Effect of Exenatide, Sitagliptin, or Glimepiride on β-Cell Secretory Capacity in Early Type 2 Diabetes

OBJECTIVE
Agents that augment GLP-1 effects enhance glucose-dependent β-cell insulin production and secretion and thus are hoped to prevent progressive impairment in insulin secretion characteristic of type 2 diabetes (T2D). The purpose of this study was to evaluate GLP-1 effects on β-cell secretory capacity, an in vivo measure of functional β-cell mass, early in the course of T2D.

RESEARCH DESIGN AND METHODS
We conducted a randomized controlled trial in 40 subjects with early T2D who received the GLP-1 analog exenatide (n = 14), the dipeptidyl peptidase IV inhibitor sitagliptin (n = 12), or the sulfonylurea glimepiride (n = 14) as an active comparator insulin secretagogue for 6 months. Acute insulin responses to arginine (AIRarg) were measured at baseline and after 6 months of treatment with 5 days of drug washout under fasting, 230 mg/dL (glucose potentiation of arginine-induced insulin release [AIRpot]), and 340 mg/dL (maximum arginine-induced insulin release [AIRmax]) hyperglycemic clamp conditions, in which AIRmax provides the β-cell secretory capacity.

RESULTS
The change in AIRpot was significantly greater with glimepiride versus exenatide treatment (P < 0.05), and a similar trend was notable for the change in AIRmax (P = 0.1). Within each group, the primary outcome measure, AIRmax, was unchanged after 6 months of treatment with exenatide or sitagliptin compared with baseline but was increased with glimepiride (P < 0.05). α-Cell glucagon secretion (AGRmin) was also increased with glimepiride treatment (P < 0.05), and the change in AGRmin trended higher with glimepiride than with exenatide (P = 0.06).

CONCLUSIONS
After 6 months of treatment, exenatide or sitagliptin had no significant effect on functional β-cell mass as measured by β-cell secretory capacity, whereas glimepiride appeared to enhance β- and α-cell secretion.

The main pathophysiologic abnormalities in type 2 diabetes (T2D) are impaired tissue sensitivity to insulin action (i.e., insulin resistance) and impaired β-cell insulin secretion (1). Autopsy studies have observed a relative β-cell mass reduction of 40% from normal by the time impaired fasting glucose develops (≥110 mg/dL) and >60% reduction with overt T2D (2). This decline in β-cell mass has been associated with increased β-cell apoptosis (2), and an emerging role of defective autophagy-associated cell death is linked with the onset of β-cell dysfunction (3,4). Functional
β-cell mass is best estimated in vivo as the β-cell secretory capacity derived from glucose potentiation of arginine-induced insulin secretion (5). Consistent with the autopsy data, metabolic studies have reported a relative β-cell secretory capacity reduction of >50% from normal as the fasting glucose increases over 110 mg/dL (1,5). The preservation of functional β-cell mass in T2D remains a major focus of research in hopes of stabilizing or reversing disease progression (6).

Agents that enhance GLP-1 action are purported to hold promise for the preservation of β-cell mass in T2D. GLP-1 is an incretin hormone secreted by L cells of the intestine in response to nutrient ingestion, enhances insulin production and secretion, and inhibits α-cell glucagon secretion in a glucose-dependent manner (7). The biologically active GLP-17–36 amide is rapidly inactivated by the ubiquitous protease dipeptidyl peptidase IV (DPP4). Raising GLP-1 to supraphysiologic levels improves β-cell sensitivity to glucose in T2D (8). Current strategies to enhance GLP-1 effects in T2D include the use of injectable GLP-1 analogues that resist inactivation by DPP4 and oral inhibitors of DPP4 that effectively increase endogenous GLP-1 levels. In rodent models, GLP-1 stimulates β-cell proliferation and exerts antiprotective effects, which, together with increased insulin production, is expected to augment functional β-cell mass in vivo (9,10). Whether GLP-1 can increase functional β-cell mass in human diabetes in vivo remains to be elucidated.

