Effect of 3 Years of Treatment With Exenatide on Postprandial Glucagon Levels

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α-Cell dysfunction contributes to hyperglycemia in type 2 diabetes and is characterized by inappropriately increased basal and postprandial glucagon levels (1). The regulation of glucagon secretion remains poorly understood. Glucagon-like peptide 1 (GLP-1), a gut-derived hormone with glucose-dependent insulinotropic effects, has been shown, albeit mostly in short-term studies, to reduce fasting and postprandial glucagon levels. Thus, the glucagonostatic effect of GLP-1 receptor agonists has been considered as one of the key mechanisms by which they improve glycemia (2). However, in a recent 48-week study with the GLP-1 receptor agonist liraglutide, a paradoxical postprandial increase in glucagon levels was observed (3). This study challenged our understanding of the effects of GLP-1 receptor agonists on glucagon.

We assessed the effects of 3-year treatment with the GLP-1 receptor agonist exenatide (EXE) versus insulin glargine (GLAR) on fasting and postprandial glucagon levels. Details of the study design were reported previously (4). In short, 36 metformin-treated patients with type 2 diabetes (25 males, 11 females; mean ± SD age 59 ± 7.9 years and BMI 29.7 ± 4.2 kg/m^2) completed the study on EXE (n = 16) or GLAR (n = 20) treatment. Two sequential meal tests (breakfast and lunch: 50 g of fat, 75 g of carbohydrates, and 35 g protein) were performed, where EXE was given prior to breakfast but not before lunch. GLAR was administered the evening before the test meal. Blood was drawn from an intravenous catheter at specified times (Fig. 1) into chilled EDTA tubes containing aprotinin. Plasma glucagon, glucose, and HbA_{1c} concentrations were assessed by a central laboratory (Quintiles, Livingston, U.K.).

Glycemic control was similar for both groups. HbA_{1c} values were 6.6 ± 0.2% for EXE and 6.9 ± 0.2% for GLAR (between-group difference P = 0.186). As a result of the treat-to-target titration, the GLAR group showed a significantly greater reduction in fasting plasma glucose as compared with the EXE group (−2.0 ± 0.4 vs. −0.2 ± 0.5 mmol/L, respectively; P < 0.001). No differences in fasting glucagon levels were observed between EXE and GLAR treatment (Fig. 1). Following breakfast, glucagon levels decreased with EXE treatment and an increase was seen during GLAR treatment. However, following the second meal, glucagon levels increased in the EXE group, whereas a similar response to that following breakfast was seen in the GLAR group.

The lack of effect of EXE on fasting and postlunch glucagon is likely caused by the short half-life of approximately 2.5 h. In line with previous short-term studies, 3-year treatment with EXE reduces postbreakfast glucagon levels in apparent contrast to long-term liraglutide treatment (3). Possibly, prolonged continuous exposure to high GLP-1 levels induces different responses than intermittent GLP-1 receptor stimulation, as has been observed for gastric emptying. The paradoxical increase in glucagon secretion after the second meal corroborates earlier observations in patients with type 2 diabetes following mixed meals (5). Taken together, this study demonstrates that in patients treated with EXE for 3 years the glucagon response to a mixed breakfast remains suppressed.

Duality of Interest. This study was sponsored by Amylin Pharmaceuticals, Inc., and Eli Lilly and Co. The study was collectively initiated and designed by the investigators from the study sites. The investigators had full access to the trial data and had control over the statistical analysis and interpretation of the study results.

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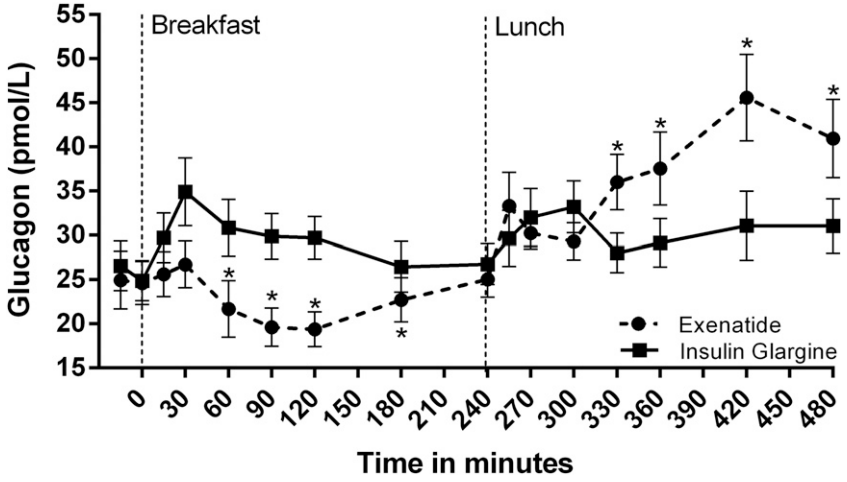

Figure 1—Effects of EXE (circles, dashed line) and GLAR (squares, solid line) on glucagon levels in the fasting state and after two mixed meals. *Statistically significant difference ($P < 0.05$) between the treatment groups.

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