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Brief Report

Effects of Ezetimibe on Glucose Metabolism in Patients With Type 2 Diabetes: A 12-Week, Open-Label, Uncontrolled, Pilot Study

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ABSTRACT

BACKGROUND: A potential effect of ezetimibe, a novel cholesterol-absorption inhibitor, on insulin resistance has been reported in an animal model.

OBJECTIVE: The aim of this study was to evaluate the effects of ezetimibe on glucose metabolism in patients with type 2 diabetes mellitus (T2DM).

METHODS: Between March and June 2008, outpatients with T2DM who were being treated at Yokohama Sakae Kyosai Hospital, Yokohama, Japan, were enrolled in this pilot study if they had not achieved the target lipid levels recommended by the Japan Atherosclerosis Society Guidelines despite diet and exercise or a statin therapy for ≥3 months. At baseline and at 4 and 12 weeks after open-label treatment with ezetimibe 10 mg/d, the levels of lipid parameters, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA_{1c}), and high-sensitivity C-reactive protein were measured. Adverse effects (AEs) were assessed at each study visit by patient interviews and laboratory testing.

RESULTS: A total of 21 consecutive patients (10 men, 11 women; mean [SD] age, 72 [9] years; weight, 63.4 [10.5] kg; body mass index, 25.5 [3.2] kg/m^2) were enrolled in this study. The mean (SD) level of LDL-C decreased significantly from 146 (31) to 114 (27) mg/dL (−21%; $P < 0.001$) after 12 weeks of treatment with ezetimibe. The mean level of remnant-like particle cholesterol also decreased significantly from 6.5 (3.8) to 4.8 (2.2) mg/dL (−15%; $P = 0.03$). Treatment with ezetimibe was associated with a reduction in FPG level from 127 (31) to 119 (30) mg/dL ($P = 0.02$), and HbA_{1c} from 6.3% (0.6%) to 6.1% (0.7%) ($P = 0.003$). No AEs were observed or reported during the study period.

CONCLUSION: In this small, open-label, uncontrolled, pilot study, ezetimibe was associated with a significant decrease in lipid parameters and improvement in glucose metabolism in these patients with T2DM. (*Curr Ther Res Clin Exp.* 2010;71:252–258) © 2010 Excerpta Medica Inc.

KEY WORDS: cholesterol, type 2 diabetes mellitus, ezetimibe, RLP-C.

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INTRODUCTION

Ezetimibe is a cholesterol-absorption inhibitor that strongly inhibits the absorption of biliary and dietary cholesterol at the brush border of the intestine without affecting the absorption of fat-soluble vitamins.[1,2] Ezetimibe appears to inhibit cholesterol absorption by binding with the cholesterol transporter, Niemann-Pick C1-like 1 (*NPC1L1*) protein.[3] Although the main effect of ezetimibe is to decrease total cholesterol (TC) and LDL-C levels, several studies have found that ezetimibe is also associated with decreased triglyceride (TG) levels.[4,5]

A 2007 study reported a potential effect of ezetimibe on insulin resistance and liver steatosis in an animal model,[6] and ezetimibe was found to improve postprandial hyperlipidemia by reducing free fatty acid (FFA) absorption.[7] Based on these considerations, we hypothesized that ezetimibe would improve glucose metabolism in patients with type 2 diabetes mellitus (T2DM). This hypothesis was tested prospectively in patients with T2DM and dyslipidemia.

PATIENTS AND METHODS

PATIENTS

Between March and June 2008, outpatients with T2DM who were being treated at the Yokohama Sakae Kyosai Hospital, Yokohama, Japan, were enrolled in this pilot study if they had not achieved the target lipid levels (LDL-C, ≥120 mg/dL or ≥100 mg/dL in patients with coronary artery disease) recommended by the Japan Atherosclerosis Society Guidelines[8] despite diet and exercise or a statin therapy for ≥3 months. Patients were excluded from the study for the following reasons: treatment with nonstatin lipid-lowering drugs (eg, fibrates, nicotinic acid, cholestyramine, probucol); dyslipidemia associated with hypothyroidism, nephrotic syndrome, gallbladder obstruction, biliary disease, pancreatitis, or immunologic abnormalities such as collagen diseases; dyslipidemia induced by steroids or other drugs; positive viral hepatitis B or C; alcoholism or heavy alcohol intake; T2DM treated with insulin or that was poorly controlled (glycosylated hemoglobin [HbA_{1c}] >8.0%); and any other reason for which the patient was considered inappropriate for this study by the attending physician.

STUDY DESIGN

Written informed consent was obtained from all patients, and the Ethics Committee of our hospital approved the study protocol.

Ezetimibe* 10 mg/d was administered to all patients for 12 weeks. The patients were required to visit the hospital at 4 and 12 weeks after enrollment. The lipid parameters, fasting plasma glucose (FPG), HbA_{1c}, and high-sensitivity C-reactive protein (hs-CRP) were measured at baseline, and at 4 and 12 weeks. Adverse effects (AEs) were assessed at each study visit by patient interviews and laboratory testing.

