The baseline laboratory data and the data after 16 weeks of treatment were compared by the paired *t*-test for continuous variables with a normal distribution and by the Wilcoxon signed rank test for continuous variables with a non-normal distribution. A value of P < 0.05 was considered significant.

Results

Baseline patient characteristics

Table 1 shows the patient characteristics. In all patients, average age, BMI, and the percentages of male, HT, DM, and CAD were 61.0 ± 8.8 years, 26.3 ± 3.4 kg/m^2, 59.5% (n = 25), 87.8% (n = 36), 57.1% (n = 24), and 11.9% (n = 5), respectively. The percentage of DM in the MetS group was significantly greater than that in non-MetS group (MetS group: 77.3% vs. non-MetS group: 35.0%, P = 0.006).

Laboratory data

Laboratory data at baseline and after 16 weeks of treatment with ezetimibe are shown in Table 2. At baseline, TG and RLP-chol in the MetS group were significantly higher than those in the non-MetS group (TG: 178 ± 61 mg/dL vs. 120 ± 64 mg/dL, P = 0.004 and RLP-chol: 7.4 (6.8 - 9.1) mg/dL vs. 4.6 (3.7

Table 1. Patient Characteristics

	All (n = 42)	MetS (n = 22)	Non-MetS (n = 20)	P value (MetS vs. non-MetS)
Age, years	61.0 ± 8.8	61.1 ± 9.8	60.9 ± 7.8	1.0
Male, n (%)	25 (59.5)	16 (72.7)	9 (45.0)	0.07
BMI, kg/m^2	26.3 ± 3.4	27.0 ± 3.3	25.4 ± 3.3	0.1
HT, n (%)	36 (87.8)	18 (81.8)	18 (90.0)	0.2
DM, n (%)	24 (57.1)	17 (77.3)	7 (35.0)	0.006
CAD, n (%)	5 (11.9)	3 (13.6)	2 (10.0)	0.7

MetS: metabolic syndrome; BMI: body mass index; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease. P values showed comparison between MetS vs. non-MetS groups.

- 5.5) mg/dL, P = 0.0002). T-chol, HDL-chol, LDL-chol, and adiponectin in the MetS group were not significantly different than those in the non-MetS group. T-chol and LDL-chol were significantly decreased during 16 weeks of treatment with ezetimibe in all patients (T-chol: baseline 242 ± 33 mg/dL, 16 weeks of treatment: 208 (191 - 223) mg/dL, P < 0.0001; and

Table 2. Laboratory Data on Pre- and Post-Treatment With Ezetimibe for 16 Weeks

Valuables	All (n = 42)	MetS (n = 22)	Non-MetS (n = 20)	P value (MetS vs. non-MetS)
0 week				
WBC, /µL	5,552 ± 1,494	5,705 ± 1,383	4,850 (4,150 - 6,300)	0.2
hs-CRP, µg/dL	741 (294 - 1,350)	1,027 ± 882	969 ± 941	0.8
BUN, mg/dL	13.7 ± 3.3	13.8 ± 3.2	13.6 ± 3.5	0.8
Cr, mg/dL	0.78 (0.65 - 0.87)	0.79 (0.71 - 0.87)	0.74 (0.61 - 0.88)	0.5
AST, IU/L	23 (19 - 28)	23 (19 - 31)	23 (20 - 24)	0.5
ALT, IU/L	26 (18 - 38)	28 (19 - 47)	27.0 ± 14.5	0.3
T-chol, mg/dL	242 ± 33	249 ± 35	234 ± 29	0.2
TG, mg/dL	150 ± 68	178 ± 61	120 ± 64	0.004
HDL-chol, mg/dL	54.3 ± 12.6	52.6 ± 12.3	56.2 ± 13.1	0.4
LDL-chol, mg/dL	165 ± 29	171 ± 30	158 ± 26	0.1
RLP-chol, mg/dL	6.4 (4.4 - 7.8)	7.4 (6.8 - 9.1)	4.6 (3.7 - 5.5)	0.0002
Adiponectin, µg/mL	4.3 (2.3 - 5.7)	3.4 (2.0 - 5.6)	4.7 (3.5 - 7.7)	0.1
16 weeks				
WBC, /µL	5,539 ± 1,335	5,621 ± 1,098	5,458 ± 1,563	0.7
hs-CRP, µg/dL	588 (349 - 1,070)	596 (296 - 1,200)	543 (360 - 1,070)	0.8
BUN, mg/dL	13.1 ± 3.3	12.8 ± 3.5*	13.5 ± 3.1	0.5
Cr, mg/dL	0.76 (0.64 - 0.88)	0.80 (0.70 - 0.93)	0.73 (0.60 - 0.86)	0.2
AST, IU/L	22 (18 - 28)	23 (19 - 36)	22 (18 - 25)	0.5
ALT, IU/L	24 (18 - 43)	29 (18 - 53)	24 (17 - 37)	0.2
T-chol, mg/dL	208 (191 - 223)*	213 ± 39*	210 ± 21*	0.7
TG, mg/dL	127 (113 - 144)	166 ± 51	118 (96 - 129)	0.01
HDL-chol, mg/dL	56.5 ± 13.5	54.9 ± 15.8	58.1 ± 10.9	0.5
LDL-chol, mg/dL	127 (113 - 144)*	134 ± 31*	132 ± 24*	0.8
RLP-chol, mg/dL	4.8 (4.0 - 6.9)*	6.5 ± 2.5*	4.5 ± 1.4	0.01
Adiponectin, µg/mL	4.6 (2.1 - 6.4)	2.6 (1.9 - 6.0)	4.9 (3.4 - 6.7)	0.2

