The Use of Exenatide in Islet Transplant Recipients with Chronic Allograft Dysfunction: Safety, Efficacy, and Metabolic Effects

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Background. A current limitation of islet transplantation is reduced long-term graft function. The glucagon-like peptide-1 receptor agonist, exenatide (Byetta, Amylin Pharmaceuticals, CA) has properties that could improve existing islet function, prevent further loss of islet mass and possibly even stimulate islet regeneration.

Methods. This prospective study evaluated the safety, efficacy, and metabolic effects of exenatide in subjects with type 1 diabetes mellitus and islet allograft dysfunction requiring exogenous insulin.

Results. Sixteen subjects commenced exenatide, 12 continue (follow-up 214±57 days; range 108–287), four (25%) discontinued medication because of side effects. At 6 months, exogenous insulin was significantly reduced with stable glycemic control (0.15±0.02 vs. 0.11±0.025 U/kg per day; P<0.0001); three subjects discontinued insulin from 4, 5, and 9 U/day, respectively, two sustained insulin independence with A1c reduction below graft dysfunction criteria. Postprandial capillary blood glucose was significantly decreased (129.4±3.8 vs. 118.7±4.6 mg/dL; P<0.001), C-peptide and C-peptide-to-glucose ratio increased significantly by 5th and 6th months of treatment (ratio, 1.09±0.15 vs. 1.52±0.18; P<0.05). Weight loss more than 3 kg occurred in 8 of 12 (67%) subjects. Stimulation testing demonstrated improved glucose disposal and C-peptide secretion (glucose area under the curve 52,332±3,219 vs. 42,072±1,965; P=0.002 mgmin^{-1}dL^{-1}, mixed meal stimulation index 0.50±0.06 vs. 0.66±0.09; P=0.03 pmol·min^{-1}L^{-1}), with marked suppression of glucagon secretion and progressive increase in amylin secretion. Side effects were more frequent and severe compared with published reports in type 2 diabetes, tolerated doses were lower.

Conclusions. Exenatide was tolerated in this patient population after appropriate dose titration and there appeared to be gradual but sustained positive effects on glycemic control and islet graft function.

Keywords: Islet, Transplant, Function, GLP-1, Safety, Efficacy.

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Islet transplantation is moving into the arena of a clinical therapy for selected individuals with type 1 diabetes mellitus (T1DM) complicated by unstable control or hypoglycemia unawareness (1). After 6 years of islet transplantation in the “Edmonton Protocol” era, a consistent observation has been that while graft function persists, exogenous insulin must be restarted in 80% to 100% of transplant recipients by 4 to 5 years to maintain normoglycemia (2–5). Although the benefits of more stable control, lack of severe hypoglycemia and improved quality of life remain (6), the graft dysfunction is more often than not progressive.

The causes of the observed graft dysfunction remain to be elucidated and it is likely that multiple variables contribute
to this phenomenon (7). Possibilities include low numbers of islets that survive the transplant procedure resulting in a marginal islet mass at outset; gradual exhaustion of this marginal islet mass because of a relatively high metabolic demand; suboptimal intrahepatic location which may increase metabolic demand while exposing islets to relatively high levels of immunosuppression and other toxins (8–10); immunological losses (allorejection and recurrent autoimmunity) (11–13); and acute/chronic islet toxicity of immunosuppressive drugs (14, 15).

In the search for ways to improve islet function and preserve islet mass, the use of incretins [that is glucagon-like peptide (GLP-1) and GLP-1 receptor agonists] is appealing. Glucagon-like peptide-1, at the level of the β-cell, has demonstrable insulinotrophic actions that include stimulation of insulin gene transcription, insulin biosynthesis, and insulin secretion (16–18). Glucagon-like peptide-1/mimetics also demonstrate, in various animal models, the ability to act as growth factors, stimulating formation of new pancreatic islets (neogenesis) while slowing β-cell death (apoptosis) (19–22). Exenatide (Byetta, Amylin Pharmaceuticals, CA), is a recently US Food and Drug Administration approved synthetic GLP-1 receptor agonist. Studies using exenatide, in patients with type 2 diabetes mellitus (T2DM), resulted in a significant reduction in A1c, weight and fasting glucose levels at both 30 and 82 weeks of treatment (23–26). Thus, GLP-1 receptor agonists could be of potential benefit to islet transplant recipients with partial function to improve remaining islet function and glycemic control while preserving islet mass over time.

