Effect of liraglutide on lipids in patients with type 2 diabetes: a pilot study

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Abstract. The mechanism for the cholesterol-lowering effect of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) remains unknown in patients with type 2 diabetes. We evaluated the effect of liraglutide on serum lipid profiles, including cholesterol synthesis and absorption markers, during daily clinical practice in Japanese patients with type 2 diabetes. We enrolled 38 patients with type 2 diabetes mellitus who were not treated with a GLP-1 RA (≥20 years of age, HbA1c ≥6.5%). Liraglutide, a GLP-1 RA, was administered subcutaneously once a day for three months to these patients. Blood samples and body weights were collected at 0, 1, and 3 months. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) at 1 month, and non-high-density lipoprotein cholesterol (non-HDL-C) and calculated TC at 1 and 3 months, were decreased, while the cholesterol synthesis and cholesterol absorption markers were unchanged by this treatment. In patients with LDL-C levels over 100 mg/dL, LDL-C, non-HDL-C, TC, and calculated TC levels were decreased significantly by the treatment at 1 and 3 months, and the cholesterol absorption marker, campesterol, was decreased at 3 months. The administration of liraglutide for 3 months decreased non-HDL-C and calculated TC significantly, while the cholesterol synthesis and absorption markers were not changed by this treatment.

Key words: Liraglutide, Cholesterol, Type 2 diabetes

DIPEPTIDYL PEPTIDASE-4 (DPP-4) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are used to treat patients with type 2 diabetes. Their use improves hyperglycemia in a glucose-dependent fashion by increasing serum insulin and decreasing serum glucagon levels [1, 2]. It is very important to control the lipid levels in patients with diabetes for the prevention of cardiovascular events [3-5]. GLP-1 RAs, such as liraglutide, semaglutide, albiglutide, and dulaglutide, are reported to decrease such events [6-9]. Liraglutide also has an anti-atherosclerotic effect in apolipoprotein E knockout mice [10]. In a meta-analysis, GLP-1 RAs were found to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG) levels, but did not change high-density lipoprotein cholesterol (HDL-C); however, their mechanism was not clear [11].

Recently, we evaluated the effect of anaglaptin, a DPP-4 inhibitor, on lipids in patients with type 2 diabetes [12, 13]. After treatment with anaglaptin for 1 month, the cholesterol synthesis marker, lathosterol, decreased significantly, whereas no changes in campesterol, sitosterol, or cholestanol (markers of cholesterol absorption) were observed [12]. After treatment with anaglaptin for 3 months, these cholesterol synthesis and absorption markers were not changed [13]. To evaluate the lipid lowering ability of GLP-1 RAs, we evaluated the effects of liraglutide on serum lipid profiles and these markers in daily clinical practice in Japanese patients with type 2 diabetes.
Patients and Methods

Subjects

The study was approved by the Institutional Ethics Review Committee of Yokohama City University Hospital, and the protocol was registered in the UMIN Clinical Trial Registry as UMIN000014097. This study was conducted in Yokohama City University Hospital, Yokohama Minami Kyousai Hospital, Miura Central Clinic, and Nakajima Naika Clinic. Informed consent was obtained from each of the subjects before initiating the study. Because we evaluated the lipid lowering effect of anagliptin in 30 outpatients with type 2 diabetes previously [10], the current sample size was determined to be 30 prior to the study. We enrolled male and female patients with type 2 diabetes mellitus who were not being treated with GLP-1 RAs (≥20 years of age, HbA1c ≥6.5%).

Study design

Liraglutide was administered subcutaneously once a day for three months. The dosage was started at 0.3 mg/day and titrated up to a maximum of 0.9 mg/day in increments of 0.3 mg/day at least weekly, based on package insert information. The final dosage of liraglutide was dependent on the physician’s judgement. Dosages of other anti-diabetic drugs and insulin were not changed throughout the study as much as possible. Blood samples and body weights were collected at 0, 1 (3–7 weeks), and 3 months (10–14 weeks). For patients who were taking a DPP-4 inhibitor, the inhibitor was stopped and liraglutide was administered as described above.