Current investigations suggest the acute improvement in β-cell sensitivity to glucose observed with enhancing GLP-1 effects in human T2D (8) may not extend to long-term effects on functional β-cell mass. Bunck et al. (11,12) demonstrated that 1-year treatment with exenatide in T2D significantly improved β-cell secretory capacity while on the drug; however, this benefit was not sustained 1 month after discontinuation. Similarly, there was a significant increase in β-cell secretory capacity in drug-naive T2D subjects treated with the DPP4 inhibitor vildagliptin for 1 year that again was not maintained after a 3-month washout period (13). These studies indicate an acute effect of GLP-1 analogues or DPP4 inhibitors to increase β-cell secretion but do not demonstrate a modifying effect of either drug on functional β-cell mass. These conflicting GLP-1 effects in rodents versus human T2D may be due to the lengthy duration of the washout period, during which glycemic control worsened in both clinical studies such that glucotoxicity may have obviated any previous improvement in β-cell secretory capacity (11–13).

The purpose of this investigation was to address if increasing GLP-1 effects early in the course of T2D would preserve or increase functional β-cell mass as measured by β-cell secretory capacity derived from the glucose-potentiated arginine (GPA) test. In this study, we present the results of a randomized controlled trial comparing the effects of exenatide or sitagliptin with glimepiride as an active comparator insulin secretagogue on β-cell secretory capacity before and after 6 months of treatment 5 days off drug in subjects with impaired fasting glucose or early T2D (fasting glucose ≥110 but <160 mg/dL). The 5-day washout period was designed to eliminate any acute effects of the study drugs on β-cell sensitivity to glucose while avoiding any deterioration in glycemic control to ensure that any trophic effects of the drugs would not be negated by the development of glucotoxicity. GLP-1 analogues and DPP4 inhibitors have been shown to increase both insulin production and secretion (14–16) and so were expected to have a positive effect on functional β-cell mass. Since sulfonylureas induce insulin secretion without affecting production, they have been theorized to deplete insulin stores (17). We, therefore, hypothesized that exenatide and/or sitagliptin would increase β-cell secretory capacity compared with a decrease with glimepiride.

**RESEARCH DESIGN AND METHODS**

**Subjects**

Subjects were males and females age 18–70 years with impaired fasting plasma glucose or early T2D as defined by a plasma glucose concentration between 110 and 159 mg/dL following a >12-h overnight fast performed off any antiabeticogenic agent for ≥2 weeks (6 weeks for thiazolidinediones) and of stable body weight (±5%) for at least 2 weeks. Exclusion criteria included any prior exposure to GLP-1 analogues or DPP4 inhibitors and active cardiovascular, liver, or kidney disease and are provided in full detail under ClinicalTrials.gov identification number NCT00775684. The study protocol was approved by the University of Pennsylvania Institutional Review Board, and all subjects provided written informed consent. One hundred seventy subjects underwent the screening process, out of which 50 subjects were enrolled (Supplementary Fig. 1). Randomization was performed with stratification designed to balance sex and tiers of age (18–44 and 45–70 years), fasting glucose level (110–126 and 127–159 mg/dL), and BMI (<35 and 35–44 kg/m²) among the three groups.