The objective of this prospective trial was to evaluate the feasibility of treatment, side effect profile, efficacy, and metabolic effects of exenatide in subjects with T1DM demonstrating islet allograft dysfunction requiring exogenous insulin therapy.

**MATERIALS AND METHODS**

Islet transplant recipients were transplanted in islet alone (IA) or islet after kidney (IAK) protocols using an Edmonton-like protocol of immunosuppression (3, 28). Graft dysfunction warranting insulin therapy was considered present if capillary blood glucose (CBG) values were more than 140 mg/dL (7.8 mmol/L) fasting, or more than 180 mg/dL (10.0 mmol/L) postprandial on three or more occasions in a single week, or two sequential A1c values were more than 6.5% (29). Any subject on exogenous insulin or who met the above criteria of graft dysfunction was eligible for enrollment into the study. Severe gastroparesis, judged clinically, was considered an exclusion criterion. Subjects were counseled as to the risks and benefits of this medication and all enrolled subjects signed an informed consent approved by the institutional review board.

Eligible subjects underwent a baseline visit and follow-up visits at our center at 3 and 6 months. Thereafter, they continued their pre-exenatide follow-up schedule at semianual intervals. Subjects were educated in the administration and refrigerated storage of the medication. During protocol follow-up, graft function was continuously evaluated using fingerstick capillary blood glucose values, laboratory glucose, C-peptide, basal insulin, and A1c levels (5, 29). Each follow-up visit included history and physical (including height, weight, body mass index), nutritional assessment, baseline laboratory testing, and stimulation testing. Mixed meal tolerance testing (MMTT) with and without administration of exenatide was performed at 3 and 6 months. At baseline, MMTT without exenatide only was performed (5).

Subjects were maintained on their immunosuppressive regimen and commenced on exenatide 5 μg twice a day, either morning and evening or with the two largest meals of the day (except one insulin independent subject who was commenced at 2.5 μg every day because of concern of hypoglycemia). Dose was increased or decreased up to three injections and a target total daily dose (TDD) of 30 μg, in an attempt to maximize possibility of islet regeneration. At time of commencement of exenatide, insulin TDD was reduced by 30% to 40% as per protocol; this included cessation of all meal coverage coincident with exenatide administration, and a variable reduction in basal insulin coverage. Toxicity assessments were done at regular intervals. Immunosuppression levels were closely monitored because of the concern that altered gastric emptying may affect trough levels.

**RESULTS**

Seventeen subjects (6 IAK, 11 IA recipients) were evaluated for enrollment into the study. Sixteen met the criteria for inclusion. Safety data is presented in an “intent to treat” format, that is, all 16 subjects who started on the medication were included in the analysis. The remaining data of long-term effects of the medication are presented in an “efficacy” format, that is, only those 12 subjects who continued the medication were analyzed. The primary endpoint of the study was insulin independence. Secondary endpoints included measures of glycemic control and graft function.
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<th>BMI (kg/m²)</th>
<th>Islet infusions (No.)</th>
<th>Insulin independence (POD)</th>
<th>Islet transplant f/u (POD)</th>
<th>Insulin requirement a</th>
<th>A1c (%)</th>
<th>Max dose exenatide (μg)</th>
<th>Exenatide treatment duration (d)</th>
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<tr>
<td>16</td>
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<td>441</td>
<td>10.9</td>
<td>0.19</td>
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</table>