Measurements

Body weight, HbA1c, TC, LDL-C, HDL-C, and TG levels were measured after 1 and 3 months of treatment. TC, LDL-C, HDL-C, and TG levels were measured via direct methods. Each parameter was measured at the same laboratory throughout the study. Remnant cholesterol (RC) was calculated as follows: RC = TC − HDL-C − LDL-C. TC (F) was also calculated by the Friedewald formula using TG less than 400 mg/dL because the number of patients for whom TC levels were decreased directly was smaller than the number of patients for whom LDL-C, HDL-C, and TG were measured directly. Lathosterol, campesterol, sitosterol, and cholesterol serum levels were also measured at each point using gas chromatography at SRL, Inc. (Tokyo, Japan).

Statistical analysis

Data are expressed as means ± standard error and analyzed using Statistical Analysis System software, version 9.2 (SAS Institute, Cary, NC, USA). Comparisons of 1 or 3 months with 0 month were analyzed using a linear mixed model. Differences were considered significant at p < 0.05.

Results

Twenty-two male and sixteen female patients with a mean body mass index of 30.6 ± 0.8 kg/m² were enrolled (Table 1). The mean age was 60 ± 2 years and the duration of diabetes was 12 ± 1 years. The mean dosages of liraglutide at 1 and 3 months were 0.7 ± 0.0 and 0.8 ± 0.0 mg/day, respectively. Before the study, 21 patients were treated with insulin and nine were treated with DPP-4 inhibitors. Concerning lipid lowering drugs (LLDs), 21 patients were treated with a statin, two with a statin + ezetimibe, one with a statin + fenofibrate, one with a statin +icosapentate, and one with fenofibrate. One patient was dropped from the study due to redness of the skin, two were dropped due to abdominal fullness and/or nausea, and one was dropped due an increase of creatinine. In patients who were treated for 3 months, four had constipation, four had nausea, one had abdominal fullness, and one had an abdominal disturbance.

In all patients, body weight decreased significantly at 3 months and HbA1c levels were decreased significantly at both 1 and 3 months with liraglutide treatment (Table 2). The body weight tended to decrease for all patients at 1 month; however, this was not statistically significant (p = 0.108). LDL-C, TC, and Ln TG levels were decreased at 1 month, and non-HDL-C and TC (F) levels were decreased significantly at 1 and 3 months. TG, lathosterol, campesterol, sitosterol, and cholesterol levels were not changed by liraglutide treatment.

Next, we analyzed these parameters based on the pre-treatment LDL-C level (Table 3). In the higher baseline LDL-C (≥100 mg/dL) group, the LDL-C, non-HDL-C, TC (F) and TC levels were decreased significantly by 1 and 3 months of liraglutide treatment. TG and Ln TG levels were decreased significantly by 1 month treatment. The absorption marker, campesterol, was decreased at 3 months. In the lower baseline LDL-C (<100 mg/dL)

Table 1  Baseline characteristics of all patients

| Men/women (n) | Age (y) | HbA1c (%) | Duration of diabetes (y) | Body height (cm) | Body weight (kg) | BMI (kg/m²) |
|---------------|---------|-----------|--------------------------|------------------|-----------------|------------|
| 22/16         | 60 ± 2  | 8.6 ± 0.2 | 12 ± 1                  | 165 ± 2          | 83.5 ± 3.0      | 30.6 ± 0.8 |
group, the LDL-C, non-HDL-C, and TC levels were not affected significantly by 1 and 3 months of treatment. The cholesterol synthesis and absorption markers were not decreased.

We also analyzed these parameters in patients treated with or without LLDs (Table 4). In patients without LLDs (n = 12), the levels of TC (F) and Ln TG were decreased significantly at 1 and 3 months. However, LDL-C, non-

| Table 2 | Comparison of parameters before and after treatment with liraglutide |
|---------|------------------------|
| Months  | 0          | 1          | 3          |
| BW (kg) | 83.5 ± 3.0 | 83.0 ± 2.9 | 82.8 ± 3.2* |
| HbA1c (%) | 8.6 ± 0.2 | 8.2 ± 0.2** | 7.9 ± 0.2*** |
| LDL-C (mg/dL) | 103 ± 5 | 96 ± 6* | 98 ± 5 |
| HDL-C (mg/dL) | 52 ± 2 | 51 ± 2 | 52 ± 2 |
| Non HDL-C (mg/dL) | 131 ± 6 | 121 ± 6* | 121 ± 6* |
| TC (mg/dL) | 186 ± 6 | 173 ± 7* | 175 ± 6 |
| TC (F) (mg/dL) | 197 ± 7 | 186 ± 7** | 187 ± 7* |
| TG (mg/dL) | 264 ± 60 | 209 ± 29 | 193 ± 19 |
| Ln TG | 5.3 ± 0.1 | 5.1 ± 0.1* | 5.1 ± 0.1 |
| RC (mg/dL) | 26 ± 3 | 24 ± 3 | 23 ± 2 |
| Lathosterol (µg/mL) | 2.2 ± 0.3 | 2.2 ± 0.3 | 2.2 ± 0.3 |
| Campesterol (µg/mL) | 4.7 ± 0.4 | 4.6 ± 0.4 | 4.6 ± 0.3 |
| Sitosterol (µg/mL) | 2.6 ± 1.2 | 2.5 ± 0.2 | 2.5 ± 0.2 |
| Cholestanol (µg/mL) | 2.2 ± 0.1 | 2.1 ± 0.1 | 2.1 ± 0.1 |

