Efficacy and Safety of the Human Glucagon-Like Peptide-1 Analog Liraglutide in Combination With Metformin and Thiazolidinedione in Patients With Type 2 Diabetes (LEAD-4 Met+TZD)

Bernard Zinman, MD1
John Gerich, MD2
John B. Buse, MD, PhD3
Andrew Lewin, MD4
Sherwyn Schwartz, MD5

PHILIP RASKIN, MD6
PAULA M. HALE, PHD7
MILAN ZDRAVKOVIC, PHD7
LAWRENCE BLONDE, MD®
THE LEAD-4 STUDY INVESTIGATORS*

OBJECTIVE — To determine the efficacy and safety of liraglutide (a glucagon-like peptide-1 receptor agonist) when added to metformin and rosiglitazone in type 2 diabetes.

RESEARCH DESIGN AND METHODS — This 26-week, double-blind, placebo-controlled, parallel-group trial randomized 533 subjects (1:1:1) to once-daily liraglutide (1.2 or 1.8 mg) or placebo in combination with metformin (1 g twice daily) and rosiglitazone (4 mg twice daily). Subjects had type 2 diabetes, A1C 7–11% (previous oral antidiabetes drug controlled, parallel-group trial randomized 533 subjects (1:1:1) to once-daily liraglutide (1.2 or 1.8 mg) or liraglutide placebo in combination with metformin (1 g twice daily) and rosiglitazone (4 mg twice daily). Subjects had type 2 diabetes, A1C 7–11% (previous oral antidiabetes drug controlled, parallel-group trial randomized 533 subjects (1:1:1) to once-daily liraglutide (1.2 or 1.8 mg) or placebo (mean ± SE −1.5 ± 0.1% for both 1.2 and 1.8 mg liraglutide and −0.5 ± 0.1% for placebo). Fasting plasma glucose decreased by 40, 44, and 8 mg/dl for 1.2 and 1.8 mg and placebo, respectively, and 90-min postprandial glucose decreased by 47, 49, and 14 mg/dl, respectively (P < 0.001 for all liraglutide groups vs. placebo). Dose-dependent weight loss occurred with 1.2 and 1.8 mg liraglutide (1.0 ± 0.3 and 2.0 ± 0.3 kg, respectively) (P < 0.0001) compared with weight gain with placebo (0.6 ± 0.3 kg). Systolic blood pressure decreased by 6.7, 5.6, and 1.1 mmHg with 1.2 and 1.8 mg liraglutide and placebo, respectively. Significant increases in C-peptide and homeostasis model assessment of β-cell function and significant decreases in the proinsulin-to-insulin ratio occurred with liraglutide versus placebo. Minor hypoglycemia occurred more frequently with liraglutide, but there was no major hypoglycemia. Gastrointestinal adverse events were more common with liraglutide, but most occurred early and were transient.

RESULTS — Mean A1C values decreased significantly more in the liraglutide groups versus placebo (mean ± SE −1.5 ± 0.1% for both 1.2 and 1.8 mg liraglutide and −0.5 ± 0.1% for placebo). Fasting plasma glucose decreased by 40, 44, and 8 mg/dl for 1.2 and 1.8 mg and placebo, respectively, and 90-min postprandial glucose decreased by 47, 49, and 14 mg/dl, respectively (P < 0.001 for all liraglutide groups vs. placebo). Dose-dependent weight loss occurred with 1.2 and 1.8 mg liraglutide (1.0 ± 0.3 and 2.0 ± 0.3 kg, respectively) (P < 0.0001) compared with weight gain with placebo (0.6 ± 0.3 kg). Systolic blood pressure decreased by 6.7, 5.6, and 1.1 mmHg with 1.2 and 1.8 mg liraglutide and placebo, respectively. Significant increases in C-peptide and homeostasis model assessment of β-cell function and significant decreases in the proinsulin-to-insulin ratio occurred with liraglutide versus placebo. Minor hypoglycemia occurred more frequently with liraglutide, but there was no major hypoglycemia. Gastrointestinal adverse events were more common with liraglutide, but most occurred early and were transient.

CONCLUSIONS — Liraglutide combined with metformin and a thiazolidinedione is a well-tolerated combination therapy for type 2 diabetes, providing significant improvements in glycemic control.
blood pressure (SBP) has been previously demonstrated (7–10). No major hypoglycemic events occurred during the randomised treatment period when liraglutide was used as monotherapy or with metformin (7,9). The current study investigated liraglutide treatment in combination with metformin and a thiazolidinedione (TZD) (rosiglitazone) as part of the LEAD program. These three glucose-lowering agents are of particular interest, as they have complementary modes of action and are not generally associated with increased risk of hypoglycemia.