MetS: metabolic syndrome; WBC: white blood cell; hs-CRP: high-sensitivity C-reactive protein; BUN: blood urea nitrogen; Cr: creatinine; AST: aspartate transaminase; ALT: alanine transaminase; T-chol: total cholesterol; TG: triglyceride; HDL-chol: high-density lipoprotein cholesterol; LDL-chol: low-density lipoprotein cholesterol; RLP-chol: remnant-like particles cholesterol. P values showed comparison between MetS vs. non-MetS groups. *P < 0.05 compared to same group between 0 week and 16 weeks.
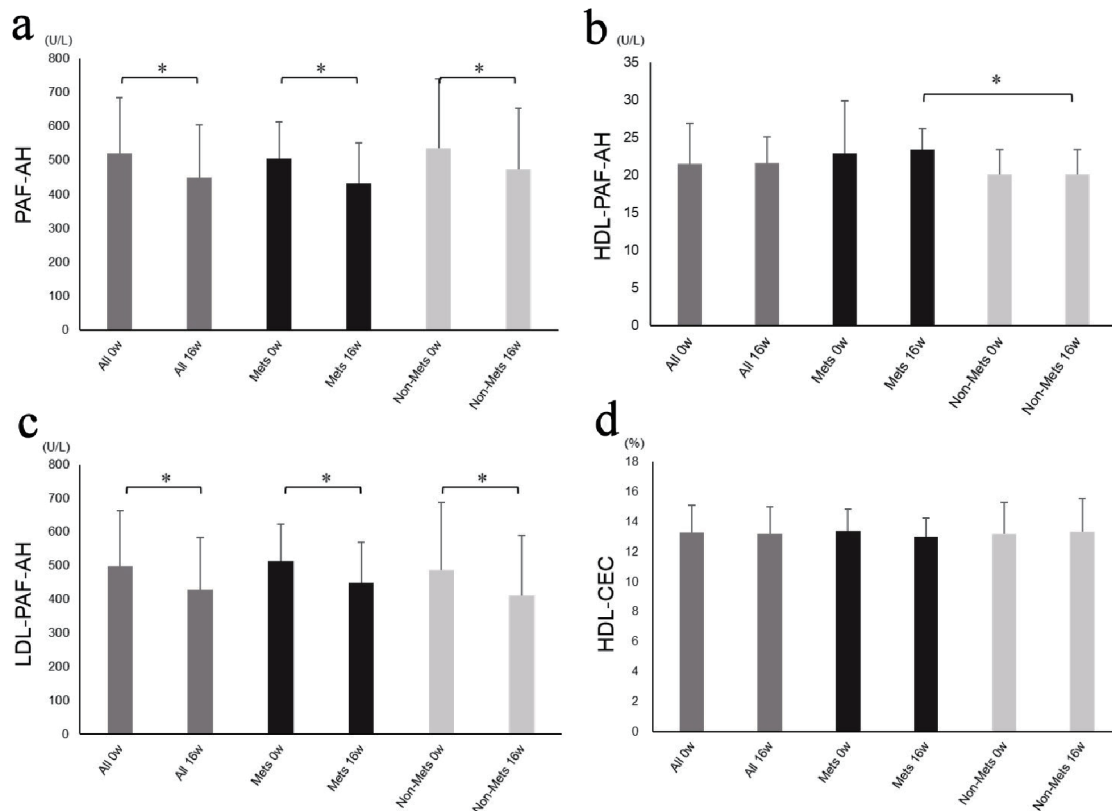
Figure 1. Platelet-activating factor acetylhydrolase activity and high-density lipoprotein cholesterol efflux capacity. PAF-AH (a), HDL-PAF-AH (b), LDL-PAF-AH activity (c) and HDL-CEC (d) at baseline and after 16 weeks of treatment in all patients and in the MetS and non-MetS groups. PAF-AH: platelet-activating factor acetylhydrolase; HDL-PAF-AH: high-density lipoprotein-associated PAF-AH; LDL-PAF-AH: low-density lipoprotein-associated PAF-AH; HDL-CEC: high-density lipoprotein cholesterol efflux capacity; MetS: metabolic syndrome. *P < 0.05.