Data are expressed as the mean ± SE. BW, body weight; RC, remnant cholesterol; TC (F), calculated TC; Ln, natural logarithm.* p < 0.05, ** p < 0.01, and *** p < 0.001 vs. 0 month.

| Table 3 | Comparison of parameters at 0, 1, and 3 months according to the baseline LDL level |
|---------|-----------------------------------------------|
| Months  | LDL ≥100 (n = 22) | LDL <100 (n = 16) |
|         | 0          | 1          | 3          | 0          | 1          | 3          |
| BW (kg) | 81.9 ± 4.4 | 81.4 ± 4.2 | 81.0 ± 4.5 | 85.8 ± 3.7 | 85.4 ± 3.7 | 85.2 ± 3.8 |
| HbA1c (%) | 8.3 ± 0.3 | 8.0 ± 0.3 | 7.7 ± 0.4*** | 8.9 ± 0.3 | 8.5 ± 0.2* | 8.2 ± 0.3*** |
| LDL-C (mg/dL) | 125 ± 4 | 113 ± 7** | 115 ± 6** | 72 ± 5 | 72 ± 5 | 76 ± 6 |
| HDL-C (mg/dL) | 54 ± 3 | 53 ± 3 | 54 ± 2 | 49 ± 4 | 48 ± 4 | 50 ± 4 |
| Non HDL-C (mg/dL) | 151 ± 6 | 137 ± 7* | 132 ± 6** | 105 ± 4 | 97 ± 6 | 105 ± 10 |
| TC (mg/dL) | 203 ± 7 | 187 ± 9* | 183 ± 6* | 162 ± 6 | 154 ± 6 | 164 ± 11 |
| TC (F) (mg/dL) | 217 ± 6 | 198 ± 9** | 203 ± 8* | 163 ± 9 | 165 ± 10 | 159 ± 10 |
| TG (mg/dL) | 190 ± 17 | 159 ± 15* | 168 ± 17 | 366 ± 139 | 283 ± 65 | 229 ± 39 |
| Ln TG | 5.2 ± 0.1 | 5.0 ± 0.1** | 5.0 ± 0.1 | 5.4 ± 0.2 | 5.4 ± 0.2 | 5.2 ± 0.2 |
| RC (mg/dL) | 25 ± 3 | 22 ± 3 | 23 ± 2 | 27 ± 5 | 26 ± 5 | 23 ± 4 |
| Lathosterol (µg/mL) | 2.4 ± 0.4 | 2.5 ± 0.3 | 2.6 ± 0.4 | 2.1 ± 0.7 | 1.9 ± 0.4 | 1.7 ± 0.4 |
| Campesterol (µg/mL) | 5.2 ± 0.6 | 4.9 ± 0.6 | 4.9 ± 0.5* | 4.0 ± 0.4 | 4.1 ± 0.5 | 4.1 ± 0.5 |
| Sitosterol (µg/mL) | 2.8 ± 0.3 | 2.6 ± 0.3 | 2.6 ± 0.2 | 2.3 ± 0.2 | 2.2 ± 0.3 | 2.3 ± 0.3 |
| Cholestanol (µg/mL) | 2.4 ± 0.1 | 2.2 ± 0.1 | 2.3 ± 0.1 | 1.9 ± 0.2 | 1.9 ± 0.2 | 1.8 ± 0.2 |

Data are expressed as the mean ± SE. BW, body weight; RC, remnant cholesterol; TC (F), calculated TC; Ln, natural logarithm.* p < 0.05, ** p < 0.01, and *** p < 0.001 vs. 0 month.
HDL-C, and cholesterol synthesis and absorption markers were unchanged. In patients treated with LLD (n = 26), LDL-C, non-HDL-C, TC, TC (F), TG, and cholesterol synthesis and absorption markers were not changed.