Mean ± SEM
48.1 ± 2.1 64.9 ± 3.1 22.6 ± 0.6 55.0 ± 9.5 640.3 ± 99.1 1111.1 ± 81.2 9.9 ± 1.8 0.2 ± 0.02 6.5 ± 0.1 18.3 ± 1.6 35.8 ± 5.9

Add demographics of other four that started the medication.

a Mean 1 month pre-exenatide commencement.

b Received a supplemental infusion during exenatide treatment.

c Never achieved insulin independence.
for exenatide treatment, one IAK subject did not meet inclusion/exclusion criteria because of clinical symptoms of severe gastroparesis. All IAK and nine IA subjects were using exogenous insulin, two IA subjects were insulin independent and qualified through elevation of A1C as previously described (Table 1).

Four subjects (25%, one IA and three IAK subjects) did not tolerate exenatide and discontinued treatment after a mean of 36±12 days (range 16–42), before any follow-up visit. Reasons for exenatide discontinuation were general malaise (n=1), exacerbation of gastroparesis (n=1), and nausea (n=2). Twelve subjects continue on the medication, current mean follow-up is 214±16.5 days (range 108–287). Of these 12 subjects, eight continue on exenatide therapy alone, four received supplemental infusions, based on protocol eligibility criteria, when the primary outcome was not achieved, three during the 6th month and one during the 7th month of treatment. Data on these subjects are included up until the day of supplemental infusion. The four supplemental infusions were performed with administration of exenatide 1 hr before islet infusion and all resulted in achievement of insulin independence. Although these subjects remain on exenatide, data postsupplemental infusion was not included.

Exenatide target TDD was 30 μg. Only one subject (6%) achieved the target dose at any time during the initial 6 months of follow-up, but this was not sustained. Seven subjects (44%) achieved a TDD of more than or equal to 20 μg at any time during follow-up; currently four subjects (25%) continue to take more than or equal to 20 μg. At 6 months, exenatide median TDD was 15 μg (range 2.5–25); subjects took up to 4 months to achieve their maximum daily dose. There was no obvious reason for the wide range in dosage observed; this was not weight related. Subcutaneous administration was well tolerated by all subjects.

The primary outcome of insulin independence was achieved in 5 of 16 subjects (31%). Two subjects were insulin independent before exenatide treatment and sustained this with a reduction in HbA1c to less than 6.5%. Three subjects were using 4, 5, and 9 U/day insulin and all maintained a normal HbA1c off insulin. In one subject, insulin had to be reintroduced after 3 months. Supplemental infusions were performed in four subjects who did not achieve insulin independence after 3 months or who showed little or no response to exenatide. Supplemental infusions were not performed in the remaining 11 subjects because of patient preference, previous supplemental infusion, or medical contraindications.

Fifteen of 16 subjects (94%) experienced nausea of varying degrees. Four subjects (25%), excluding those who discontinued the medication, required dose reduction or prolonged continuation of a lower dose because of side effects (primarily nausea). Of the four subjects who discontinued the medication, nausea was the primary reason in two (Table 2).

Weight was measured at follow-up visits only and these occurred at 3 and 6 months postonset of treatment. A weight reduction more than 3 kg occurred in seven subjects (44%), requiring dose reduction in two. Maximum weight loss was 9.3 kg (13% initial body weight); this subject was trying to lose weight and had begun a diet shortly before starting exenatide. A second subject lost 5 kg in 3 months (9% initial body weight), exenatide dose was reduced until weight stabilized. In six subjects (38%) there was no significant weight change at 3 or 6 months (weight within 1 kg of starting weight). Overall, weight decreased, becoming significant by 6 months (pre: 65.5±3.1, 3 months: 64.0±3.4 [diff=1.5, P=0.052], 6 months: 62.8±3.43 [diff=2.75, P=0.024] kg) (Fig. 1A). In general weight loss was more pronounced during the first 3 months, however, continued during the second 3 months also (Fig. 1A). In the 12 subjects who continued taking exenatide, weight loss was more pronounced in the first 3 months and less pronounced between 3 and 6 months suggesting stabilization. Precise data regarding daily oral intake are analyzed separately, however, most subjects reported anorexia/nausea/early satiety as cause of weight loss.