**RESEARCH DESIGN AND METHODS** — Subjects with type 2 diabetes were screened and enrolled if they were aged 18–80 years, had A1C between 7 and 11% (prestudy OAD monotherapy for ≥3 months) or 7–10% (prestudy combination OAD therapy for ≥3 months), and had BMI ≤45 kg/m². Subjects who used insulin during the previous 3 months (except short-term treatment) were excluded. The protocol was approved by local institutional review boards, and subjects provided written informed consent before the initiation of any trial-related activities. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines (12).

This 26-week, double-blind, randomised, placebo-control, parallel-group, multicenter (96 sites), two-country (U.S. and Canada) trial randomized subjects (1:1:1) to receive 1.2 or 1.8 mg of once-daily liraglutide (Novo Nordisk, Bagsvaerd, Denmark) or liraglutide placebo (Novo Nordisk) injected subcutaneously once daily at any time of the day in the upper arm, abdomen, or thigh using a prefilled pen device. Subjects were encouraged to use liraglutide during the same overall time period. The titration period was followed by a 24-week maintenance period during which the doses of study drugs were to be maintained.

The primary outcome measure was change in A1C from randomization to the end of the study. Secondary end points included changes in body weight; FPG; seven-point plasma glucose profiles; β-cell function based on fasting insulin, fasting C-peptide, and fasting proinsulin-to-insulin ratio; the homeostasis model assessment (HOMA) for β-cell function (HOMA-B) and insulin resistance (HOMA-IR) (13); and lipids. Laboratory analyses were performed by a central laboratory (MDS Pharma Services in Canada and Switzerland). A1C was assayed by a method certified by the National Glycohemoglobin Standardization Program. Subjects were provided with MediSense Precision Xtra/MediSense Optium glucose meters (Abbott Laboratories, Abbott Park, IL) calibrated to plasma glucose to determine self-measured plasma glucose (SMPG) and were asked to record values in their diaries. The seven-point SMPG profile measurements were performed before and 90 min after meals and at bedtime for 2 consecutive days at weeks 0 (randomization), 12, and 26. Serum insulin and C-peptide values were determined using a chemiluminescence immunoassay, and proinsulin was measured in serum using an enzyme-linked immunosorbent assay.

Safety variables included adverse events, vital signs, electrocardiogram, biochemical and hematology measures, and subject-reported hypoglycemic episodes (plasma glucose <56 mg/dl [<3.1 mmol/l]). A serious adverse event was defined as an adverse event that resulted in death, hospitalization, disability, or a birth defect; was life threatening; or required medical or surgical intervention to prevent one of the other outcomes. Minor hypoglycemic episodes were defined as those that could be self-treated; major episodes were defined as requiring third-party assistance or medical intervention. Nausea was patient reported.

**Statistical analysis** — The analysis of efficacy end points was based on the intent-to-treat population, defined as subjects who were exposed to at least one dose of trial product and had one postbaseline measurement of the parameter. Each end point was analyzed using an ANCOVA model with treatment, country, and previous antidiabetes treatment as fixed effects and baseline as the covariate. Missing data were imputed as the last observation carried forward. Sample size calculations were based on showing A1C and body weight differences of 0.5 and 3%, respectively. The combined power (calculated as the product of the marginal powers for A1C and weight) was >95%.

Superiority of glycemic control with liraglutide versus comparators was concluded if the upper limit of the two-sided 95% CI for the treatment difference in change in A1C was <0%; equivalence was also tested. The proportion of subjects achieving A1C targets (American Diabetes Association [ADA] target: <7%; American Association of Clinical Endocrinologists [AACE]/International Diabetes Federation [IDF] target: ≤6.5%) was compared between treatments using a logistic regression model with treatment and baseline A1C as covariates. CIs for secondary end points were corrected using Dunnett’s test. Hypoglycemic episodes were analyzed using a general linear model including treatment as a fixed effect. The significance level was set at P < 0.05.