### Discussion

The most important finding of this study was that the administration of liraglutide decreased non-HDL-C and TC (F) at 1 and 3 months, as well as TC and LDL-C at 1 month, whereas cholesterol synthesis and cholesterol absorption markers were not changed. However, in patients with baseline LDL-C (>100 mg/dL), LDL-C, non-HDL-C, TC, and TC (F) levels were decreased significantly by the treatment at 1 and 3 months, and the absorption marker campesterol was decreased at 3 months. This might indicate decreased food intake mediated by liraglutide in patients with higher baseline LDL-C levels. As the effect of liraglutide on cholesterol was small compared to that of sati, it would be difficult to investigate the associated mechanism based on these cholesterol synthesis and absorption markers. Some reports in animal models indicated another mechanism underlying improved cholesterol metabolism through the actions GLP-1 RAs. For example, liraglutide restored the mRNA expression of insulin-induced gene-2, the LDL-receptor, and peroxisome proliferator-activated receptor α, and also upregulated hydroxymethylglutaryl-CoA reductase and sterol regulatory element-binding protein-2 in the livers of mice [16]. Exendin-4 prevents fructose-induced dyslipidemia and hepatic VLDL overproduction in Syrian golden hamsters [17]. In HepG2 cells or db/db mice, liraglutide decreases protein convertase subtilisin/kexin type 9 via hepatocyte nuclear factor 1 alpha [18]. Further studies on the effect of liraglutide on cholesterol are needed.

### Table 4  Comparison of parameters at 0, 1, and 3 months with or without lipid-lowering drugs (LLDs)

| Months | Without LLD (n = 12) | With LLD (n = 26) |
|--------|---------------------|------------------|
|        | 0       | 1       | 3       | 0       | 1       | 3       |
| BW (kg)| 84.1 ± 6.9 | 82.8 ± 6.5 | 82.6 ± 7.3* | 83.3 ± 3.1 | 83.2 ± 3.1 | 82.8 ± 3.1 |
| HbA1c (%)| 7.9 ± 0.2 | 7.6 ± 0.4 | 7.4 ± 0.4* | 8.9 ± 0.3 | 8.5 ± 0.3** | 8.2 ± 0.3*** |
| LDL-C (mg/dL)| 124 ± 8 | 117 ± 10 | 120 ± 10 | 93 ± 6 | 85 ± 6 | 89 ± 6 |
| HDL-C (mg/dL)| 55 ± 4 | 53 ± 4 | 55 ± 3 | 50 ± 3 | 50 ± 3 | 51 ± 3 |
| Non HDL-C (mg/dL)| 156 ± 9 | 138 ± 9 | 140 ± 10 | 121 ± 7 | 114 ± 8 | 114 ± 6 |
| TC (mg/dL)| 207 ± 8 | 186 ± 9 | 190 ± 11 | 177 ± 7 | 167 ± 7 | 164 ± 7 |
| TC (F) (mg/dL)| 222 ± 10 | 200 ± 13** | 209 ± 13* | 186 ± 8 | 178 ± 9 | 175 ± 8 |
| TG (mg/dL)| 233 ± 58 | 147 ± 21* | 169 ± 28 | 278 ± 84 | 239 ± 41 | 204 ± 45 |
| Ln TG| 5.2 ± 0.2 | 4.9 ± 0.1** | 5.0 ± 0.2* | 5.3 ± 0.1 | 5.3 ± 0.1 | 5.2 ± 0.1 |
| RC (mg/dL)| 23 ± 5 | 17 ± 3 | 22 ± 5 | 27 ± 3 | 27 ± 4 | 23 ± 2 |
| Lathosterol (µg/mL)| 3.7 ± 0.4 | 4.0 ± 0.4 | 4.3 ± 0.4 | 1.5 ± 0.4 | 1.5 ± 0.2 | 1.3 ± 0.1 |
| Campesterol (µg/mL)| 5.0 ± 0.6 | 4.7 ± 0.6 | 4.8 ± 0.6 | 4.6 ± 0.5 | 4.5 ± 0.5 | 4.4 ± 0.4 |
| Sitosterol (µg/mL)| 2.7 ± 0.3 | 2.6 ± 0.3 | 2.6 ± 0.3 | 2.6 ± 0.2 | 2.4 ± 0.2 | 2.4 ± 0.2 |
| Cholesterol (µg/mL)| 2.6 ± 0.2 | 2.5 ± 0.2 | 2.6 ± 0.2 | 2.0 ± 0.1 | 1.9 ± 0.1 | 1.9 ± 0.1 |

Data are expressed as the mean ± SE. BW, body weight; RC, remnant cholesterol; TC (F), calculated TC; Ln, natural logarithm.