During exenatide treatment, there were no episodes of severe hypoglycemia, however, 12 of 16 subjects (75%) experienced mild to moderate hypoglycemia, defined as a CBG reading less than 54 mg/dL (3.0 mmol/L) or hypoglycemia symptomatology requiring oral intake to treat (Table 3). In 11 of 12 subjects these events occurred while still taking basal insulin, however, one subject (no. 13) experienced postprandial hypoglycemia (CBG 46–49 mg/dL) 17 days after all exogenous insulin had been discontinued and this coincided with an increase in exenatide dose from 5 to 10 μg twice a day. In all subjects the majority of hypoglycemic events were postprandial. Overall there was an increase in the frequency of hypoglycemia, (6 months on exenatide: 34 events in 9 subjects [5.67 events/pt/yr] compared with 6 months pre: 29 events in 7 subjects [4.83 events/pt/yr]).

### TABLE 2. Side effects associated with exenatide treatment

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<tr>
<th>Side effect (n=16)</th>
<th>Total frequency</th>
<th>Mild (grade 1&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Moderate (grade 2&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Severe (grade 3&lt;sup&gt;a&lt;/sup&gt;)</th>
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<td>%</td>
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<td>%</td>
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<td>15</td>
<td>94</td>
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<tr>
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<td>19</td>
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<sup>a</sup> NCI criteria (version 3.0B).
Subsequent results are presented as efficacy data, that is, data only from the 12 subjects continuing the exenatide long term is considered. Glycemic control was significantly altered during exenatide treatment. Fasting CBG levels increased significantly at all time points after commencement of exenatide, however, levels decreased over time as insulin was readjusted upward to restore normoglycemia (pre: 110.0 ± 3.4 [diff = 10.8; P = 0.001], 6–12 months: 121.2 ± 3.1 [diff = 9.2; P = 0.001]).

Postmeal CBG values demonstrated an immediate reduction, this decreased further and reached statistical significance during months 5 to 6 (pre: 129.4 ± 3.4, 1–4 months: 124.5 ± 3.2 [diff=8.8; P=0.001] mg/dL). The ability of exenatide to abrogate meal excursions was more clearly evident when data in exenatide-treated subjects, was subanalyzed comparing postprandial CBG in meals with or without exenatide (meals without exenatide: 152.8 ± 4.6 mg/dL, with exenatide: 119.3 ± 2.1 mg/dL; P = 0.001). A1c levels rose slightly during the 6 months before exenatide treatment (5.97% ± 0.66%– 6.46% ± 0.46%). Exenatide treatment did not result in any significant change in A1c although levels were slightly lower by months 5 to 6 (pre: 6.38% ± 0.11%, 1–4 months: 6.33% ± 0.13% [NS], 5–6 months: 6.33% ± 0.13% [NS]%).

Initial iatrogenic reduction in insulin requirements over the first month of exenatide treatment was 46.27% (from 0.15 ± 0.03 to 0.08 ± 0.07 U/kg per day) as recommended in the protocol. Despite titration upwards to re-establish optimal glycemic control, levels remained significantly (28%) reduced postexenatide (pre: 0.15 ± 0.03, 1–4