LDL-chol: 165 ± 29 mg/dL, 127 (113 - 144) mg/dL, P < 0.0001) and in both the MetS (T-chol: 249 ± 35 mg/dL, 213 ± 39 mg/dL, P < 0.0001 and LDL-chol: 171 ± 30 mg/dL, 134 ± 31 mg/dL, P < 0.0001) and non-MetS (T-chol: 234 ± 29 mg/dL, 210 ± 21 mg/dL, P < 0.0001 and LDL-chol: 158 ± 26 mg/dL, 132 ± 24 mg/dL, P < 0.0001) groups. RLP-chol was significantly decreased after 16 weeks of treatment with ezetimibe in all patients (6.4 (4.4 - 7.8) mg/dL, 4.8 (4.0 - 6.9) mg/dL, P = 0.003) and the MetS group (7.4 (6.8 - 9.1) mg/dL, 6.5 ± 2.5 mg/dL, P < 0.0001), but not the non-MetS group (4.6 (3.7 - 5.5) mg/dL, 4.5 ± 1.4 mg/dL, P = 0.1). After 16 weeks of treatment with ezetimibe, TG and RLP-chol in the MetS group were still significantly higher than those in the non-MetS group (TG: 166 ± 51 mg/dL vs. 118 (96 - 129) mg/dL, P = 0.01 and RLP-chol: 6.5 ± 2.5 mg/dL vs. 4.5 ± 1.4 mg/dL, P = 0.01).

PAF-AH and HDL-CEC

Data regarding PAF-AH and HDL-CEC are shown in Figure 1. There were no significant differences between the MetS and non-MetS groups at baseline. PAF-AH and LDL-PAF-AH were significantly decreased after 16 weeks of treatment with ezetimibe in all patients (PAF-AH: 521 ± 164 U/L, 450 ± 155

U/L, P < 0.0001 and LDL-PAF-AH: 499 ± 163 U/L, 428 ± 154 U/L, P < 0.0001) and in both the MetS (PAF-AH: 506 ± 108 U/L, 431 ± 119 U/L, P < 0.0001 and LDL-PAF-AH: 514 ± 109 U/L, 450 ± 119 U/L, P < 0.0001), and non-MetS (PAF-AH: 537 ± 203 U/L, 473 ± 180 U/L, P < 0.0001 and LDL-PAF-AH: 486 ± 202 U/L, 411 ± 178 U/L, P < 0.0001) groups. HDL-PAF-AH and HDL-CEC were not significantly changed by 16 weeks of treatment in either of all patients, the MetS group, or the non-MetS group.