*Trademark: Zetia® (Bayer Yakuhin Ltd., Osaka, Japan).

T2DM was diagnosed if the FPG level was ≥126 mg/dL, a random plasma glucose level was ≥200 mg/dL, the HbA_{1c} level was ≥6.5%, or in case of treatment with either oral hypoglycemic agents or insulin.[9] During the study period, there were no lifestyle changes, nonstudy antidyslipidemic agents were prohibited, and antihypertensive and antidiabetic treatments used at enrollment were continued without dose modifications.

LABORATORY DETERMINATIONS

Blood samples were obtained after overnight fasting for 12 hours. The HbA_{1c} level was measured by HPLC (Adams A1c HA-8160; Arkray Inc., Kyoto, Japan) and the plasma glucose level was measured using the glucose oxidation method (chemical reagent and Glucose AUTO and STAT GA-1160 analyzer; Arkray Inc.). Serum levels of TC, LDL-C, and HDL-C were measured using commercial enzymatic kits (Kyowa Medex, Tokyo, Japan). TG was measured enzymatically (Kyowa Medex). Serum levels of apolipoproteins (apos), remnant-like particle cholesterol (RLP-C), and hs-CRP were measured at a central laboratory (SRL Inc., Tokyo, Japan). The serum level of RLP-C was measured using an immune-separation technique.

STATISTICAL ANALYSIS

Statistical analyses were performed using Statview 5.0 software (SAS Institute Inc., Cary, North Carolina). Results are expressed as mean (SD). The Wilcoxon signed rank test was used to compare the data before and after ezetimibe treatment. The statistical significance level was set at $P < 0.05$. Corrections for multiple comparisons and a sample-size calculation were not performed.

RESULTS

A total of 21 consecutive patients (10 men, 11 women; mean [SD] age, 72 [9] years; weight, 63.4 [10.5] kg; body mass index, 25.5 [3.2] kg/m^2) were enrolled in this study. The baseline characteristics of the subjects are shown in **Table I**. Seven patients (33%) had received antidiabetic drugs and the other 14 patients (67%) were being treated with diet and exercise therapy alone. Fifteen patients (71%) were already being treated with statins.

The effects of ezetimibe administration on lipid parameters, FPG, HbA_{1c} and hs-CRP are shown in **Table II**. After 12 weeks of treatment with ezetimibe, the mean (SD) levels of TC, LDL-C, apo B, and RLP-C decreased significantly from 223 (35) to 183 (29) mg/dL (−17%; $P < 0.001$), 146 (31) to 114 (27) mg/dL (−21%; $P < 0.001$), 114 (20) to 94 (17) mg/dL (−16%; $P < 0.001$), and 6.5 (3.8) to 4.8 (2.2) mg/dL (−15%; $P = 0.03$), respectively. The mean level of TG decreased from 164 (81) to 144 (52) mg/dL, but it was not statistically significant. The HDL-C level did not show a significant change. The mean levels of FPG and HbA_{1c} decreased significantly from 127 (31) to 119 (30) mg/dL ($P = 0.02$) and 6.3% (0.6%) to 6.1% (0.7%) ($P = 0.003$), respectively. The mean level of hs-CRP decreased from 2.3 (3.4) to 0.5 (0.8) mg/L, but did not reach statistical significance.

Table I. Baseline characteristics of subjects (N = 21). Data are mean (SD) unless otherwise indicated.

Variable	Value
Age, y	72 (9)
Sex, male/female	10/11
Height, cm	157.4 (10.2)
Weight, kg	63.4 (10.5)
BMI, kg/m^2	25.5 (3.2)
TC, mg/dL	223 (35)
LDL-C, mg/dL	146 (31)
HDL-C, mg/dL	58 (12)
TG, mg/dL	164 (81)
RLP-C, mg/dL	6.5 (3.8)
FPG, mg/dL	127 (31)
Smoking, no. (%)	0
History of CAD, no. (%)	13 (62)
Hypertension, no. (%)	15 (71)
Statins, no. (%)	15 (71)
Antidiabetic drugs, no. (%)	7 (33)
Sulfonylurea	4 (57)
Pioglitazone	1 (14)
Biguanide + α-GI	1 (14)
Sulfonylurea + biguanide + α-GI	1 (14)

BMI = body mass index; TC = total cholesterol; TG = triglycerides; RLP-C = remnant-like particle cholesterol; FPG = fasting plasma glucose; CAD = coronary artery disease; α-GI = α-glucosidase inhibitor.

No AEs, including the occurrence of clinical symptoms or changes in the biochemical parameters, were observed or reported during the study period.