**Study Design**

This study was a randomized controlled trial of open-label exenatide or sitagliptin versus an active comparator insulin secretagogue, glimepiride. The sulfonylurea glimepiride was chosen rather than a placebo to ensure adequate glycemic control was maintained in the comparator group while preventing confounding of β-cell effects by use of other agents that affect insulin sensitivity. Sulfonylureas bind to their receptor that inhibits the KATP on the β-cell membrane, leading to depolarization triggering insulin release (17–19). Glimepiride, in particular, was selected, as it has been shown to carry the least risk of hypoglycemia among the sulfonylureas (20). After completing a baseline oral glucose tolerance test (OGTT) and GPTA test on separate days, subjects were randomized to receive exenatide 5 μg subcutaneous twice daily, sitagliptin 100 mg, or glimepiride 0.5 mg orally each morning. All subjects received a study glucometer and test strips (OneTouch Ultra; LifeScan, Milpitas, CA) to monitor glucose each morning and evening to detect and report any hypoglycemia (blood glucose <70 mg/dL). Exenatide was increased after 1 month per labeling to 10 μg twice daily. All subjects remained on this dose until completion of the study except for two subjects who experienced side effects but tolerated 5 or 10 μg once daily in each case. Sitagliptin remained at 100 mg for the duration of...
study and was well tolerated by all subjects. Glimepiride was increased by 0.5–1.0-mg increments in the morning or evening at weekly intervals (maximum total daily dose 4.0 mg, divided) to achieve an average fasting glucose level <110 mg/dL while avoiding any hypoglycemia. No clinically significant hypoglycemia was detected with any treatment arm. Augmentation of meal-related in-
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There were no significant differences in the change in AIR_{arg} after 6 months of exenatide or sitagliptin treatment compared with glimepiride (Supplementary Fig. 3 and Table 2), whereas the change in AIR_{inh} was significantly lower in the exenatide group, but not in the sitagliptin group, when compared with the glimepiride group (P < 0.05 for exenatide vs. glimepiride; Table 2), and a similar trend was also evident for the change in AIR_{max} (P = 0.1 for exenatide vs. glimepiride; Table 2). In fact, within each group, β-cell secretory capacity (AIR_{max}) increased only in the glimepiride group at 6 months compared with baseline (P < 0.05; Table 2). β-Cell sensitivity to glucose (PG_{50}) was not different at baseline and remained unchanged following any treatment (Table 2). The glucose infusion rates (M), second-phase insulin levels (I), and the resulting estimate of insulin sensitivity (M/I) were not different at baseline and after 6 months across all three groups (Table 2).

Fasting proinsulin and APRs were not different across the groups at baseline or in response to treatment. P/I ratios and proinsulin secretory ratios were unchanged from baseline to 6 months with no significant differences between the exenatide or sitagliptin and glimepiride groups (data not shown).

There were no significant differences in the change in AGR_{arg} and AGR_{inh} with exenatide or sitagliptin treatment after 6 months compared with glimepiride; however, there was a statistical trend when comparing the change in AGR_{min} with exenatide, but not sitagliptin, to glimepiride (P = 0.06 for exenatide vs. glimepiride; Table 2). Within each group, glucagon secretion was increased only in the glimepiride group at 6 months compared with baseline for AGR_{min} (P < 0.05; Table 2).

CONCLUSIONS

This study evaluated functional β-cell mass as determined by the β-cell secretory capacity in subjects with early T2D treated with exenatide, a GLP-1 analogue, or sitagliptin, a DPP4 inhibitor.
compared against an active comparator sulfonylurea, glimepiride. Our results demonstrate that in early T2D, 6-month treatment with a GLP-1 analogue or DPP4 inhibitor does not increase functional β-cell mass relative to treatment with a sulfonylurea. While these data were contrary to our hypothesis, they are consistent with previous reports demonstrating no sustained effects of GLP-1 on β-cell secretory capacity (11–13). Unlike previous studies in which the drug washout period was ≥1 month, during which any potential beneficial effects could be reversed by documented worsening glycemic control, our results were obtained 5 days after discontinuation of the study medication to ensure effective drug washout while avoiding development of hyperglycemia. Indeed, fasting plasma glucose was controlled within each group at the 6-month visit compared with baseline. Thus, these are the first data to demonstrate a lack of improvement in β-cell secretory capacity with a GLP-1 analogue or a DPP4 inhibitor off drug and in the absence of overt hyperglycemia, while demonstrating a remarkable increase in β-cell secretory capacity with sulfonylurea treatment.

Exenatide-treated subjects experienced a decrease in weight and consequently BMI, although this was not statistically different from a neutral weight effect seen in the glimepiride group. In the exenatide-treated subjects, there was also an increase in plasma HDL cholesterol that has previously been demonstrated (30). Sitagliptin treatment was effective in increasing the endogenous GLP-1 response 2.3-fold to oral glucose in our study that is consistent with previous reports (31). In contrast to previous studies, there was no significant effect of exenatide or sitagliptin on HbA1c. This is likely attributable to the early T2D in our subjects who were at the threshold of overt diabetes (average HbA1c of 6.5% [48 mmol/mol]), while most outcomes studies have included subjects with more advanced T2D (average HbA1c ≥8.5% [69 mmol/mol]) (32,33). Our study is limited by its small sample size and short duration and thus does not allow us to determine whether prolonged treatment with exenatide or sitagliptin early in the course of T2D may prevent deterioration in glycemic control, perhaps through mechanisms other than affecting the β-cell secretory capacity.

