



Exenatide Improves HDL Particle Counts and Size Distribution in Patients With Long-standing Type 1 Diabetes

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Glucagon-like peptide 1 agonists such as exenatide have been reported to improve fasting and postprandial lipid profiles and cardiovascular outcomes in patients with type 2 diabetes but to have minimal effects on fasting profiles in patients with type 1 diabetes based on standard lipid measurements.

In this study, we used nuclear magnetic resonance (NMR) to determine the effects of exenatide on lipoprotein particle characteristics, which might be indicative of a change in cardiovascular risk in patients with type 1 diabetes.

This is an ancillary study of a previously published clinical trial (ClinicalTrials.gov identifier NCT00064714) (1). Briefly, 14 patients were randomized to receive exenatide (10 μ g four times daily) either in the first or the second 6-month study period in addition to insulin (1). The patients were also randomized to treatment with or without the immunomodulatory drug daclizumab for 12 months (1). Patients underwent repeated mixed-meal tests after an overnight fast. Tests were conducted at the beginning and end of each 6-month period. To estimate the mean differences between treatment

groups, linear mixed models were used to control for sequence and period effects and to allow for correlation within the same group using Stata's `pcross` command for the analysis of crossover experiments. Results are expressed as mean \pm SD.

At baseline, the 14 study participants (50% female) were 37.3 ± 10.7 years old, had type 1 diabetes for 20.5 ± 11.8 years, had a BMI of 26.1 ± 3.5 kg/m², and had an HbA_{1c} of $7.0 \pm 0.8\%$ (1). A total of 11 of 14 patients were on statin treatment.

Results of the fasting standard lipid panels showed that exenatide treatment increased fasting HDL cholesterol (HDL-C) by 4.5 mg/dL ($P = 0.004$), a mean increase of $\sim 8\%$. Exenatide did not change fasting LDL cholesterol (LDL-C), total cholesterol, or triglycerides. Postprandial standard lipid results also documented a significant postprandial increase of total HDL-C area under the curve (AUC) by 7.2% ($P = 0.002$). Fasting large HDL particles (HDLp) measured with NMR increased by 13.2% after exenatide treatment ($P = 0.011$), with no major change in total, small, and medium HDLp. No effect was observed on other fasting lipid profiles, including total, large, medium,

and small VLDL particles (VLDLp) and total, large, and small LDL particles (LDLp). In addition, postprandial lipoprotein analyses with NMR showed a similar increase in large HDLp (AUC 13.2%, $P = 0.012$) and the sum of medium and large HDLp (AUC 20.5%, $P = 0.022$). Exenatide treatment also decreased postprandial AUCs of medium and small VLDLp with a simultaneous increase in the large VLDLp, but the change was not statistically significant (Table 1).

Our study shows that exenatide treatment increased total fasting HDL-C, fasting large HDLp, and postprandial large and medium HDLp. This finding is important given that large, lipid-enriched HDLp are associated with a decreased cardiovascular disease risk compared with small HDLp (2).

Patients on exenatide had an average weight loss of 4.1 ± 2.9 kg and decreased meal-associated insulin requirements (from 0.26 ± 0.09 units/kg/day off exenatide to 0.18 ± 0.05 units/kg/day on exenatide) (1). Given that insulin stimulates hepatic lipase—which generates small HDL and small LDL—it is possible that the effects on HDL were partially

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Table 1—Fasting and postprandial baseline and AUC values on and off exenatide