* p < 0.05, ** p < 0.01, and *** p < 0.001 vs. 0 month.
GLP-1 RAs have been reported to decrease serum TG levels [11, 19]. To reduce TG, GLP-1 decreases gastric emptying and intestinal lipid production [20]. In hamster enterocyte cultures, GLP-1R activation by exendin-4 decreases the secretion of ApoB-48 [21]. In all patients treated with liraglutide, the TG level was not changed and Ln TG levels were decreased at 1 month. Because we measured casual TG levels including fasting and postprandial levels, we would like to measure fasting TG levels in the next study.

Treatment with sitagliptin for 3 months decreases TC, LDL-C, and non-HDL-C levels, particularly in patients using strong statins [22]. GLP-1 RA decreases LDL-C in patients with type 2 diabetes treated with statins [14]. Stains were administered to most patients treated with LLD as described in the results section. However, in our study, no significant decrease in TC, LDL-C, or non-HDL-C was seen in patients taking LLD treated with liraglutide (Table 4).

The present study has several limitations. First, the number of patients was small. In addition, because we evaluated the lipid-lowering effects of liraglutide in daily clinical practice, there was no placebo group. Finally, because the duration of liraglutide treatment was only 3 months, LDL-C levels might not be maximally decreased. Therefore, a larger-scale, double-blinded study for a longer period of time is needed to confirm our findings.

In summary, the administration of liraglutide for 3 months decreased non-HDL-C and TC (F) significantly, and cholesterol synthesis and absorption markers were not changed by this treatment.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research (B) 21390282 and (B) 24390235 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, and a Medical Award from the Japan Medical Association.

Disclosure

Yasu Terauchi has received honoraria for lectures from MSD K.K.; Ono Pharmaceutical Co., Ltd.; Nippon Boehringer Ingelheim Co., Ltd.; Novartis Pharma K.K.; Takeda Pharmaceutical Co., Ltd.; Mitsubishi Tanabe Pharma Corp.; Daiichi Sankyo Co., Ltd.; Sanwa Kagaku Kenkyusho Co., Ltd.; Kowa Pharmaceutical Co., Ltd.; Novo Nordisk Pharma Ltd.; Eli Lilly Japan K.K.; Sanofi K.K.; Shionogi & Co., Ltd.; Bayer Yakuhin, Ltd.; and AstraZeneca K.K. and has obtained research support from MSD K.K.; Ono Pharmaceutical Co., Ltd.; Nippon Boehringer Ingelheim Co., Ltd.; Novartis Pharma K.K.; Takeda Pharmaceutical Co., Ltd.; Mitsubishi Tanabe Pharma Corp.; Daiichi Sankyo Co., Ltd.; Sanwa Kagaku Kenkyusho Co., Ltd.; Novo Nordisk Pharma Ltd.; Eli Lilly Japan K.K.; Sanofi K.K.; Dainippon Sumitomo Pharma Co., Ltd.; Shionogi & Co., Ltd.; Bayer Yakuhin, Ltd.; Astellas Pharma, Inc.; Pfizer Japan, Inc.; and AstraZeneca K.K.

Kazutaka Aoki has obtained research support from Sanwa Kagaku Kenkyusho Co., Ltd.

Masahiro Takihata has received honoraria for lectures from Astellas Pharma Inc.; MSD K.K.; AstraZeneca K.K., Ono Pharmaceutical Co., Ltd.; Sanofi K.K.; Dainippon Sumitomo Pharma Co., Ltd.; Daiichi Sankyo Co., Ltd.; Taisho Pharmaceutical Co. Ltd.; Takeda Pharmaceutical Co., Ltd.; Mitsubishi Tanabe Pharma Corp. and has obtained research support from Taisho Pharmaceutical Co. Ltd.

Hiroshi Kamiyama, Masataka Taguri, Eriko Shibata, Shinoda Kazuaki, Taishi Yoshii, Shigeru Nakajima declare that they have no conflicts of interest.

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