Improvement of Postprandial Endothelial Function after a Single Dose of Exenatide in Individuals with Impaired Glucose Tolerance and Recent Onset Type 2 Diabetes Mellitus

Running Title: Exenatide and Postprandial Endothelial Function

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Objective: Endothelial dysfunction is frequently present in individuals with insulin resistance or type 2 diabetes and can be induced by high fat or high carbohydrate meals. Because exenatide reduces postprandial glucose and lipid excursions we hypothesized that it may also improve postprandial endothelial function (EF).

Research Design and Methods: In a double-blinded, randomized cross-over design, postprandial EF was examined in 28 individuals with impaired glucose tolerance or recent onset type 2 diabetes after a single injection of exenatide or placebo given just prior to a high-fat meal. EF was determined with peripheral arterial tonometry pre- and postprandially.

Results: Postprandial EF was higher after exenatide compared with placebo (p=0.0002). In the placebo phase, postprandial change in EF was inversely associated with mean postprandial concentrations of triglycerides (r=-0.62, p=0.0004). Changes in postprandial triglyceride concentrations explained 64% of exenatide’s effect on postprandial EF.

Conclusions: Exenatide ameliorates postprandial endothelial dysfunction after a high-fat meal.
Endothelial dysfunction frequently occurs in insulin resistance and type 2 diabetes (1) and can be induced by high fat or high carbohydrate meals (2). Recent data indicate that exenatide, a diabetes medication that lowers glucose predominantly through postprandial actions (3; 4), may also reduce postprandial lipid excursions (5; 6). The present study investigated whether exenatide would improve postprandial endothelial function (EF) in individuals with impaired glucose tolerance (IGT) and recent type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

All participants provided written informed consent before participation in the study approved by the local Institutional Review Board. Eligibility criteria included age 35-70 years; fasting triglycerides 1.6-5.6 mmol/l; IGT or diet controlled (HbA1c <7.5), recent onset (<3 years) type 2 diabetes. The study consisted of two clinical research unit test-periods separated by 1-3 weeks, both commenced in the morning following an overnight fast. Participants rested in a recumbent position in a quiet and darkened room for at least 15 minutes before measurement of EF by reactive-hyperemia peripheral arterial tonometry (RH-PAT) (7). A double-masked subcutaneous injection of exenatide (10 µg, Amylin Pharmaceuticals, San Diego, CA) or normal saline was then administered in the lower right abdominal quadrant. Within 15 minutes after the injection the participants consumed a standardized solid meal (600 kcal/m^2; 45% fat - 60% saturated, 40% carbohydrates, 15% protein). Blood samples were collected at 120 and 240 minutes and RH-PAT was repeated 210 minutes after meal ingestion. The effects of exenatide were evaluated by repeated measures analysis of covariance (ANCOVA) using the SAS program (v9.2; Cary, NC, USA). Further details on participants and methods are available in the online supplemental materials.

**RESULTS**

Baseline characteristics of the study group are shown in supplemental Table 1. Transient nausea after ingestion of the study meal tended to occur more frequently, as expected, with exenatide (n=14) than with placebo (n=3). All but 5 subjects ingested their entire meal on both occasions; 4 of these ingested lower amounts during the placebo phase.

In the entire cohort, postprandial PAT-index (adjusted for baseline) was higher after exenatide then after placebo (Figure 1A). In a subset analyses by glucose tolerance, in individuals with IGT (n=16) PAT-index remained unchanged after the meal during the placebo phase, tended to increase after exenatide (p=0.1), and was higher compared with the placebo period (Figure 1B). Among those with type 2 diabetes (n=12), postprandial PAT-index declined during the placebo phase (p=0.006), this decline was largely prevented by exenatide, and postprandial EF after exenatide trended higher than after placebo (Figure 1C). However, the improvement in postprandial PAT-index conferred by exenatide was similar between these two subgroups (p=0.7 for the effect of glucose tolerance status in the entire cohort).

Exenatide reduced postprandial rises in glucose, insulin and triglyceride concentrations (supplemental Table 2). In the placebo phase, postprandial PAT-index inversely correlated with mean (average of 2 and 4 hour) postprandial concentrations of TG (r=-0.62, p=0.0004) whereas it was not associated with
postprandial glucose ($r=-0.29$, $p=0.1$) or insulin concentrations ($p=1.0$). In multivariate analysis, mean postprandial triglycerides but not glucose or insulin concentrations significantly predicted postprandial change in PAT-index. Change in postprandial triglycerides after exenatide accounted for 64% of the estimated effect of exenatide on postprandial EF (Supplemental Figure 1, which is available in the online appendix at http://care.diabetesjournals.org).

CONCLUSIONS

The present data confirmed marked postprandial impairment of EF in individuals with type 2 diabetes (2), and suggest that this susceptibility may develop early in the evolution of diabetes as a postprandial decline in EF was seen in those with newly diagnosed diabetes and was absent in those with IGT. Most importantly, a single exenatide injection improved postprandial EF in the overall group and the degree of postprandial EF improvement with exenatide was similar in those with IGT and diabetes.

Postprandial glucose and triglyceride concentrations have been shown to be associated with endothelial dysfunction following meal challenges (2). In the present study, improvement of postprandial EF after exenatide was related to declines in triglyceride but not glucose concentrations. This could be explained by the predominantly high fat content of the meal resulting in a relatively small postprandial increment in serum glucose concentrations, and by sample size that did not permit detection of such modest effect. Although almost two thirds of the effect of exenatide on postprandial EF in present study was accounted for by changes in postprandial triglycerides, the unexplained residual portion leaves open the possibility that exenatide also improves EF by additional mechanisms. In fact, GLP-1 has been shown to improve vascular function independently of its action on glucose, lipid or energy metabolism both ex vivo, in preconstricted pulmonary arteries (8), and in vivo, in salt-sensitive hypertensive rats (9), healthy humans (10) and in subjects with type 2 diabetes (11).

The systemic character of endothelial dysfunction supports the use of EF measured on peripheral arteries as a reasonable surrogate of coronary EF. EF measured by RH-PAT correlates well with coronary EF (12) and with standard cardiovascular risk factors (13). Since this study investigated the effect of a single exenatide injection on 3.5-hour post-meal EF, we cannot conclude that EF will be improved throughout the day with typical morning and evening exenatide administration. In fact, as a morning injection of exenatide appears to decrease triglyceride levels after a morning meal but not after a noon meal (6), it remains unclear whether the favorable effect of exenatide on EF would be preserved at mid-day. This will presumably depend in part on whether there are vascular benefits of exenatide by pathways that are independent of its triglyceride lowering effects. Finally, as our study included only individuals with IGT or recent type 2 diabetes with optimal glycemic control, we cannot assume that exenatide will improve EF in those with a longer history of diabetes, in whom the extent of vasculature injury may be more advanced and less responsive to intervention.

As endothelial dysfunction appears to be an early indicator of vascular damage and predicts both progression of atherosclerosis (14) and incidence of cardiovascular events (15), exenatide and possibly other incretin-based strategies
may provide additional cardiovascular benefit beyond improved glycemic control.

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**Figure 1** The effects of exenatide and placebo on postprandial endothelial function (PAT-index) in the entire cohort (Panel A), and in those with impaired glucose tolerance (panel B) or type 2 diabetes (panel C). Endothelial function was measured before and after a single high-fat breakfast meal. Participants received placebo and exenatide on separate visits in a crossover design. P-values denote statistical significance of differences in post-meal values (adjusted for pre-meal and test sequence) between exenatide and placebo. Data are displayed as means ± SE.
REFERENCES