| Variables | On exenatide (N = 14) | Off exenatide (N = 14) | P |
|--|-----------------------|------------------------|--------|
| Fasting, standard lipids | | | |
| HDL-C (mg/dL) | 63.9 (13.0) | 59.4 (13.8) | 0.004* |
| LDL-C (mg/dL) | 65.1 (24.0) | 65.7 (32.1) | 0.76 |
| TC (mg/dL) | 136 (30) | 132 (36) | 0.70 |
| TG (mg/dL) | 62 (22) | 63 (24) | 0.696 |
| Fasting, NMR particles | | | |
| LDLp (nmol/L) | 617 (241) | 644 (349) | 0.539 |
| s-LDLp (nmol/L) | 166 (138) | 184 (165) | 0.446 |
| l-LDLp (nmol/L) | 275 (196) | 272 (214) | 0.961 |
| VL-LDLp (nmol/L) | 711 (225) | 740 (320) | 0.486 |
| HDLp (μmol/L) | 33.1 (4.4) | 31.8 (5.6) | 0.374 |
| s-HDLp (μmol/L) | 12.3 (6.5) | 13.7 (7.7) | 0.328 |
| m-HDLp (μmol/L) | 11.1 (7.5) | 9.4 (7.0) | 0.276 |
| l-HDLp (μmol/L) | 8.9 (3.1) | 7.9 (3.1) | 0.011* |
| lm-HDLp (μmol/L) | 20.8 (7.9) | 18.1 (8.0) | 0.079 |
| VLDLp (nmol/L) | 25.5 (13.3) | 30.0 (13.6) | 0.290 |
| s-VLDLp (nmol/L) | 20.7 (10.8) | 23.9 (9.7) | 0.457 |
| m-VLDLp (nmol/L) | 6.6 (3.0) | 8.1 (7.3) | 0.283 |
| l-VLDLp (nmol/L) | 1.8 (2.1) | 1.4 (1.3) | 0.168 |
| lm-VLDLp (nmol/L) | 7.0 (3.9) | 7.9 (7.4) | 0.398 |
| Postprandial AUC, standard lipids | | | |
| HDL-C (mg/dL) | 15,593 (3,183) | 14,545 (3,021) | 0.002* |
| LDL-C (mg/dL) | 14,138 (3,818) | 14,669 (5,735) | 0.501 |
| TC (mg/dL) | 31,569 (6,169) | 31,194 (6,523) | 0.895 |
| TG (mg/dL) | 14,264 (4,782) | 15,294 (6,576) | 0.304 |
| Postprandial AUC, NMR particles | | | |
| LDLp (nmol/L) | 135,260 (40,601) | 145,037 (71,367) | 0.368 |
| s-LDLp (nmol/L) | 39,533 (35,499) | 47,061 (47,691) | 0.259 |
| l-LDLp (nmol/L) | 61,316 (43,734) | 61,105 (40,252) | 0.924 |
| VL-LDLp (nmol/L) | 158,956 (39,147) | 168,666 (67,637) | 0.335 |
| HDLp (μmol/L) | 7,879 (1,033) | 7,664 (1,324) | 0.347 |
| s-HDLp (μmol/L) | 2,180 (1,413) | 2,895 (1,891) | 0.118 |
| m-HDLp (μmol/L) | 3,350 (1,860) | 2,625 (1,659) | 0.073 |
| l-HDLp (μmol/L) | 2,185 (746) | 1,931 (720) | 0.012* |
| lm-HDLp (μmol/L) | 5,701 (1,779) | 4,731 (1,855) | 0.022* |
| VLDLp (nmol/L) | 6,133 (3,031) | 7,061 (4,012) | 0.166 |
| s-VLDLp (nmol/L) | 5,168 (2,650) | 5,631 (2,577) | 0.241 |
| m-VLDLp (nmol/L) | 1,368 (692) | 1,768 (1,327) | 0.193 |
| l-VLDLp (nmol/L) | 437 (424) | 73 (390) | 0.701 |
| lm-VLDLp (nmol/L) | 1,472 (723) | 1,871 (1,544) | 0.194 |

Data are mean (SD). This table presents the mean values of fasting and postprandial values of the outcome measures when comparing the same set of patients (N = 14) on exenatide and off exenatide. The P values are based on a mixed model for crossover design, incorporating period and sequence effects. l, large; lm, large and medium; m, medium; s, small; TC, total cholesterol; TG, triglycerides; VL-LDLp, sum of VLDLp and LDLp. *P < 0.05.

due to weight loss. However, other studies have shown that even a single dose of exenatide can improve postprandial lipids in patients with type 2 diabetes irrespective of weight loss. In addition, weight loss tends to affect mainly LDL-C and to a lesser degree HDL-C (3,4). Limitations of this study include the sample size, which was too small to calculate the effect of exenatide irrespective of weight loss, and the use of exenatide at a dose approximately twice as high as typically prescribed. Furthermore, most of the

study participants were on statin treatment, and 50% had been assigned to treatment with daclizumab. It is unlikely, however, that daclizumab contributed to the observed lipid changes, as it is not known to affect glucose or lipid metabolism (5).

Our preliminary results suggest that exenatide might improve cardiovascular outcomes in patients with type 1 diabetes by improving large HDLp. Additional studies are clearly needed to examine the biological effects of exenatide on HDL

function and whether these effects are sustained at lower exenatide doses and for a prolonged period of time, as well as whether they can be validated in a larger group of obese patients and/or patients with poorly controlled type 1 diabetes.

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