Objectives — Glucagon-like peptide 1 (GLP-1) is an insulinotropic gut hormone that, when given exogenously, may be a useful agent in the treatment of type 2 diabetes. We conducted a 3-month trial to determine the efficacy and safety of GLP-1 in elderly diabetic patients.

Research Design and Methods — A total of 16 patients with type 2 diabetes who were being treated with oral hypoglycemic agents were enrolled. Eight patients (aged 75 ± 2 years, BMI 27 ± 1 kg/m²) remained on usual glucose-lowering therapy and eight patients (aged 73 ± 1 years, BMI 27 ± 1 kg/m²), after discontinuing hypoglycemic medications, received GLP-1 delivered by continuous subcutaneous infusion for 12 weeks. The maximum dose was 120 pmol·kg⁻¹·h⁻¹. Patients recorded their capillary blood glucose (CBG) levels (four times per day, 3 days per week) and whenever they perceived hypoglycemic symptoms. The primary end points were HbA₁c and CBG determinations. Additionally, changes in β-cell sensitivity to glucose, peripheral tissue sensitivity to insulin, and changes in plasma ghrelin levels were examined.

Results — HbA₁c levels (7.1%) and body weight were equally maintained in both groups. The usual treatment group had a total of 87 CBG measurements of ≤3.6 mmol/l during the study, and only 1 such measurement (3.5 mmol/l) was recorded in the GLP-1 group. Infusion of GLP-1 enhanced glucose-induced insulin secretion (pre: 119 ± 21 pmol/l; post: 202 ± 31 pmol/l, P < 0.05) and insulin-mediated glucose disposal (pre: 29.8 ± 3.3; post: 35.9 ± 2.3 μmol·kg⁻¹·min⁻¹, P < 0.01). No effect of GLP-1 treatment was seen on the fasting plasma ghrelin levels. Although plasma ghrelin levels decreased during both portions of the clamp, a drug effect was not present.

Conclusions — A GLP-1 compound is a promising therapeutic option for elderly diabetic patients.

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Glucagon-like peptide 1 (GLP-1), which is secreted from enteroendocrine cells of the intestine in response to food (1,2), is insulinotropic in type 2 diabetic patients (1–5). Even with pharmacological concentrations, it does not cause hypoglycemia because it has little or no insulinotropic effect on glucose levels <4 mmol/l (1,2). GLP-1 is, therefore, a promising agent for the treatment of type 2 diabetes.

Aging is characterized by a progressive increase in the prevalence of diabetes; by 75 years of age, ~20% of the population is afflicted (6). Many patients are treated with sulfonylureas and ultimately with insulin. Unfortunately, the risk of severe hypoglycemia associated with these agents increases with age (6). We previously demonstrated that GLP-1 has insulinotropic activity in elderly diabetic patients and it enhances their insulin- and non–insulin-mediated glucose uptake (7–9). Because of its ability to ameliorate multiple metabolic defects and because hypoglycemia might not be an issue, GLP-1 and its analogs may prove to be valuable therapeutic agents in this population. GLP-1 also has pleiotropic effects (10): it decreases glucagon release, inhibits gastric emptying, and increases islet cell proliferation and differentiation. Therefore, it might have long-term beneficial consequences in type 2 diabetes not seen with other therapies. We conducted a 3-month trial of continuous subcutaneous administration of GLP-1 in elderly type 2 diabetic patients. We wished to see whether GLP-1 would maintain its insulinotropic properties when given continuously over such a long period, and we wished to compare its efficacy to the best standard of care available, using oral agents. Because elderly individuals have the highest prevalence of diabetes, we believed it was appropriate to study that particular age-group.

Research Design and Methods

Selection of volunteers Retiree patients with well-controlled type 2 diabetes by HbA₁c estimation were recruited from the Diabetes Center at the Vancouver Hospital. The Committees on Human Investigation at each investigator’s institution approved this study. All...
Effects of GLP-1 in elderly patients with type 2 diabetes

Participants gave written informed consent before participation.