Six months of treatment with glimepiride was effective in decreasing capillary blood glucose and lowering HbA1c without producinghypoglycemic episodes or weight gain with careful dose titration. Postmarketing reports and clinical trials have demonstrated significant increases in weight with glimepiride treatment but these observations were notably with higher concentrations of glimepiride (4–8 mg) titrated rapidly over a 1–4-week period (34). Similar to our finding of an increase in β-cell secretory capacity evident after 6 months, Karunakaran et al. (35) demonstrate a significant improvement in β-cell function with glimepiride treatment for 1 year while demonstrating lower fasting plasma glucose and HbA1c without adversely affecting weight. Interpretation of our study’s results with glimepiride must be made cautiously, however, as glimepiride was included as an active comparator without a placebo group for comparison.

While the increase in β-cell secretory capacity after 6 months of treatment with glimepiride observed in this study requires confirmation and further assessment of durability, there are a few speculative mechanisms to explain such an effect. Compared with the exenatide and sitagliptin groups, the glimepiride–treated subjects experienced a reduction in capillary glucose. This improved glycemic control may have positively affected the β-cell secretory capacity. Another possibility may be a more specific effect of sulfonylureas against autophagy–associated cell death. Autophagy is a self-digestive mechanism that regulates protein turnover, and current evidence links impaired autophagy with accumulation of autophagic vacuoles in the β-cells of T2D when compared with non-diabetic islets (4). Altered autophagic
mechanisms are evident when there is a mismatch between insulin production and secretion, as may occur in T2D, in which there is impaired β-cell sensitivity to glucose (36). As sulfonylureas such as glimepiride have no effect on insulin production but stimulate insulin secretion (36), these agents may correct a synthetic mismatch and protect against autophagy-associated cell death. Whether such effects may be associated with increases in functional β-cell mass as measured by β-cell secretory capacity warrants further study.

Curiously, α-cell glucagon secretion was increased after 6 months of exposure to glimepiride. The effect of sulfonylureas on α-cells remains unclear at present due to conflicting results that may be attributed to variation in model systems—i.e., with intact islets in which paracrine signaling remains intact versus diseased islets in which paracrine signaling is disrupted versus isolated α-cells (37,38). For example, Cheng-Xue et al. (37) demonstrated a glucagonotropic effect of tolbutamide when paracrine signaling by somatostatin was disrupted. These authors postulate that glucagon secretion is controlled by two mechanisms, one that is direct from the closure of KATP channels and one that is indirect via control from paracrine signaling (37). Thus, glimepiride may induce depolarization of the α-cell, and under normal, nondiseased conditions, glucose, insulin, and/or somatostatin via paracrine action can inhibit glucagon release. However, in T2D, there may be an uncoupling phenomenon in which glucagon secretion can become independent of these paracrine inhibitory signals, and the stimulatory effect of sulfonylureas at the α-cells predominates such that 6-month treatment may be glucagonotropic, as reported in this study. Whether long-term benefits of sulfonylureas that may enhance functional β-cell mass outweigh any adverse consequence of the increased glucagon secretion on glycemic control remains to be determined.

Figure 1—Subject characteristics over the 6-month study period. Means ± SE of weight, fasting capillary glucose as determined by glucometer readings, and HbA1c in each group. Also shown for the glimepiride group is the average dose at each monthly visit. Changes in weight over time were not significantly different across the three groups [F(12, 222) = 1.1013; P = 0.4]. Average capillary glucose was significantly different [F(12, 204) = 2.53; P < 0.01] when comparing across all three groups. HbA1c was different by trend [F(4, 74) = 2.28; P < 0.1] when comparing across all three groups. *P < 0.05 when comparing Δ from baseline within each group at each time point.