FIGURE 1. (A) Weight changes in exenatide subjects. Single measure in each subject at follow-up visits demonstrates weight loss during initial 3 months with some stabilization thereafter (mean pre: 65.5 ± 3.1 (n = 16, range 48.2–92.3), 3 months: 64.0 ± 3.4 (n = 14, range 48.2–91.8) [diff = 1.5, P = 0.052], 6 months: 62.8 ± 3.43 (n = 14, range 44.1–92.3) [diff = 2.75, *P = 0.024]) kg). (B) Monthly mean ± SEM insulin requirements (insulin/day) demonstrate a significant reduction at all time points. Initially reduction is iatrogenic but at the end of 5 or 6 months of treatment, insulin requirements remain significantly decreased (pre: 0.15 ± 0.03, 5–6 months: 0.12 ± 0.03 [diff = 0.04, P = 0.001]). By comparison, insulin requirements tend to increase over the 6 months before exenatide. (C and D) Exenatide subjects demonstrated a significant increase in C-peptide levels by 5 to 6 months posttreatment compared with baseline (pre: 1.13 ± 0.14, 1–4 months: 1.22 ± 0.15 [NS], 5–6 months: 1.58 ± 0.17 [diff = 0.46, *P = 0.001]) mg/dL and CPGR (pre: 1.08 ± 0.16, 1–4 months: 1.17 ± 0.16 [NS], 5–6 months: 1.36 ± 0.18 [diff = 0.43, *P = 0.001]).
TABLE 3. Hypoglycemic events in islet transplant recipients receiving exenatide treatment

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* Meal coverage became necessary when exenatide alone was not sufficient to prevent postprandial hyperglycemia.

months: 0.09 ± 0.03 [diff = 0.06, P < 0.0001], 5–6 months: 0.12 ± 0.03 [diff = 0.04, P < 0.0001] units/kg per day) (Fig. 1B).

Measures of islet function also improved significantly. Exenatide treatment resulted in a gradual increase in basal C-peptide levels which reached statistical significance during months 5 to 6 (pre: 1.13 ± 0.14, 1–4 months: 1.22 ± 0.15 [NS], 5–6 months: 1.58 ± 0.17 [diff = 0.46, P = 0.001] ng/mL) (Fig. 1C). When correcting for basal glucose using C-peptide-to-glucose ratio (CPGR) (29), the elevation of CPGR was also significant during months 5 to 6 levels (pre: 1.08 ± 0.15, 1–4 months: 1.17 ± 0.16 [NS], 5–6 months: 1.36 ± 0.18 [diff = 0.43, P = 0.001]) (Fig. 1D).

Mixed meal tolerance testing stimulation testing at 3 and 6 months, performed without exenatide administration, demonstrated progressive improvement of the glucose area under the curve (AUC) although without normalization of glucose values (pre: 52,332 ± 3219, 3 months: 44,732 ± 2418 [diff = 7601, P = 0.052], 6 months: 42,072 ± 1965 [diff = 10,261, P = 0.002] mg/min·1·dL−1) (Fig. 3A). C-peptide AUC improved at 6 months, but did not reach statistical significance (pre: 761 ± 71, 3 months: 707 ± 76 [diff = −54, P = 0.30], 6 months: 842 ± 118 [diff = 81, P = 0.35] ng/min·1·mL−1) (Fig. 3B). When glucose levels were taken into consideration using mixed meal stimulation index, there was significant improvement by 6 months (pre: 0.50 ± 0.06, 3 months: 0.55 ± 0.07 [diff = 0.04, P = 0.31], 6 months: 0.66 ± 0.09 [diff = 0.15, P = 0.03] pmol/mL−1). There was a pronounced increase in amylin AUC (pre: 318 ± 781, 3 months: 3678 ± 942 [diff = 3069, P = 0.004], 6 months: 7777 ± 1504 [diff = 4060, P = 0.02] pg/min·1·dL−1) (Fig. 3C).

To assess the acute effect of exenatide during a meal, MMTT was also performed with exenatide administration. There was marked suppression of glucose excursion when exenatide was administered (3 months, glucose AUC exenatide negative: 44,732 ± 2418, 3 months exenatide positive: 36,635 ± 1522 [diff = 8097, P = 0.002] mg/min·1·dL−1) (Fig. 3D) with concomitant suppression of glucagon secretion (3 months, glucagon AUC exenatide negative: 25,681 ± 2802, exenatide positive: 18,522 ± 1835 [diff = 7159, P = 0.0001] pg/min·1·dL−1) (Fig. 3E). Exenatide administration at time of MMTT resulted in lower C-peptide levels compared with testing without exenatide, although over time, C-peptide levels increased (C-peptide AUC pre: 761 ± 71, 3 months: 659 ± 111, 6 months: 771 ± 86 ng/min·1·mL−1) (Fig. 3F).