DISCUSSION

Although the main effect of ezetimibe is to decrease the TC and LDL-C levels, a significant decrease in RLP-C was observed in the present study. The percentage changes in TC, LDL-C, apo B, and RLP-C after 12 weeks of treatment with ezetimibe were −17%, −21%, −16%, and −15%, respectively. Recently, we reported the results of a prospective, open-label, uncontrolled study to evaluate the effect of ezetimibe on RLP-C in patients with dyslipidemia that found a 21% decrease in the mean RLP-C level ($P < 0.001$).[10] The same result was observed in the present study in these patients with T2DM.

Although mean (SD) HbA_{1c} decreased significantly from 6.3% (0.6%) to 6.1% (0.7%), the mechanism by which ezetimibe treatment improves glucose metabolism

Table II. Effects of ezetimibe on lipid parameters, highly selective C-reactive protein (hs-CRP), fasting plasma glucose (FPG), and glycosylated hemoglobin (HbA_{1c}). Data are mean (SD) mg/dL, unless otherwise indicated.

Parameter	Baseline	4 Weeks	12 Weeks
TC	223 (35)	187 (30)*	183 (29)*
LDL-C	146 (31)	113 (26)*	114 (27)*
HDL-C	58 (12)	61 (14)	56 (10)
TG	164 (81)	134 (55)	144 (52)
RLP-C	6.5 (3.8)	4.8 (2.1)†	4.8 (2.2)†
Apo AI	141 (27)	145 (25)	141 (25)
Apo B	114 (20)	94 (17)*	94 (17)*
Apo E	4.3 (1.0)	4.0 (0.8)†	4.1 (1.0)
hs-CRP, mg/L	2.3 (3.4)	0.9 (2.0)	0.5 (0.8)
FPG	127 (31)	117 (29)	119 (30)†
HbA_{1c}, %	6.3 (0.6)	6.2 (0.6)†	6.1 (0.7)†

TC = total cholesterol; TG = triglycerides; RLP-C = remnant-like particle cholesterol; Apo = apolipoprotein.
*$P < 0.001$ versus baseline.
†$P = 0.03$ versus baseline.
‡$P = 0.02$ versus baseline.

is still not fully understood. Physiologic elevation of the plasma FFA level causes muscle and hepatic insulin resistance, resulting in increased rates of endogenous glucose production related to the prevailing degree of hyperinsulinemia, as well as decreased glucose uptake by muscle.[11] This can lead to an increase in the plasma glucose concentration and eventually to T2DM. The sustained reduction of FFA in the plasma is associated with improved oral glucose tolerance and enhanced peripheral and hepatic insulin sensitivity.[12] Deushi et al[6] reported that ezetimibe was associated with reduced FFA (–31%) in an experimental study in rats. Masuda et al[7] also reported the results of a prospective, open-label, uncontrolled study in which ezetimibe was associated with reduced FFA levels in the oral fat loading test ($P = 0.004$). This reduction in FFA is the first reason why ezetimibe might improve glucose metabolism. Because ezetimibe inhibits direct uptake of cholesterol from the intestinal lumen, less cholesterol is transported in chylomicrons, implying a reduction in the cholesterol reaching the liver in chylomicron remnants.[3,13] Ezetimibe reduces hepatic cholesterol by inhibiting *NPC1L1* activity not only in the intestine, but also in the liver.[14] It seems possible that these effects of ezetimibe alleviate hepatic steatosis[6,15] and lead to improvement of insulin resistance.[6] This reduction in hepatic cholesterol is the second reason why ezetimibe might improve glucose metabolism.

No AEs were observed during the study period. The results of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial,[16] a multicenter, prospective, randomized,

double-blind study to evaluate the effect of simvastatin plus ezetimibe on aortic stenosis, has led to the hypothesis that adding ezetimibe to statin therapy to achieve stronger LDL-C reduction may increase the incidence of cancer (105 vs 70; $P = 0.01$). However, long-term statin treatment has not been associated with an increased incidence of, or death from, cancer.[17] Peto et al[18] found that the available results of 3 trials do not provide credible evidence of any AEs of ezetimibe associated with the rates of cancer. Because ezetimibe has been studied less extensively than statins, further studies are necessary to assess the cancer risk.

STUDY LIMITATIONS

This was a small, open-label, uncontrolled, pilot study and the observation period was only 12 weeks. Additionally, we evaluated only a few glycemic parameters and most patients were already on statin therapy. Therefore, further, adequately powered, randomized, controlled trials are necessary to confirm the effects of ezetimibe on glucose metabolism.

CONCLUSION

In this small, open-label, uncontrolled, pilot study, ezetimibe was associated with significantly decreased lipid parameters and improved glucose metabolism in these patients with T2DM.

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Dr. Nozue contributed to the study design, data interpretation, manuscript preparation, and performed the statistical analyses. Drs. Michishita and Mizuguchi contributed to the study design and data interpretation.

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