Discussion

We investigated the effects of ezetimibe monotherapy for PAF-AH and HDL-CEC in patients with dyslipidemia. Ezetimibe significantly reduced PAF-AH and LDL-PAF-AH in addition to reducing T-chol and LDL-chol regardless of the presence or absence of MetS, and did not change the levels of HDL-PAF-AH and HDL-CEC.

Ezetimibe improved T-chol and LDL-chol in all patients and in both the MetS and non-MetS groups. These are reasonable effects of ezetimibe due to the selective inhibition of intestinal absorption of cholesterol. Ezetimibe also improved RLP-chol in all patients and the MetS group, but not the non-

MetS group, because the level of RLP-chol in the non-MetS group was within the normal range at baseline. The incidence of diabetes in the MetS group was significantly higher than that in the non-MetS group, because diabetes is one of the diagnostic criteria of MetS [17].

Effect for PAF-AH by ezetimibe monotherapy

Packard et al reported that inflammatory markers, especially PAF-AH, are predictors of coronary events [9]. Tsimikas et al reported that an increased PAF-AH level was associated with MetS, and the incidences of both fatal and non-fatal CVD [18]. In this study, ezetimibe significantly reduced PAF-AH in both the MetS and non-MetS groups. Ezetimibe selectively inhibits the intestinal absorption of cholesterol and decreases serum LDL-chol. Since PAF-AH is reportedly strongly influenced by LDL-chol [18], it is possible that ezetimibe significantly reduced PAF-AF due to its effect of lowering LDL-chol. These results indicate that ezetimibe monotherapy may have a potential role in suppressing CVD regardless of the presence or absence of MetS. We previously reported the efficacies of HDL-PAF-AH and LDL-PAF-AH [6, 7]. In this study, HDL-PAF-AH was not significantly improved after 16 weeks of treatment with ezetimibe monotherapy because almost no PAF-AH was detected in apoB-depleted serum (LDL-PAF-AH). In this study, isolation of PAF-AH into HDL- and LDL-PAF-AH might be unrelated to the efficacy of ezetimibe monotherapy.

Effect for HDL-CEC by ezetimibe monotherapy

HDL-CEC is one of the effects of HDL-chol against atherosclerosis [10]. In this study, ezetimibe monotherapy was expected to improve HDL-CEC, since previous reports demonstrated that ezetimibe affects reverse cholesterol transport [19, 20]. On the other hand, it was reported that treatment with a combination of atorvastatin plus ezetimibe did not increase HDL-CEC [21, 22]. Ezetimibe monotherapy did not improve HDL-CEC in this study. Although we previously reported that total CEC was positively correlated with HDL-chol levels [12], ezetimibe monotherapy did not change the levels of HDL-chol in this study. Taken together the results of PAF-AH, ezetimibe monotherapy had an effect for LDL-chol-associated factors rather than HDL-chol-associated factors.

Limitation

This study has several limitations. For example, a sufficient sample size was needed for several investigations. Although we discontinued statin treatment with a 4-week washout period before enrollment, statins may exert a legacy effect for CVD [23]. Ezetimibe monotherapy decreased levels of both LDL-chol and LDL-PAF-AH, and delta LDL-chol was significantly associated with changes in LDL-PAF-AH (data not shown). The reduction of LDL-PAF-AH might be due to the reduction of LDL-chol. We can expect that ezetimibe mono-

therapy would have an atheroprotective effect in addition to an LDL-chol-lowering effect, since PAF-AH has been shown to be an independent predictor of atherosclerosis regardless of the lipid profile [9].

In conclusion, ezetimibe significantly reduced PAF-AH in addition to reducing T-chol and LDL-chol regardless of the presence or absence of MetS.

Conflict of Interest

None to declare.

Informed Consent

In the Zenith Trial, each subject signed an informed consent form after the protocol was explained. For this investigation, the Zenith Trial including the current investigation was approved by the Independent Review Board (IRB) of Fukuoka University (2017M160). In current investigation, there was no informed consent because the current investigation was a retrospective study.

Author Contributions

Acquisition: YS, K. Tano and NKK; conception and design: YS and SM; analysis: K. Tano, YM, YS and NKK; interpretation: K. Tashiro, TK and SM.

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