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Letter to the Editor

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Effects of Liraglutide, a Human Glucagon-Like Peptide-1 Analog, on Glucose/Lipid Metabolism, and Adipocytokines in Patients With Type 2 Diabetes

Hidekatsu Yanai[a, b, d], Hidetaka Hamasaki[a], Hiroki Adachi[a], Sumie Moriyama[a], Yuji Hirowatari[c]

Letter to the Editor:

The glucagon-like peptide 1 (GLP-1), one of gastrointestinal hormones, stimulates insulin secretion from pancreatic ß-cells in a glucose-dependent manner. Recently, liraglutide, a human GLP-1 analog, has been introduced as therapeutic strategies for type 2 diabetes mellitus. Clinical studies have demonstrated reduction in blood glucose and body weight, improvements in pancreatic ß-cell function and a low risk for hypoglycemia with liraglutide [1, 2]. Since diabetes is significantly associated with cardiovascular events, it is very important to understand effects of anti-diabetic drugs on other cardiovascular risk biomarkers. Therefore, we studied effects of liraglutide on glucose/lipid metabolism and adipocytokines in patients with type 2 diabetes.

Five patients (4 females and one male) with type 2 diabetes participated in this study. The mean ± SD of age, body height, body weight, body mass index and hemoglobin A1c were 60.2 ± 8.9 years old, 156.1 ± 5.4 cm, 71.6 ± 15.6 kg, 29.5 ± 7.0 kg/m^2 and 9.1 ± 2.1%, respectively. We measured high-sensitivity C-reactive protein (hs-CRP), adiponectin, interleukin-6, and small dense low-density lipoprotein (sd-LDL), oxidized LDL (ox-LDL) and cholesterol level in each lipoprotein fraction using the high-performance liquid chromatography (HPLC) method before and after the two weeks treatment using liraglutide (0.3 mg for one week and 0.6 mg for one week) [3].

The data are presented in Figure 1. A statistical significant increase in serum fasting C-peptide levels was observed following two week treatment with liraglutide. However, fasting plasma glucose levels were elevated. Although statistical significances were not obtained compared with baseline, serum levels of total cholesterol (TC) and triglyceride (TG) tended to decrease. Liraglutide also tended to reduce TG-rich lipoproteins such as chylomicron, intermediate density-lipoprotein (IDL), very low density-lipoprotein (VLDL) and sd-LDL. Although statistical significances were not also obtained compared with baseline, serum adiponectin levels decreased, and interleukin-6 and hs-CRP levels increased. Further, serum ox-LDL increased following liraglutide treatment.

In the LEAD (Liraglutide Effect and Action in Diabetes) 4 study, serum C-peptide levels significantly increased, and serum levels of TC, TG, LDL-cholesterol (LDL-C), free fatty acids (FFA) significantly decreased following 26-week treatment with liraglutide [4]. Seino Y et al performed the 24-week, multicenter, double blind, randomized parallel-group trial compared the efficacy and safety of liraglutide and glibenclamide monotherapy in Japanese subjects with type 2 diabetes [5]. Liraglutide significantly reduced serum FFA levels compared with glibenclamide, however, there were no significant differences in serum levels of TC, LDL-C, VLDL-C, HDL-C and TG between the two groups. In our study, liraglutide significantly increased serum C-peptide levels compared with baseline, which supports the results of LEAD 4 study and our previous study and also suggests that two weeks is sufficient to increase serum C-peptide [4, 6]. To our knowledge, our report is the first to study serum levels of IDLC, CM-C, sd-LDL following liraglutide treatment. Although statistical significant differences were not obtained compared with baseline, liraglutide tended to reduce TG, TG-rich lipoprotein, and sd-LDL. In the LEAD 4 and study by Seino Y et al, liraglutide significantly decreased serum FFA levels [4, 5]. Liraglutide has been reported to reduce postprandial glucagon levels by 20% [7]. Glucagon stimulates lipolysis in adipocytes and increase plasma FFA levels [8]. Reduction of glucagon-mediated increase in serum FFA

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[a]Department of Internal Medicine, National Center for Global Health and Medicine, Kohnodai Hospital, Chiba 272-8516, Japan
[b]Clinical Research Center, National Center for Global Health and Medicine, Kohnodai Hospital, Chiba 272-8516, Japan
[c]Bioscience Division, Tosoh Corporation, Kanagawa, Japan
[d]Corresponding author: Hidekatsu Yanai, Department of Internal Medicine, National Center for Global Health and Medicine, Kohnodai Hospital, 1-7-1 Kohnodai, Chiba 272-8516, Japan.
Email: dyanai@hospk.ncgm.go.jp

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	before	2 weeks after the use of liraglutide
fasting plasma glucose (mg/dl)	106.4±16.7	130.8±23.4
serum fasting C-peptide (ng/ml)	1.11±0.38	2.10±0.91*
serum total cholesterol (mg/dl)	195.4±46.7	181.8±32.5
serum triglyceride (mg/dl)	227.0±134.2	163.6±62.6
serum LDL-C (mg/dl)	109.6±25.5	108.1±31.8
serum HDL-C (mg/dl)	40.4±2.8	41.0±4.3
HPLC-CM-C (mg/dl)	2.98±0.94	2.62±0.75
HPLC-IDL-C (mg/dl)	9.84±2.95	8.82±2.13
HPLC-VLDL-C (mg/dl)	27.3±22.7	17.4±7.8
HPLC-LDL-C (mg/dl)	119.0±23.8	118.9±34.8
HPLC-HDL-C (mg/dl)	36.4±5.3	38.0±3.3
small dense LDL (mg/dl)	39.1±30.0	32.5±16.8
oxidized LDL (U/l)	140.8±49.6	149.0±82.7
adiponectin (μg/ml)	11.2±10.8	7.1±5.7
interleukin-6 (pg/ml)	2.5±1.4	2.7±1.8
high sensitivity CRP (ng/ml)	1009.4±1099.1	1621.0±2639.5

Presented values indicate mean±S.D., *P < 0.05 vs. values before the use of liraglutide by Wilcoxon's signed ranked test. LDL-C, low-density lipoprotein-cholesterol; HDL, high-density lipoprotein; HPLC-CM-C, chylomicron-cholesterol measured by high-performance liquid chromatography (HPLC); IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein; sd-LDL, small dense LDL; CRP, C-reactive protein

Figure 1. Effects of liraglutide on glucose and lipid metabolism and adipocytokines.

may be one of the underlying mechanisms for liraglutide-mediated amelioration in serum lipids profile.

Courreges JP et al also measured adipocytokines following 14 week liraglutide treatment [9]. There was a non-significant, but dose-dependent reduction in hs-CRP levels by liraglutide. There were no treatment effects on levels of adiponectin and interleukin-6 with liraglutide. In the study by Seino Y et al, liraglutide significantly reduced hs-CRP levels [5]. In our study, there were no treatment effects on levels of adiponectin, interleukin-6 and hs-CRP with liraglutide. To understand the effects of liraglutide on adipocytokines clearly, further studies should be performed.

In conclusion, the present study showed that two week treatment with liraglutide significantly increased serum fasting C-peptide levels. To elucidate the effects of liraglutide on lipid metabolism, adipocytokines and chronic inflammations, further studies, preferably with larger numbers of subjects, will be needed.

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