Treatment with GLP-1

Subjects were randomized to usual treatment (n = 8, 6 men and 2 women, aged 75 ± 2 years, BMI 27 ± 1 kg/m², duration of diabetes 12 ± 3 years) or GLP-1 therapy (n = 8, 1 man and 7 women, aged 73 ± 1 years, BMI 27 ± 1 kg/m², duration of diabetes 10 ± 2 years). The randomization was based on a block design and not a block randomization for drug and sex. Normal electrocardiographic findings, serum electrolyte levels, liver and renal function, and hematocrit ≥ 38 in men and ≥ 34 in women were requirements for entering the study. Volunteers’ exclusion criteria included any evidence of microvascular or macrovascular diseases and significant history (physical or laboratory evidence) of hepatic, renal, pulmonary, endocrine (other than type 2 diabetes), or gastrointestinal disease or any evidence of autonomic insufficiency. Therapy with insulin, corticosteroids (sex or adrenal), diuretics, amphetamines, dipeptidyl peptidase IV inhibitors, enteroactive agents, or any medications that may influence carbohydrate metabolism (other than hypoglycemic agents) were also exclusion criteria. Oral hypoglycemic agents were withheld for 48 h before the first clamp study. A total of 10 patients were being treated with ACE inhibitors. All patients were being treated with oral agents before the study; 11 were treated with metformin and 8 were treated with sulfonylureas. In the usual treatment group, two patients were being treated with diet alone, two were taking β-cell secretagogues only (gliclazide 80 mg daily, repaglinide 0.5 mg t.i.d.), one was taking metformin only (750 daily), and three were taking both metformin (maximum dose 500 mg) and glyburide (5 mg in one patient and 10 mg in two patients).

These were all insulin-naïve patients. All subjects were instructed on the use of capillary blood glucose (CBG) measurement and were asked to measure CBG levels (4 times per day, 3 days per week) during the study. The control group remained on their usual oral hypoglycemic agents, without dose alteration, throughout the study. In the GLP-1 group, oral hypoglycemic agents were discontinued 1 week before the study. The GLP-1 was administered by continuous subcutaneous infusion into the periumbilical region using a MiniMed pump (Sylmar, CA). The initial dose of GLP-1 was 100 pmol · kg⁻¹ · h⁻¹. All subjects were examined weekly. If mean CBG levels were > 8 mmol/l or if mean premeal CBG levels were > 11 mmol/l after 1 week of therapy with GLP-1, the infusion rate was increased by 20%. Therefore, four subjects received 120 pmol · kg⁻¹ · h⁻¹ after the first week. GLP-1 treatment was terminated after completion of the second clamp after 3 months of therapy.

Recombinant GLP-1 (7–36 amide) was produced by prokaryotic fermentation, and a COOH-terminal amide was added to the peptide as previously described (11). This preparation is > 99% pure and displays a single peak on high-performance liquid chromatography. All GLP-1 used in this protocol was from a single lot.

Hyperglycemic and hyperinsulinemic-euglycemic clamps

Each subject underwent two glucose clamp studies at the beginning and end of the 3-month trial. Testing began at 0700 after a 12-h fast. Patients were weight and activity stable before the initial clamp. This sequential clamp procedure has been validated for normal and diabetic volunteers and reported in detail (12). The clamp consisted of three steps: 1) a hyperglycemic clamp for 1 h (5.4 mmol/l above basal), 2) 1 h of glycemic recovery immediately followed by 3) a hyperinsulinemic-euglycemic clamp for 2 h (480 pmol · m⁻² · min⁻¹), Humulin [Eli Lilly, Indianapolis, IN]. In type 2 diabetic volunteers, during the recovery period (step 2), the plasma glucose level does not decrease to “normal” levels. Therefore, during the hyperinsulinemic-euglycemic clamp period (step 3), we did not start the 20% glucose infusion (spiked with tritiated glucose, “hot Ginf”) (13) until the plasma glucose level approached 5.3 mmol/l.