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Table 2—Measures of β-cell secretory capacity, β-cell sensitivity to glucose, insulin sensitivity, and glucagon secretion derived from the GPA test

|                      | Exenatide (n = 14) | Sitagliptin (n = 12) | Glimepiride (n = 14) |
|----------------------|--------------------|----------------------|----------------------|
|                      | Baseline          | 6 months*            | Δ                    | Baseline          | 6 months*            | Δ                    | Baseline          | 6 months*            | Δ                    |
| AIPavg (μU/mL)       | 52 ± 14           | 52 ± 11              | −0.2 ± 9             | 35 ± 4            | 34 ± 6              | −2 ± 7               | 44 ± 6            | 42 ± 4              | −2 ± 7               |
| AIPpot (μU/mL)       | 138 ± 31          | 108 ± 21             | −30 ± 20*            | 83 ± 12           | 80 ± 15             | −2 ± 8               | 97 ± 16           | 119 ± 19            | 22 ± 12              |
| AIPmax (μU/mL)       | 214 ± 60          | 188 ± 34             | −25 ± 501            | 149 ± 20          | 158 ± 30            | 9 ± 21               | 133 ± 19          | 202 ± 35*           | 69 ± 33              |
| PGiso (mg/dL)        | 175 ± 13          | 190 ± 14             | 25 ± 20              | 226 ± 12          | 209 ± 16            | −5 ± 24              | 168 ± 17          | 182 ± 10            | 10 ± 26              |
| M (mg·kg⁻¹·min⁻¹)    | 5.5 ± 0.3         | 5.8 ± 0.4            | 0.27 ± 0.4           | 5.4 ± 0.4         | 5.3 ± 0.4            | −0.1 ± 0.4           | 5.5 ± 0.4         | 5.8 ± 0.4            | 0.35 ± 0.4           |
| I (μU/mL)            | 41 ± 13           | 39 ± 9               | −2 ± 9               | 22 ± 2            | 23 ± 4              | 1 ± 3                | 28 ± 7            | 26 ± 2              | −2 ± 5               |
| M/I (mg·kg⁻¹·min⁻¹/μU/mL) | 0.3 ± 0.1       | 0.3 ± 0.1            | −0.01 ± 0.0          | 0.3 ± 0.0         | 0.3 ± 0.1            | 0.04 ± 0.1           | 0.3 ± 0.1         | 0.3 ± 0.1            | −0.04 ± 0.0          |
| AGRavg (pg/mL)       | 60 ± 12           | 63 ± 8               | 3 ± 17               | 77 ± 13           | 60 ± 11              | −17 ± 6              | 40 ± 9            | 62 ± 8              | 22 ± 17              |
| AGRmin (pg/mL)       | 63 ± 12           | 58 ± 13              | −3 ± 6               | 64 ± 13           | 55 ± 16              | −10 ± 10             | 46 ± 7            | 59 ± 7              | 11 ± 7               |
| AGRmin (pg/mL)       | 51 ± 12           | 52 ± 12              | 2 ± 5*               | 55 ± 8            | 59 ± 19              | 4 ± 21               | 37 ± 6            | 59 ± 3*             | 21 ± 8               |

Data are means ± SE. Δ, change from baseline to 6 months with each value. *P < 0.05 when comparing values within each group. **P < 0.05 when comparing Δ between the exenatide and glimepiride groups. *P ≤ 0.1 (statistical trend) when comparing Δ between exenatide and glimepiride groups.

In conclusion, the implication of the current study is that a 6-month treatment with the GLP-1 analogue exenatide or DPP4 inhibitor sitagliptin does not increase β-cell secretory capacity in human T2D as purported in rodent models. Furthermore, our study indicates that the sulfonylurea glimepiride may be effective in at least short-term improvement in β-cell secretory capacity associated with improved glycemic control early in the course of T2D. Clinically, these findings support T2D treatment algorithms that place sulfonylureas ahead of incretin-based approaches (39), with special consideration for third-generation sulfonylureas such as glimepiride, in which careful dose titration as conducted in this study may avoid weight gain and hypoglycemia.

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