**DISCUSSION**

In virtually all recipients with intraportal islet transplants under the Edmonton protocol of immunosuppression a progressive graft dysfunction is observed over time (3–5), the origin of which remains obscure. Future progress in β-cell replacement therapies lies in improving long-term graft function and insulin independence both of which depend on preserving transplanted islets.

The pattern of islet graft dysfunction is a gradual one in most subjects. Glycemic control through CBG testing is usually the earliest indicator. Although there may be an elevation of fasting glucose levels, often it is the coverage of meal excursions that becomes difficult for the lower mass of islets to control (5). Stimulation testing confirms this observation; we have shown that as graft function deteriorates there is progressive elevation of peak glucose, prolonged time to peak glucose, prolonged time to peak C-peptide and ultimately a reduction in peak C-peptide during MMTT, whereas intravenous glucose tolerance testing demonstrates a reduction/loss of first phase insulin release (30). Concomitantly there is a
grafts, to stabilize or even improve existing graft function. Great potential benefit also in subjects with existing alloplantation and continued indefinitely, however, there is a need for preserving functional islet mass. With the emergence of strategies for immunosuppression and cytoprotection are being evaluated for de novo transplant recipients (32), existing transplant recipients are an excellent group to test strategies for preserving functional islet mass. With the emergence of agents that mimic or increase GLP-1 there is renewed optimism that their use in islet transplantation will result in improved long-term islet function. It is clear that if effective, these agents should be introduced at the time of islet transplantation and continued indefinitely, however, there is great potential benefit also in subjects with existing allografts, to stabilize or even improve existing graft function.

FIGURE 2. (A) In exenatide subjects fasting CBG levels increase significantly at all time points, although values are approaching baseline by 5 to 6 months (pre: 110.0 ± 2.9, 1–4 months: 120.8 ± 3.0 [P < 0.001], 5–6 months: 113.2 ± 3.1 [P < 0.001] mg/dL). (B) In exenatide subjects reduction in postprandial CBG levels is immediate and significant by 6 months (pre: 129.4 ± 3.8, months 1–4: 125.5 ± 3.8 [P = 0.06], months 5–6: 120.6 ± 4.0 [P = 0.0004] mg/dL). (C) Subanalysis of meal excursions demonstrates more clearly the acute effects of exenatide. During months 5 to 6 of treatment, meal excursions are markedly diminished when exenatide is administered; when exenatide is not administered, excursions are greater than baseline likely secondary to a reduction in TDD insulin. Postmeal CBG values (mean ± SEM: meals without exenatide: 152.8 ± 7.8; meals with exenatide: 119.3 ± 2.1 [diff = 16.2 P < 0.001] mg/dL). (D) In exenatide-treated subject only, chronological changes in preprandial and postprandial CBG levels are shown (mean ± SEM) during the follow-up period and compared with stable levels before initiation of exenatide.

**Explanation of Results**

It has already been demonstrated that transplanted islets seem to retain the ability to respond to GLP-1 (33). However, prolonged usage in this population has not yet been described. After at least 6 months of continuous treatment in this group of 12 subjects, consistent changes in glycemic control were demonstrated. During the 6 months before onset of exenatide treatment there was an overall trend of progressive graft dysfunction with rising insulin requirements, rising glucose, and A1c values without a significant change in C-peptide. After onset of exenatide treatment, there was an immediate improvement in postprandial CBG values which was sustained. This can be ascribed to the acute effects of exenatide which include decreased gastric emptying, increased satiety, suppression of glucagon secretion, increased glucose dependent insulin secretion, and possibly increased peripheral sensitivity to insulin (34). It is not clear which is the predominant effect in this subject group. Decreased gastric emptying likely plays a large role and although not directly measured, anecdotally almost all subjects described getting full quicker with less food and feeling fuller for a longer period after the meal. Acetaminophen testing is prospectively...
underway to assess the effect of exenatide on gastric emptying. Suppression of glucagon, as demonstrated in the stimulation tests where exenatide was administered, compared with the paradoxical glucagon elevation in response to a meal typically seen in patients with T1DM and noted during stimulation testing without exenatide, is likely another important contributor to the change in blood glucose levels.