Glucose production rates before and during the clamp were determined by a primed, constant infusion of [3-¹⁴C]glucose (Dupont-NEN, Boston, MA) as previously described (5). Two hours before the start of the clamp, a priming dose of [3-¹³C]glucose (8.7 kBq/kg) was administered, followed by a continuous infusion of [3-¹³C]glucose (87 Bq · kg⁻¹ · min⁻¹) for the duration of the experiment (to 240 min). The priming dose was adjusted for each patient by the ratio of the fasting plasma glucose to 5.3 mmol/l, as previously described (13). During step 3, the 20% glucose solution was spiked with tritiated glucose (“hot Ginf”) to maintain a stable plasma glucose specific activity (13). Steady-state glucose specific activity is achieved 90 min after the start of tritiated infusion. To confirm this and to assess fasting glucose levels, specific activity of glucose, and hormone/substrate level, four arterialized (14) blood samples were obtained from a hand vein at 10-min intervals starting at ~30 min. With the start of the clamp at time 0, blood samples were obtained every 2 min from 0 to 10 min for determination of glucose and insulin levels, every 5 min thereafter for determination of glucose and every 10 min for determination of hormone/substrate and specific activity of glucose. Additionally, two samples were obtained during the final 10 min of the basal, hyperglycemic, and hyperinsulinemic-euglycemic clamps (n = 6 in each volunteer) for measurement of plasma ghrelin. During the hyperglycemic portion of the clamp and during the euglycemic portion, on achieving plasma glucose of 5.3 mmol/l, plasma glucose levels were maintained within 5% of the goal in each patient.

Analytical techniques

Plasma glucose and HbA1c levels were first measured and then plasma was aliquoted and stored at −70°C for analysis of insulin, C-peptide, glucagon, and nonesterified fatty acid (NEFA), as previously described (15,16). Plasma ghrelin levels were measured with radioimmunoassay, which has a range of 10–1,280 pg/ml and IC₂₀, 50, and 80 of ~323, 90, and 33 pg/ml (Phoenix Pharmaceuticals, Belmont, CA).

Statistical analyses

The rates of total appearance (Ra) and disappearance of glucose (Rd) were calculated with Steele’s equation as modified for the use of “hot Ginf” (7). The volume of distribution of glucose was assumed to be 210 ml/kg. Endogenous glucose production was estimated as the difference between the Ra and the exogenous glucose infusion for the appropriate time interval during the clamp. During the hyperinsulinemic-euglycemic portion of the clamp, the metabolic clearance rate of insulin was calculated from the constant insulin infusion rate divided by the plasma insulin levels. Plasma insulin levels were cor-
Table 1—Weight, HbA1c, fasting glucose, hormone, and NEFA levels before the start of each clamp

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>GLP-1</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 5</td>
<td>78 ± 5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>75 ± 2</td>
<td>—</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.0 ± 0.2</td>
<td>7.0 ± 0.2</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>7.8 ± 0.7</td>
<td>8.1 ± 0.7</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>95 ± 21</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>C-peptide (nmol/l)</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Glucagon (pmol/l)</td>
<td>20 ± 6</td>
<td>20 ± 6</td>
</tr>
<tr>
<td>GLP-1 (pmol/l)</td>
<td>8 ± 2</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Ghrelin (pg/ml)</td>
<td>567 ± 127</td>
<td>497 ± 75</td>
</tr>
<tr>
<td>NEFA (mmol/l)</td>
<td>0.46 ± 0.07</td>
<td>0.52 ± 0.04</td>
</tr>
</tbody>
</table>

Data are means ± SE.

rected for endogenous insulin secretion when both were at steady state, as previously described (17). The trapezoidal rule was used to calculate the integrated responses of the first-phase insulin release (0–10 min) and over 30-min intervals. The integrated responses were divided by the time interval, which resulted in mean concentration or values. All data were analyzed using SAS version 8.2 (SAS Institute, Cary, NC). Standard methods were used to compute means, SEM, and Pearson correlation coefficients. Mixed-model analysis for repeated-measures design was used to analyze hormone and metabolite responses. Differences between pretreatment and posttreatment were evaluated using Student’s t test. All statistical tests were two tailed. Data are means ± SE, and P values <0.05 were regarded as statistically significant.

RESULTS

Safety

One patient receiving GLP-1 experienced mild fatigue and dry eyes for the duration of the study. Two patients receiving GLP-1 had mild nausea during the first week of therapy, which subsequently resolved without changing infusion rates. In the usual treatment group, the four patients taking sulfonylureas recorded a total of 87 blood glucose values ≤3.6 mmol/l. The highest values were between 12 and 13 mmol/l. In the GLP-1 group, only one value <3.6 mmol/l was recorded (3.5 mmol/l). The highest values were between 10 and 11 mmol/l. No patients withdrew from the study. There were no significant changes from baseline in laboratory parameters, vital signs, physical examination, or electrocardiography in either group by the end of the study.

