Improvement of Postprandial Endothelial Function After a Single Dose of Exenatide in Individuals With Impaired Glucose Tolerance and Recent-Onset Type 2 Diabetes

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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.

RESEARCH DESIGN AND METHODS — In a double-blinded randomized crossover design, postprandial endothelial function 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 before a high-fat meal. Endothelial function was determined with peripheral arterial tonometry pre- and postprandially.

RESULTS — Postprandial endothelial function was higher after exenatide compared with placebo ($P = 0.0002$). In the placebo phase, postprandial change in endothelial function 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 endothelial function.

CONCLUSIONS — Exenatide ameliorates postprandial endothelial dysfunction after a high-fat meal.

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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 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 (A1C <7.5%), and 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 after an overnight fast. Participants rested in a recumbent position in a quiet and darkened room for at least 15 min before measurement of endothelial function by reactive-hyperemia peripheral arterial tonometry (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 min 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 min and reactive-hyperemia PAT was repeated 210 min after meal ingestion. The effects of exenatide were evaluated by repeated-measure ANCOVA using the SAS program (version 9.2; SAS, Cary, NC). Further details on participants and methods are available in the online appendix (available at http://care.diabetesjournals.org/cgi/content/full/dc09-1961/DC1).

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 five subjects ingested their entire meal on both occasions; four of these ingested lower amounts during the placebo phase.

In the entire cohort, postprandial PAT index (adjusted for baseline) was higher after exenatide than after placebo (Fig. 1*A*). In 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 (Fig. 1*B*). Among individuals 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 endothelial function after exenatide

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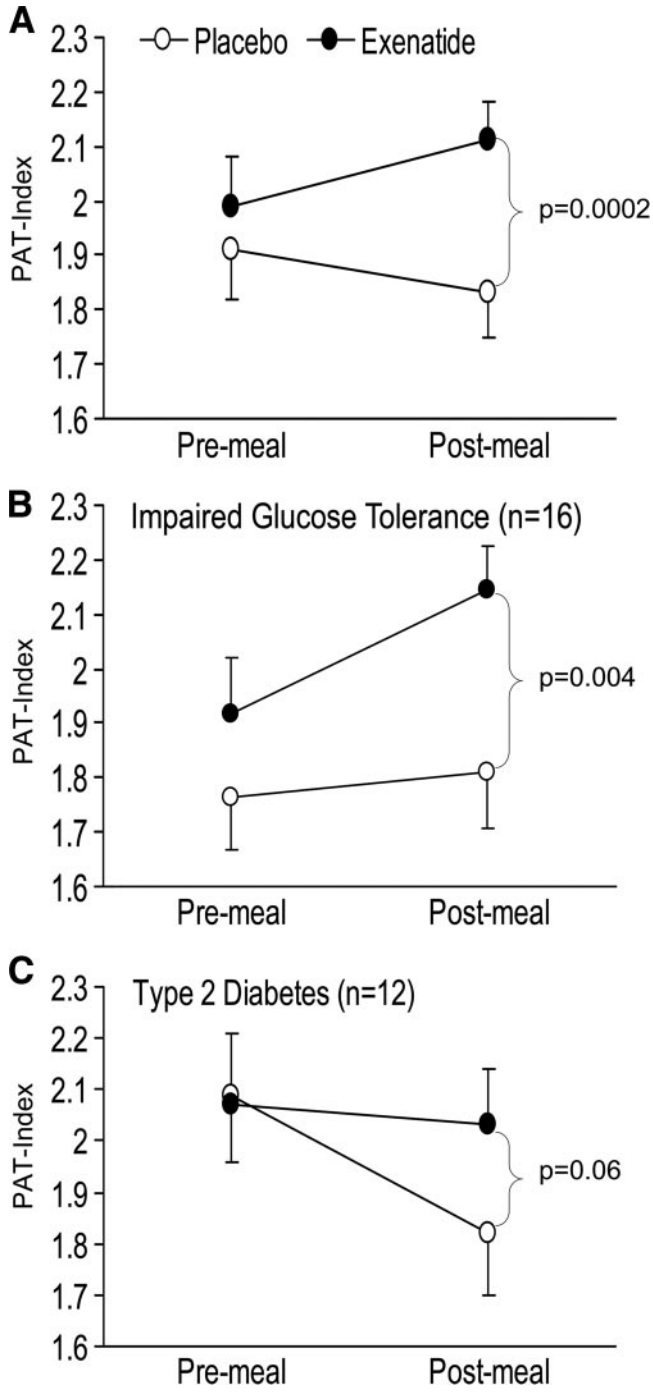

Figure 1—*Data are means ± SE. The effects of exenatide and placebo on postprandial endothelial function (PAT index) in the entire cohort* (A) *and in subjects with IGT* (B) *or type 2 diabetes* (C). *Endothelial function was measured before and after a single high-fat breakfast meal. Participants received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

trended higher than after placebo (Fig. 1*C*). 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 h) postprandial concentrations of triglycerides ($r = -0.62$, $P = 0.0004$), 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 endothelial function (supplemental Fig. 1).

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

Postprandial glucose and triglyceride concentrations have been shown to be associated with endothelial dysfunction after meal challenges (2). In the present study, improvement of postprandial endothelial function 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 a sample size that did not permit detection of such a modest effect. Although almost two-thirds of the effect of exenatide on postprandial endothelial function in the present study was accounted for by changes in postprandial triglycerides, the unexplained residual portion leaves open the possibility that exenatide also improves endothelial function by additional mechanisms. In fact, glucagon-like peptide-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), in healthy humans (10), and in subjects with type 2 diabetes (11).

The systemic character of endothelial dysfunction supports the use of endothelial function measured on peripheral arteries as a reasonable surrogate of

coronary endothelial function. Endothelial function measured by reactive-hyperemia PAT correlates well with coronary endothelial function (12) and with standard cardiovascular risk factors (13). Because this study investigated the effect of a single exenatide injection on 3.5-h postmeal endothelial function, we cannot conclude that endothelial function 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 endothelial function 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 endothelial function in individuals 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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