**RESULTS** — A total of 821 subjects were enrolled in the study; 533 subjects were randomly assigned to liraglutide or placebo treatment after the metformin plus rosiglitazone run-in period (288 subjects were run-in failures due to FPG values out of range [135–230 mg/dl; 7.5–12.8 mmol/l] or other reasons). Three subjects were randomized but were with-
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Table 1—Characteristics of randomized population and subject disposition

|                      | 1.2 mg Liraglutide | 1.8 mg Liraglutide | Placebo |
|----------------------|--------------------|--------------------|---------|
| Sex (%) (men/women)  |                    |                    |         |
| Age (years)          | 55 ± 10            | 55 ± 11            | 55 ± 10 |
| Race (%)/C/B/A/I/O    | 81/15/1/1/2        | 83/10/3/3/1        | 84/10/2/1/3 |
| Ethnicity (Hispanic or Latino/not) | 13/87             | 16/84              | 16/84   |
| BMI (kg/m²)          | 33.2 ± 5.4         | 33.5 ± 5.1         | 33.9 ± 5.2 |
| Duration of diabetes (years) | 9 ± 6             | 9 ± 6              | 9 ± 6   |
| Prestudy OAD treatment |                  |                    |         |
| Monotherapy          | 29 (16)            | 29 (16)            | 32 (18) |
| Combination therapy  | 149 (84)           | 149 (84)           | 145 (82) |
| A1C (%)              | 8.5 ± 1.2          | 8.6 ± 1.2          | 8.4 ± 1.2 |
| FPG [mg/dl (mmol/l)] | 182 ± 43 (10.1 ± 2.4) | 185 ± 43 (10.3 ± 2.4) | 180 ± 47 (10.0 ± 2.6) |
| SBP (mmHg)           | 129 ± 14.8         | 126 ± 14.2         | 128 ± 14.5 |
| DBP (mmHg)           | 75.8 ± 9.0         | 75.2 ± 8.4         | 76.2 ± 9.2 |
| Total cholesterol (mmol/l) | 5.01 ± 1.33 | 5.17 ± 1.43 | 4.99 ± 1.34 |
| LDL cholesterol (mmol/l) | 2.82 ± 0.95 | 2.96 ± 1.08 | 2.77 ± 0.95 |
| VLDL cholesterol (mmol/l) | 0.74 ± 0.38 | 0.76 ± 0.38 | 0.71 ± 0.36 |
| HDL cholesterol (mmol/l) | 1.26 ± 0.32 | 1.27 ± 0.31 | 1.25 ± 0.28 |
| Triglycerides (mmol/l) | 2.41 ± 2.24 | 2.39 ± 1.88 | 2.74 ± 2.80 |
| Free fatty acids (mmol/l) | 0.51 ± 0.22 | 0.55 ± 0.27 | 0.52 ± 0.34 |
| Randomized           | 178                | 178                | 177     |
| Completers           | 153 (86)           | 133 (75)           | 121 (68) |
| Withdrawals          | 25 (14)            | 45 (25)            | 56 (32) |
| Adverse events*      | 11 (6)             | 27 (15)            | 6 (3)   |
| Nausea/vomiting/diarrhea | 5 (3)           | 19 (11)            | 0       |
| Ineffective therapy  | 3 (2)              | 3 (2)              | 29 (16) |
| Noncompliance        | 4 (2)              | 4 (2)              | 5 (3)   |
| Other                | 7 (4)              | 11 (6)             | 16 (9)  |

Data are means ± SD or n (%) unless otherwise indicated. *The adverse events row includes nausea/vomiting/diarrhea: A, Asian; B, black; C, Caucasian; I, American Indian; O, other.

drawn before receiving the study drug. Baseline characteristics were balanced across treatment groups (Table 1). The majority (83%) of the randomized subjects were treated with two or more OADs before the study.

Efficacy

At the end of the study, the mean A1C values for the overall population decreased by (means ± SE) 1.5 ± 0.1% for both 1.2 and 1.8 mg/day liraglutide groups and 0.5 ± 0.1% for the placebo group. Liraglutide-treated subjects had superior glycemic control compared with those in the placebo group (liraglutide 1.2 mg/day vs. placebo: −0.9% [95% CI −1.1 to −0.8] and liraglutide 1.8 mg/day vs. placebo: −1.1% [−1.1 to −0.8]). Within the first 12 weeks of the study, mean A1C values decreased from baseline for the liraglutide-treated groups and thereafter remained steady throughout the trial (Fig. 1A).