Metabolic profiles

There were no changes, except for GLP-1 levels, in fasting plasma values of hormones measured, NEFA, weight, or HbA1c during the study in either group (Table 1). Basal plasma glucose levels were slightly higher in the usual treatment group than in the GLP-1 treatment group after 3 months of therapy; however, the difference was not significant in either group. During the hyperglycemic portion of the clamp, plasma glucose levels were very similar in both groups, before and after treatment. In the control group, the decrease in glucose levels after termination of glucose infusion at 60 min was superimposable before and after therapy. With the start of insulin infusion at 120 min, plasma glucose levels began to decrease more rapidly and reached the target level (5.3 mmol/l) by ~170–175 min in the usual treatment and GLP-1 groups before therapy and in the usual treatment group after therapy. However, in the GLP-1 group, the decrease in glucose levels was faster after therapy both in the fall-off period from the hyperglycemic clamp and after the start of the insulin infusion; the target level was reached by 150 min. After therapy, there was a tendency for reduced glucose requirement in the usual treatment group but an increased glucose requirement in the GLP-1 treatment group, neither of which were significantly different.

In response to hyperglycemia, first-phase insulin secretion was absent before treatment in both groups (105 ± 21 and 86 ± 13 pmol/l in the usual and GLP-1 treatment groups, respectively) and after therapy in the usual treatment group (74.0 ± 8 pmol/l) (Fig. 1). However, this response was increased in seven of the eight patients after therapy (Δ increase = 28 ± 13 pmol/l, P = 0.066). Second-phase insulin response decreased after 3 months of usual treatment and increased after GLP-1 treatment, neither of which were significant. During the hyperinsulinemic-euglycemic portion of the clamp, plasma insulin levels in the usual treatment group, before and after treatment, and in the GLP-1 group before treatment were similar. However, after therapy with GLP-1, plasma insulin levels were significantly higher during this time. The concentration of the insulin solution (4,800 pmol/l) and the infusion rate (480 pmol · m−2 · min−1) were identical in all studies. The metabolic clearance rate of insulin before GLP-1 treatment was 382 ± 27 ml · m−2 · min−1, which was similar to the usual treatment group both before and after 3 months. However, after GLP-1 treatment, the metabolic clearance rate decreased to 280 ± 28 ml · m−2 · min−1. The reduction in the clearance rate is responsible for the increased plasma insulin levels observed during this portion of the clamp.

Plasma C-peptide levels for both groups increased during the hyperglycemic portion of the clamp and decreased during the hyperinsulinemic-euglycemic portion of the clamp (Fig. 2). The changes in C-peptide during the clamp before and after 3 months in the usual treatment group were similar, and they also mirrored the C-peptide levels in the GLP-1 treatment group before treatment. However, in the GLP-1 treatment group, both fasting levels and response during the hyperglycemic clamp were higher after treatment. Using repeated measures in a mixed model, the change in C-peptide levels during the clamp was statistically significant in both groups. Furthermore, there was a significant effect of GLP-1 treatment, i.e., posttreatment levels were higher in the GLP-1 treatment group and did not change in the usual treatment group. There was no interaction between time and treatment in either group. The molar ratio of C-peptide to insulin during the last 30 min of the hyperglycemic clamp was not statistically different for either group, pretreatment and posttreat-
The higher C-peptide levels during the hyperinsulinemic-euglycemic portion of the clamp are due, in part, to the long half-life of C-peptide ($t_1/2 = 30$ min). Hyperinsulinemia at euglycemic levels has been shown to suppress endogenous C-peptide levels by about 50% (17).

Basal NEFA levels for both groups before and after treatment are shown in Table 1. NEFA are sensitive to prevailing insulin levels and in response to endogenously released insulin dropped during the hyperglycemic portion of the clamp. With the start of insulin infusion at 120 min and in response to the highly elevated insulin levels, plasma NEFA levels further decreased, reached a nadir by 150 min, and remained at this trough until the end of the study. In the usual treatment group, plasma NEFA levels during both clamps were nearly identical throughout both portions of the clamp. The sequential 30-min levels for the 30–60, 90–120, and 180–210 min for the usual treatment groups were $0.39 \pm 0.05$, $0.26 \pm 0.07$, and $0.06 \pm 0.03$ mmol/l, respectively. In the GLP-1 treatment group, during the hyperglycemic portion of the clamp, NEFA levels decreased at a faster rate posttreatment than pretreatment (30–60 min values: pretreatment $0.47 \pm 0.06$, posttreatment $0.34 \pm 0.03$ mmol/l). The 90–120 and 180–210 min levels before treatment were $0.33 \pm 0.06$ and $0.05 \pm 0.02$ mmol/l, respectively. The corresponding levels after GLP-1 treatment were $0.19 \pm 0.03$ and $0.05 \pm 0.02$ mmol/l, respectively. The faster decrease was clearly due to greater insulin release during this time after GLP-1 treatment ($30–60$ min values of insulin; pretreatment $119 \pm 21$ and posttreatment $202 \pm 52$ pmol/ml).