The initial deterioration in fasting CBG values observed can be explained by the pre-emptive reduction in exogenous insulin to avert hypoglycemia. As exogenous insulin was optimally titrated, fasting CBG levels approached baseline. Although weight loss is well described in patients with T2DM (23–26), it was not clear if weight loss would occur in T1DM exenatide-treated subjects because they were of normal

**FIGURE 3.** (A) In exenatide subjects levels of glucose during MMTT (without exenatide administration) demonstrated a progressive decrease over time, significant at 6 months (glucose AUC pre: 52,332 ± 3219, 3 months: 44,732 ± 2418 [diff = 7601, P = 0.052], 6 months: 42,072 ± 1985 [diff = 10,261, P = 0.002] mg min⁻¹ dL⁻¹). (B) In exenatide subjects CPGR during MMTT (without exenatide administration) demonstrated a progressive increase over time, significant at 5 months (CPGR AUC pre: 469 ± 56, 3 months: 502 ± 64 [diff = 36, P = 0.40], 6 months: 616 ± 85 [diff = 149, P = 0.03]). (C) In exenatide subjects levels of Amylin during MMTT (without exenatide administration) demonstrated a progressive increase over time, significant at both 3 and 6 months (Amylin AUC pre: 3718 ± 781, 3 months: 6787 ± 942 [diff = 3069, P = 0.004], 6 months: 7777 ± 1504 [diff = 4060, P = 0.02] mg min⁻¹ dL⁻¹). (D) In exenatide subjects levels of glucose during MMTT (with and without exenatide administration) at 3 months posttreatment demonstrated near complete abrogation of the glucose peak after meal ingestion resulting in significant reduction in glucose AUC (glucose AUC pre: 52,332 ± 3219, 3 months exenatide negative: 44,732 ± 2418, 3 months exenatide positive: 36,635 ± 1522 [diff = 8097, P = 0.002] mg min⁻¹ dL⁻¹). (E) In exenatide subjects levels of glucagon during MMTT without exenatide administration demonstrated abnormal elevation of glucagon levels after meal ingestion, while during MMTT with exenatide administration, glucagon secretion was completely inhibited resulting in significant reduction in glucagon AUC (glucagon AUC pre: 23,865 ± 3077, 3 months exenatide negative: 25,681 ± 2802, 3 months exenatide positive: 18,522 ± 1835 [diff = 7189, P = 0.0001] mg min⁻¹ dL⁻¹). (F) In exenatide subjects levels of C-peptide during MMTT with exenatide administration were lower compared with levels during MMTT without exenatide administration although when comparing C-peptide AUC during MMTT with exenatide administration at 3 and 6 months posttreatment there was a progressive rise (C-peptide AUC pre: 761 ± 71, 3 months exenatide positive: 659 ± 111, 6 months exenatide positive: 771 ± 86 ng min⁻¹ mL⁻¹).
weight at baseline. The weight loss seen in the subjects described herein coincided with side effects and was reversed as dose related side effects resolved.

There is a wealth of evidence that GLP-1 and GLP-1 receptor agonists can improve metabolic control (33, 35, 36), reduce apoptosis (37), and increase islet neogenesis and regeneration in a variety of animal models of diabetes (19, 20, 38–41). The interesting question remains whether long-term administration can increase islet mass in human islet transplant recipients. Since there is no test to assess islet mass at this time only indirect measures can be used (basal C-peptide/CPGR). Both of these measures, basal and stimulated, demonstrated a progressive and persistent increase after 3 to 4 months of treatment when compared with 6 months before exenatide treatment which was statistically significant. Stimulation testing demonstrated a significant reduction in glucose AUC and a trend toward improved C-peptide response despite lower glucose values during a meal challenge. These effects are most likely insulinotropic rather than an increase in islet mass, however, treatment in a small group of subjects continues to see if the trend continues to improve. Our findings were similar to those of Ghofaifi et al. (42) although treatment was for a shorter period of time and they did not demonstrate a change in C-peptide levels therefore concluding that there was no trophic effect on islets.

