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Chronic liraglutide administration fails to suppress postprandial glucagon levels in type 1 diabetic islet allograft recipients with graft dysfunction

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The initial success of islet transplantation for patients with type 1 diabetes is often followed by a decline of islet function¹. We previously showed that treatment with exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, improves islet graft function up to 12 months after occurrence of graft dysfunction requiring the reintroduction of insulin therapy². Exenatide treatment required 2 daily injections and was associated with gastrointestinal side effects². Liraglutide, an acylated GLP-1 receptor agonist, represents a viable therapeutic option, since it is administered once daily and has better tolerability. However, the recent LIBRA trial in patients with type 2 diabetes suggests that liraglutide chronic administration is associated with postprandial hyperglucagonemia³. To investigate the use of liraglutide as adjuvant agent for islet transplantation in relation to its effect on glucagon secretion, we retrospectively analyzed 5 cases of islet transplant recipients with graft dysfunction who were switched from exenatide to liraglutide treatment to simplify their diabetic regimen and improve gastrointestinal side effects. Patients were part of the cohort study previously described (Fig. 1A)². After being treated with exenatide (10–30 ug SQ daily divided in 2 doses) for a total of 60 months, patients were started on liraglutide (titrated from 0.6 to 1.2 mg SQ once daily) and treated for 12 months. Islet function was assessed by 5hr mixed meal tolerance test (MMTT). Initial data analysis limited to glucagon secretion revealed that for

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the entire duration of exenatide treatment glucagon levels were consistently suppressed, returned to baseline after exenatide discontinuation but surprisingly remained elevated despite starting liraglutide ($P = 0.0005$ by *Friedman test*) (Fig 1B). This finding was further investigated by comparing equivalent lengths of time for each medication after adjusting for baseline values. Exenatide consistently suppressed glucagon secretion but liraglutide failed to do so both at 6 and 12 months ($P = 0.0313$ by *Wilcoxon test*) (Fig 1C). Assessment of beta cell secretion showed that there were no significant differences in glucose and insulin profiles (Fig. 1 D, E). C-peptide levels were comparable under exenatide and liraglutide treatments at 12 months but there was a discrepancy between pro-insulin and c-peptide levels indicative of graft dysfunction (Fig. 1 F, G). Liraglutide medical adherence was confirmed by the increase in GLP-1 levels ($P = 0.0239$ by *Friedman test*) (Fig. 1 H). HbA1c, insulin doses and body weight were not significantly different under the 2 treatments. Gastrointestinal side effects, which occurred in 2 subjects with exenatide treatment were not observed with liraglutide. We recognize the limitations of this study which include the small sample size and lack of a control group. Our data suggest that the chronic administration of liraglutide may result in a lack of suppression of postchallenge glucagon levels. More studies are needed to investigate the clinical implication of these findings and their impact on islet transplantation.

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Abbreviations

GLP1	glucagon-like peptide-1
MMTT	mixed meal tolerance test
SQ	subcutaneous

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Figure 1.

Study subjects and metabolic effects of exenatide and liraglutide administration. (A) Demographic and clinical features; (B) glucagon levels under exenatide and liraglutide treatment; (C-G) metabolic outcomes at 6 and 12 months under exenatide and liraglutide treatment; (C) glucagon, (D) glucose, (E) insulin, (F) proinsulin (G) c-peptide; (H) GLP-1 levels under liraglutide treatment. Exenatide but not liraglutide was administered before each Mixed Meal Tolerance Test (MMTT) given the exenatide shorter half-life. Results are represented as area under the curve (AUC) calculated by the trapezoidal approximation and normalized by subtracting baseline values before starting exenatide treatment, units are

therefore reported as delta AUC. * Data representation limited to data available for 2 patients and not included in the statistical analysis; **after exenatide discontinuation for at least 3 days and before starting liraglutide. Time is expressed in months (m); exenatide (exn); liraglutide (lira); glucagon-like peptide-1 (GLP-1). Data were analyzed using the Wilcoxon test for matched paired comparisons and the Friedman test for multiple comparisons; p values <0.05 were considered significant.

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