Fasting plasma glucagon levels in the usual treatment group at the start of both clamps and in the GLP-1 treatment group before their first clamp were very similar at $20$ pmol/l. The fasting levels after GLP-1 treatment were $18.4 \pm 2.28$ pmol/l, which were not statistically different from pretreatment levels. Plasma glucagon levels decreased during the hyperglycemic portion of the clamp ($15.6 \pm 2.2$ pmol/l) and decreased even further during the euglycemic portion of the clamp ($14.5 \pm 1.9$ pmol/l) in both treatment groups. Using repeated measures in a mixed model, the change in glucagon levels during the clamp was statistically significant in both groups, but a drug effect was not demonstrated. Plasma GLP-1 levels were also stable and unchanged from the fasting levels during the entire clamps before initiation of the study in both groups and after 3 months in the usual treatment group (Table 1). Plasma GLP-1 levels were also stable and unchanged from fasting levels during the posttreatment clamp in the GLP-1 treatment group. However, as expected, they were substantially higher (pretreatment $9 \pm 3$, posttreatment $62 \pm 23$ pmol/l).

Fasting plasma ghrelin levels were similar in both groups before and after treatment. During the final 10 min of the hyperglycemic clamp with a modest increase in endogenous insulin level, plasma ghrelin levels decreased slightly in...
both groups (512 ± 115 and 534 ± 78 pg/ml in the usual and GLP-1 treatment groups, respectively). During the last 10 min of the hyperinsulinemic-euglycemic portion of the clamp, ghrelin levels were further suppressed in both groups (425 ± 87 and 443 ± 58 pg/ml in the usual treatment and GLP-1 treatment groups). There was no treatment effect on fasting or insulin-stimulated ghrelin suppression.

Glucose turnover rates
Basal hepatic glucose production ($R_g$) before therapy was 8.9 µmol·kg$^{-1}$·min$^{-1}$ in the GLP-1 treatment group (similar to the usual therapy group). During the hyperglycemic portion of the clamp, before therapy, $R_g$ was suppressed by 63% of fasting rate in both groups. During the fall-off of plasma glucose (60–120 min), $R_g$ increased modestly by ~11% in both groups (i.e., suppressed by 53% of fasting rate). During the hyperinsulinemic-euglycemic portion of the clamp when plasma glucose levels were 5.3 mmol/l (180–240 min), $R_g$ was suppressed to nearly 0 in both groups. In the usual treatment group, there was no significant difference in $R_g$ at 180–240 min (pretreatment 37.3 ± 3.9, posttreatment 32.9 ± 6.5 µmol·kg$^{-1}$·min$^{-1}$). In the GLP-1 treatment group, there was a significant increase in 180–240 min $R_g$ after 3 months of therapy (pretreatment 29.8 ± 3.3, posttreatment 35.9 ± 2.3 µmol·kg$^{-1}$·min$^{-1}$).

CONCLUSIONS — In this study, we demonstrate that a subcutaneous infusion of GLP-1 is safely administered to elderly type 2 diabetic patients and is well tolerated for 3 months. In this regard, GLP-1 is an exciting therapeutic agent for the elderly because of the glucose dependent nature of its insulinotropic effect and because it may be protective of $\beta$-cell function. Type 2 diabetes is characterized by resistance to insulin-mediated glucose disposal, impairment in glucose effectiveness (6), and alterations in glucose-induced insulin release, which continue to decline even with treatment (18). Recently, we have demonstrated that short-term GLP-1 infusion can partially reverse these metabolic defects (7–9).