Response to exenatide was not uniform across the group. Further evaluation of individual subjects showed that some subjects responded better (n=5) to exenatide than others (n=7). Because of the uniformity of immunosuppressive regimen it was not possible to evaluate individual immunosuppressive drug toxicity. In the responders, however, pre-exenatide, indicators of graft function tended to be better; C-peptide levels (1.4±0.5 vs. 1.1±0.7 ng/mL), CPGR (1.4±0.7 vs. 0.9±0.5) and 90 min glucose from MMTT (199.4±53.5 vs. 248.3±57.0 mg/dL). Additionally, postoperative day at time of commencement of exenatide (973.8±325.1 vs. 1281.7±195.0 days) and duration of graft dysfunction (366.6±250.1 vs. 654.1±383.5 days) were lower. None, however, reached statistical significance. Response therefore, may be limited to varying degrees by the marginal residual functional islet mass, ongoing immunological events, continued toxicity/antiregenerative effects of immunosuppression (tacrolimus or sirolimus), or reduction in efficacy of exenatide, for example, by exenatide antibodies.

**Lessons Learned**

The tolerated dose of exenatide in islet allograft recipients with T1DM is lower than that reported in patients with T2DM. At standard doses, side effects were significantly more frequent and resulted in a significantly higher number of subjects that discontinued the medication compared with studies in T2DM (23–26). Nausea was the most frequent side effect, however, there were a higher number of subjects who reported of lower gastrointestinal side effects (diarrhea and constipation) and central nervous system side effects, namely fatigue, decreased concentration/mood alteration associated with acute injection. In our study population, the side effect frequency and profile suggests a greater sensitivity to exenatide. Despite lower doses, metabolic effects were clearly apparent. After adequate dose adjustment, all subjects continued to tolerate the medication well. Those who discontinued the medication did so relatively early (mean exenatide duration 36±12 days [range 16–42]).

Reported hypoglycemia secondary to exenatide is rare in patients with T2DM occurring with concomitant sulfonylurea administration. By comparison, in subjects with T1DM and functional transplanted islets there is a significant risk of hypoglycemia. This may be explained by the normal/near-normal fasting glucose levels, dysregulation of transplanted islet in the liver where cessation of insulin secretion may be delayed and glucagon secretion inhibited by exenatide, limiting recovery mechanisms. Hypoglycemia is also exacerbated by the presence of exogenous insulin particularly concomitant meal coverage.

This study is limited by the lack of a randomized control group. It was elected to use subjects as their own controls given the small sample size.

We believe that the overall effect of exenatide administration in islet transplant recipients with graft dysfunction has been a positive one resulting in a reduction in insulin requirements, possible stabilization of graft dysfunction versus improved graft function at a cost of additional injections and the side effects experienced, perhaps the most concerning of which is hypoglycemia. These results are preliminary, and conclusive evidence of increased islet mass will likely take considerable time to gather. Unfortunately several subjects underwent a supplemental infusion and their long-term data will not be available, however, eight subjects continue on the medication at this time. Those undergoing reinfusion continued taking exenatide to improve engraftment, their data is under evaluation (43).

Although regeneration cannot be proven, there has been no further deterioration in graft function in any recipient suggesting, at the least, the gradual deterioration previously described may be ameliorated by exenatide. A noninjectable preparation with longer action would likely be more beneficial whereas the use of exenatide is better indicated from the time of initial islet transplantation when preservation of islet mass at time of implantation would likely reduce the large islet losses at this time thereby improving acute outcomes (single donor insulin independence) and long-term graft function.

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**REFERENCES**


27. Deleted in proof.