A logistic regression analysis demonstrated that a significantly greater percentage of subjects in both of the liraglutide groups achieved the ADA and AACE/IDF A1C goals compared with placebo (P < 0.0001 for all comparisons of liraglutide to placebo for both A1C goals) (Fig. 1B). At the end of the study, 57.5 and 53.7% of the randomized subjects in the 1.2 and 1.8 mg liraglutide/day groups, respectively, had an A1C value of ≤7%, compared with 28.1% in the placebo group (P < 0.0001 comparisons of all liraglutide groups to placebo). The decreases observed in the placebo group (−8 mg/dl [−0.4 mmol/l], P < 0.0001).

Mean 90-min PPG (mean of three meals, from self-monitored seven-point plasma glucose measurements at the end of the study, decreased from baseline in all treatment groups by −47 mg/dl (2.6 mmol/l) for 1.2 mg liraglutide/day, −49 mg/dl (2.7 mmol/l) for 1.8 mg liraglutide/day, and −14 mg/dl (0.8 mmol/l) for placebo (P < 0.001 comparisons of all liraglutide groups to placebo). The postprandial increment (postmeal value minus premeal) was significantly reduced after breakfast with liraglutide treatment (−16, −14, and −5 mg/dl [−0.9, −0.8, −0.3 mmol/l], respectively; P < 0.05 for both liraglutide treatment groups vs. placebo) but not for lunch and dinner.

Mean change in body weight over time is shown in Fig. 1D. Weight loss was observed in the liraglutide-treated groups (means ± SE) 1.0 ± 0.3 and 2.0 ± 0.3 kg from baseline for 1.2 and 1.8 mg liraglutide/day groups, respectively) and was significantly different (P < 0.0001) from the weight gain in the placebo group.
The weight loss in the 1.8 mg liraglutide/day group was significantly greater than the 1.2 mg liraglutide/day group ($P=0.011$). The 1.2 and 1.8 mg liraglutide/day groups had significant reductions in mean SBP compared with the placebo group (Table 2) (Fig. 1E) (placebo-corrected difference: 1.2 mg liraglutide/day: $-5.6$ mmHg, $P < 0.0001$; 1.8 mg liraglutide/day: $-4.5$ mmHg, $P = 0.0009$). There were no significant differences between treatment groups in diastolic blood pressure (DBP). Minor, but statistically significant, increases in pulse rate were observed in the liraglutide-treated groups versus placebo (2 and 3 bpm for 1.2 mg ($P = 0.0071$) and 1.8 mg liraglutide ($P = 0.0001$), respectively) with a decrease of 0.5 bpm for placebo. Changes in lipids from baseline are presented in Table 2 showing that free fatty acid values decreased with liraglutide treatment as compared with an increase with placebo, and LDL cholesterol and triglycerides decreased significantly more in the 1.2 mg liraglutide group than in the placebo group.

The decreases in the proinsulin-to-insulin ratio from baseline (baseline of 0.4 across all groups) for the liraglutide groups were significant ($P < 0.05$) compared with the placebo group, which increased from baseline (Table 2). The increase in C-peptide was significantly greater in the liraglutide groups (131 and

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**Figure 1**—A: A1C over time for the study population. B: Percentage of subjects achieving ADA and AACE/IDF A1C goals at the end of the study. C: FPG values over time. D: Change in body weight over time. E: SBP over time. F: Percentage of subjects with nausea by week. Data are intent to treat, last observation carried forward for all postbaseline values, with the exception of F, which is data from the safety analysis set. Error bars shown in A, C, D, and E are $2 \times SE$. **$P=0.0009$; ***$P < 0.0001$. 

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(0.6 ± 0.3 kg).
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Table 2—Other end points of interest/metabolic intermediates change from baseline to end of study