In the control group, patients treated with sulfonylureas experienced 87 episodes of hypoglycemia, 72 of which occurred in two subjects. This finding is even more remarkable considering that glucose values were measured only 12 times per week. The data are consistent with previous studies, which demonstrate that sulfonylureas frequently cause hypoglycemia in elderly individuals (6). In patients treated with GLP-1, only one low blood glucose level was recorded. A GLP-1–type compound is, therefore, a safe alternative to sulfonylureas in elderly patients, particularly when attempts are made to achieve optimal glycemic control. Metformin has been shown to be less effective in reducing the incidence of diabetes in elderly patients than lifestyle intervention (19), presumably because it does not lower glucose levels as much as...
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lifestyle intervention. Although thiazolidinediones are now commonly used in elderly patients because they do not cause hypoglycemia, they cannot be used in those with heart failure. In this case, GLP-1 therapy will have a clear advantage.

To our knowledge, only four previous reports discussing administration of GLP-1 were not acute studies (20–23). Two of the studies had a 7-day duration of treatment (20,22) and a third had a 3-week duration of treatment (21). All three studies showed improvement in glucose levels.

Recently, Zander et al. (23) examined the effects of 6 weeks of continuous subcutaneous administration of GLP-1, using both hyperglycemic and euglycemic clamps in 10 patients with poorly controlled type 2 diabetes (mean HbA1c 9.2%, mean age 54 years) compared with 9 patients treated only with saline (HbA1c 8.9%). They found a reduction in HbA1c (to 7.9%) with a threefold higher infusion dose than ours. They reported a weight loss of 1.9 kg, which may be due to nausea consistent with the large dose of GLP-1 administered. GLP-1 had been reported to decrease food intake in short-term studies (24–27). Ghrelin is an appetite stimulant (28), and to evaluate whether GLP-1 influences ghrelin secretion, we examined ghrelin levels. Fasting levels were unchanged in these two very homogenous (age and BMI) groups of type 2 diabetic volunteers, whereas hyperglycemia and hyperinsulinemia both reduced ghrelin levels.

Several other findings deserve comment. GLP-1 maintained its insulinotropic effect and restored first-phase insulin secretion after prolonged administration. The lower 30- to 60-min NEFA levels during the second clamp in the GLP-1 group are likely a result of increased circulating insulin levels. Glucose disposal rates were increased after 12 weeks of GLP-1 infusion, consistent with our previous findings that short-term GLP-1 administration enhances insulin-mediated and non–insulin-mediated glucose disposal in elderly individuals (7,9). The increase in glucose disposal rates, before and after 12 weeks of treatment with GLP-1, cannot be attributed to increased insulin levels because much higher levels of insulin between the two studies are necessary to account for the difference observed in glucose disposal. The higher insulin levels during the hyperinsulinemic-euglycemic portion were due to a reduction in the clearance rate of insulin by GLP-1. To our knowledge, we are the first group of investigators who have shown a reduction in insulin clearance rate with prolonged administration of GLP-1. We have also observed this effect in an acute GLP-1 infusion protocol (240 min) in type 1 diabetic volunteers (11).

We could not demonstrate change in the molar ratio of C-peptide to insulin during the hyperglycemic clamp in the GLP-1 treatment group. This is most likely due to the small changes in insulin secretion compared with changes in insulin levels during its exogenous administration and a possible type 2 error because of the small number of subjects.

Although acute studies with GLP-1 demonstrate an inhibitory glucagonostatic effect, an inhibitory effect on glucagon secretion (29,30), this was lost during our 3-month study. Neither was an inhibitory effect demonstrated by Zander et al. (23) during a 6-week GLP-1 infusion. The mechanisms underlying the glucagon-lowering effect of GLP-1 is poorly understood, and we do not have an explanation for its loss after a chronic infusion.

HbA1c, a marker of glycemic control for the previous 3 months, was not different between the two groups. This indicates that GLP-1 can regulate blood glucose levels as well as usual treatment under optimal conditions. However, the mean HbA1c levels in the usual treatment group is a reflection of a wider range of blood glucose levels because so many CBG readings were low. The HbA1c levels in the GLP-1 group reflect a tighter range of glycemic excursion.

Our study was designed to test the potential of GLP-1 treatment in elderly individuals using continuous subcutaneous administration. However, long-term administration of GLP-1 by subcutaneous infusion using currently available pumps is impractical for many patients. To allow this therapy to have broader clinical utility, newer delivery systems, dipeptidyl peptidase IV resistant analogs (31), or agonists of the GLP-1 receptor need to be developed.

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