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Original Article

Glucagon-like peptide-1 receptor agonists reduced the low-density lipoprotein cholesterol in Japanese patients with type II diabetes mellitus treated with statins

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KEYWORDS:
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BACKGROUND: Patients with type II diabetes mellitus (T2DM) often have hypercholesterolemia, and their serum low-density lipoprotein cholesterol (LDL-C) levels are not always well-controlled even by statin treatment. The glucose-lowering glucagon-like peptide-1 receptor agonists (GLP-1RAs) are reported to change the lipid profiles in T2DM patients, but their effects have been unclear.

OBJECTIVE: We examined whether GLP-1RAs affect serum cholesterol levels in T2DM patients with/without statin treatment.

METHODS: We retrospectively assessed the baseline and follow-up (median 119 days) levels of serum lipids, HbA1c, and body mass index (BMI) in 103 and 214 Japanese patients with T2DM in whom GLP-1RAs were initiated (GLP-1RA group) and not initiated (control group), stratified by the use of statins.

RESULTS: In the GLP-1RA group, the LDL-C, HbA1c, and BMI significantly decreased; high-density lipoprotein cholesterol and triglycerides did not decrease during follow-up. In the control group, these did not decrease. Among the statin users, the percentage change in LDL-C during follow-up was significantly greater in the GLP-1RA group than that in the control group (−6.5% vs −1.0%, $P = .040$). In the GLP-1RA group, the percentage reduction in LDL-C was not associated with that in BMI but was associated with that in HbA1c only among the statin users.

CONCLUSIONS: Our findings demonstrated that GLP-1RAs reduced the serum LDL-C in Japanese patients with T2DM treated with statins. The percentage reduction in LDL-C by GLP-1RAs was associated with that in HbA1c, but not associated with that in BMI. The combination of GLP-1RAs and statins may be a reasonable therapeutic option in T2DM with dyslipidemia.

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Introduction

Type II diabetes mellitus (T2DM) is known to be one of the major risk factors for cardiovascular disease (CVD), and the risk of CVD in Japanese with DM was estimated to be approximately 3-fold higher compared with Japanese without DM.[1] The United Kingdom Prospective Diabetes Study and the Japan Diabetes Complications Study showed that in both British and Japanese patients with T2DM, respectively, the leading risk factors for CVD are high levels of low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and high levels of triglycerides (TGs).[2,3]

T2DM is often complicated with dyslipidemia characterized by (1) an enhanced production of very-low-density lipoprotein (VLDL) and hypertriglyceridemia due to a decreased sensitivity to insulin[4]; (2) an enhanced absorption of exogenous cholesterol and chylomicron from the intestine via Niemann-Pick C1-Like 1 and ATP-binding cassette transporters-G5 (ABCG5) and ABCG8[5]; (3) increased small dense LDL[6]; and (4) decreased HDL.[7] Indeed, approximately 70% to 80% of the patients with T2DM that we see at our institutions were complicated by hypercholesterolemia, and their serum LDL-C levels were not well-controlled even with statin treatment (unpublished data). Because of the combination of a statin and the plasma cholesterol level–lowering drug ezetimibe further reduced the LDL-C levels and the risk of CVD,[8] it is urgent to search for new therapeutic options to further reduce the CVD risk in individuals with T2DM.

Glucagon-like peptide-1 agonists (GLP-1RAs) are used as efficacious and safe therapeutic options for managing T2DM. GLP-1/GLP-1RAs stimulate glucose-dependent insulin secretion and inhibit glucagon secretion in the pancreas.[9,10] GLP-1RAs were reported to decrease the levels of plasma TGs, total cholesterol, and lipoproteins in patients with T2DM.[11–14] In vivo and in vitro studies have demonstrated the efficacy of GLP-1RAs for the reduction of TG absorption in the small intestine,[15] lipogenesis in the liver,[16] the inhibition of VLDL production,[16–18] and the improvement of hepatic steatosis.[17,19–21]

Thus, the effects of GLP-1RAs are suitable as a therapeutic option for treating patients with T2DM with dyslipidemia. However, to date, the role of GLP-1RAs in cholesterol metabolism has not been established. Moreover, the association between GLP-1RAs and statins in the LDL-C–lowering effect has not been clarified. We hypothesized that (1) GLP-1RAs reduce serum LDL-C levels in patients with T2DM; and (2) the LDL-C–lowering effect of GLP-1RAs is affected by statins. In the present study, we investigated the effect of GLP-1RAs on cholesterol metabolism in Japanese patients with T2DM who were being treated with statins or were not being treated with statins.

Materials and methods

Subjects

This study was a single-center case–control study of Japanese patients with T2DM. Figure 1 presents the flow diagram of study subjects. From among the 6592 patients with T2DM who regularly visited the Diabetes Center, Tokyo Women's Medical University Hospital between January 2010 and December 2015, we identified 127 patients who were newly prescribed and continued to use a GLP-1RA by regular doses in Japan (ie, exenatide 20 μg/d or 2 mg/wk, liraglutide 0.9 mg/d, and lixisenatide 20 μg/d).

Patients without complete data within 6 months of prescription (n = 14), those who had discontinued GLP-1RAs within the prior 2 months (n = 6), and those who were on hemodialysis (n = 3) or were diagnosed as having familial hypercholesterolemia (n = 1) were excluded from the analysis. Overall, 103 patients with T2DM under GLP-1RA treatment were enrolled as the GLP-1RA group (Fig. 1).

Next, as the control group, we selected 214 patients with T2DM who were not being treated with a GLP-1RA and were matched with the GLP-1RA group for age, sex, duration of T2DM, serum lipid levels, HbA1c, and body mass index (BMI) using propensity scores. We further divided the patients in each group into 2 subgroups based on whether they were treated or nontreated with a statin.

Methods

All the patients' data were obtained from a clinical information system. The laboratory data based on random spot blood samples together with the BMI of each patient were collected before and after the start of treatment with GLP-1RAs in the GLP-1RA group and during the same observation period in the control group. The median (interquartile range) follow-up periods for the GLP-1RA and control groups were 119 (98–146) days and 119 (98–176) days, respectively ($P = .168$).

Serum levels of LDL-C, HDL-C, and TG were measured by direct methods using automatic analysis equipment, LABOSPECT008 (Hitachi High-Technologies clinical analyzer, Tokyo), based on Determiner L LDL-C, Metabolead HDL-C, and Determiner LTG II (Kyowa Medex, Tokyo). Blood glucose values were measured by the electrode method (Adams Glu GA1171; ARKRAY, Kyoto, Japan). HbA1c values were measured using the HPLC method (Adams A1c HA-8160; ARKRAY) and are shown as National Glycohemoglobin Standardization Program assigned values (percentage) and calculated using the International Federation of Clinical Chemistry and Laboratory Medicine reference method.[22] The percentage change during follow-up in the levels of serum lipids, HbA1c, and BMI was calculated in all patients, and the percentage change in each of these 3 parameters was compared