| Blood pressure (mmHg) | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Placebo |
|-----------------------|-------------------|-------------------|--------|
| SBP                   | -6.7 ± 1.1*       | -5.6 ± 1.1*       | -1.1 ± 1.2 |
| DBP                   | -2.3 ± 0.7        | -1.9 ± 0.7        | -0.8 ± 0.7 |
| **β-Cell function**   |                   |                   |        |
| Insulin (pmol/l)      | 6.0 ± 5.8         | 5.6 ± 5.5         | 6.8 ± 6.0 |
| C-peptide (pmol/l)    | 131 ± 32*         | 144 ± 31*         | 51 ± 34 |
| Proinsulin-to-insulin ratio | -0.029 ± 0.026* | -0.085 ± 0.26* | 0.036 ± 0.029 |
| **β-Cell function (%) (HOMA-B)** | 27 ± 4.4* | 27 ± 4.2* | 6 ± 4.5 |
| Insulin resistance (HOMA-IR) | -0.6 ± 0.3 | -0.7 ± 0.3 | -0.3 ± 0.3 |
| Proinsulin-to-C-peptide ratio | -0.007 ± 0.001* | -0.008 ± 0.001* | -0.002 ± 0.001 |
| Fasting glucagon (pg/ml) | -5.9 ± 2.9 | -6.7 ± 2.8 | -0.4 ± 3.0 |
| **Lipids**            |                   |                   |        |
| Total cholesterol (mmol/l) | -0.21 ± 0.9 | -0.20 ± 0.9 | -0.02 ± 0.10 |
| LDL cholesterol (mmol/l) | -0.28 ± 0.07* | -0.23 ± 0.07 | -0.10 ± 0.07 |
| VLDL cholesterol (mmol/l) | 0.12 ± 0.03 | 0.10 ± 0.03 | 0.11 ± 0.03 |
| HDL cholesterol (mmol/l) | -0.03 ± 0.02 | -0.04 ± 0.02 | -0.03 ± 0.02 |
| Triglycerides (mmol/l) | -0.38 ± 0.10* | -0.32 ± 0.10 | -0.13 ± 0.11 |
| Free fatty acids (mmol/l) | -0.03 ± 0.02* | -0.05 ± 0.02* | 0.02 ± 0.02 |

Data are means ± SE, unless otherwise noted. *P < 0.05 vs. placebo.

144 pmol/l for 1.2 and 1.8 mg liraglutide, respectively) compared with an increase of 51 pmol/l for placebo (P < 0.05 for comparison of both liraglutide groups to placebo). Both liraglutide treatment groups had significant improvements (increase of 27 absolute percentage points in HOMA-B for both groups from baseline values of 34 to 37%, respectively, compared with an improvement in the placebo group of 6 absolute percentage points from a baseline of 40% (P < 0.0001 for both groups vs. placebo). Insulin resistance (measured by HOMA-IR) was reduced in all three treatment groups but was not significantly different between groups. No significant differences in the change from baseline of HOMA-IR and fasting insulin and glucagon values were observed between either of the liraglutide groups versus the placebo group (Table 2).

**Safety**

Gastrointestinal disorders (including nausea, vomiting, and diarrhea) were the most frequently reported adverse events in the liraglutide groups and were reported by 45, 56, and 19% of the subjects in the 1.2 and 1.8 mg liraglutide and placebo groups, respectively. One episode or more of nausea was experienced by 29 and 40% in the 1.2 and 1.8 mg liraglutide groups, respectively, and vomiting was experienced by 7 and 17%, respectively. The majority of nausea was transient, as it occurred in the first 4 weeks of liraglutide treatment (216 events in weeks 1–4 vs. 65 events in weeks 4–26) (Fig. 1F). During the first 8 weeks of treatment, 71–84% of subjects in the liraglutide groups and 98% of subjects in the placebo group reported ≤7 days of nausea. Peripheral edema was reported by 5.1, 1.7, and 8.0% in the 1.2 mg liraglutide, 1.8 mg liraglutide, and placebo groups, respectively.

The percentages of subjects withdrawn because of adverse events were greater in the liraglutide groups than in the placebo group (14%). Nausea, vomiting, and/or diarrhea were the gastrointestinal events that lead to the withdrawal of five subjects treated with 1.2 mg liraglutide and 19 subjects treated with 1.8 mg liraglutide (Table 1). Most gastrointestinal adverse events resulting in withdrawal occurred during the first month of therapy. There were no episodes of pancreatitis, and no deaths occurred. Serious adverse events were infrequent (8 subjects [8 total events] for 1.2 mg liraglutide, 7 subjects [10 events] for 1.8 mg liraglutide, and 12 subjects [13 events] for placebo).

Minor hypoglycemia occurred at low incidence (9.0, 7.9, and 5.1% of subjects) resulting in a low rate of reported minor hypoglycemia (0.4, 0.6, and 0.2 events per year) for the 1.2 mg liraglutide, 1.8 mg liraglutide, and placebo groups, respectively. The rate of minor hypoglycemia for the 1.8 mg liraglutide group was significantly higher than placebo (P = 0.004). No major hypoglycemic event was reported.

No clinically relevant between-treatment differences were observed in physical examination findings, laboratory analyses (hematology and biochemistry analyses), electrocardiogram, or ophthalmoscopy. There was no significant treatment effect with 1.8 mg liraglutide versus placebo on calcitonin. Geometric mean–estimated repeated-measurement analysis showed calcitonin levels of 0.89, 0.83, and 0.75 ng/l for 1.2 mg liraglutide, 1.8 mg liraglutide, and placebo, respectively, at the end of the study (all values within the normal range). There was a significant increase for the 1.2 mg liraglutide group versus placebo group (P = 0.022) but no significant difference with the 1.8 mg liraglutide group. No difference in cardiovascular adverse events was reported between the liraglutide groups and placebo (five events [five subjects] with liraglutide 1.2, three events [three subjects] with liraglutide 1.8, and four events [four subjects] with placebo). There were 4.1 and 6.7% of subjects treated with 1.2 and 1.8 mg liraglutide and positive for liraglutide antibodies at the end of the study (versus none with placebo). Subjects with antibodies did not have an attenuated A1C response.

**CONCLUSIONS** — Liraglutide therapy in combination with metformin and TZD provided significant decreases in A1C, FPG, and PPG with weight loss; decreases in SBP; and a low rate of minor hypoglycemia. In addition, there were indications of improvement in β-cell func-
tion with liraglutide treatment compared with placebo. While improvement in \( \beta \)-cell function may have been a consequence of improved glucose control, it could well be a direct effect of liraglutide, which is known to stimulate glucosedependent endogenous insulin secretion. Gastrointestinal adverse events were reported more frequently with liraglutide treatment, with most of the events occurring early in treatment. The glucose-lowering effects of the two doses of liraglutide were similar, although there were significantly more gastrointestinal adverse events with the higher dose. However, it is likely that there is significant individual variation in the development of nausea and glycemic effectiveness.

The underlying pathophysiology of type 2 diabetes is complex and involves three main factors: a relative decrease in \( \beta \)-cell insulin secretory function; increased glucose production by the liver, which is at least partially mediated by inappropriately increased glucagon levels; and decreased glucose uptake by muscle. The triple therapy of metformin, TZD, and GLP-1 receptor agonists has the potential of addressing all three underlying abnormalities and results in improved glycemic control, potential weight loss, and improvements in \( \beta \)-cell function with minimal risk of hypoglycemia. The use of this triple therapy has demonstrated the largest decreases in A1C and SBP values in the LEAD program. It should be noted that \( \sim 50\% \) of the subjects initiated TZD treatment during the run-in period, and doses of metformin and TZD were maximized during this period, which may account for the improvements observed in the placebo arm of this study.

Exenatide, a commercially available GLP-1 receptor agonist, is a synthetic version of exendin-4. Unlike liraglutide, which is dosed once daily independently of meals, exenatide is dosed twice daily within 60 min of breakfast and dinner (14). The findings in this study support the findings of a previous study (15) in which 233 subjects inadequately controlled with a stable dose of TZD (rosiglitazone \( \geq 4 \) mg/day or pioglitazone \( \geq 30 \) mg/day) with or without metformin treatment (79% were treated with metformin) were randomized to add exenatide treatment (\( n = 121 \)) or placebo (\( n = 112 \)) for 16 weeks of treatment. At the end of the study, A1C values decreased by 0.89%, other measurements of glycemic control (FPG, mean SMPG, and mean postprandial SMPG values) all showed significant improvement with exenatide treatment. These studies support the effectiveness of this type of diabetes regimen, particularly as it is associated with modest weight loss and low risk of hypoglycemia.

The very significant change in SBP observed in this study appears to be of larger magnitude than that observed in the other LEAD studies. TZD treatment is associated with a modest reduction in blood pressure but is also associated with fluid retention. There may be an interaction between the cardiovascular effects of liraglutide and TZD. Further study would be of obvious interest, particularly if there was potential for long-term cardiovascular benefit.

The specific mechanism(s) of SBP reduction and the slight increases in pulse with liraglutide remain to be further studied. Based on data with native GLP-1, it could be speculated that the effect on SBP relates to reduced renal sodium reabsorption (16,17). Native GLP-1 has been shown to improve endothelial function in patients with type 2 diabetes and coronary heart disease (18) and in vitro endothelial cell models (19). The latter has also been shown for liraglutide (20). Potentially, the slight increases in pulse observed with liraglutide may be compensatory for the decreases in SBP.

In summary, this study demonstrated that the triple combination of liraglutide, metformin, and TZD is an effective and safe treatment for patients with type 2 diabetes. This combination significantly improved glycemic control and other efficacy parameters, in addition to resulting in significant weight loss and improved blood pressure.

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