The Dipeptidyl Peptidase-4 Inhibitor Vildagliptin Improves β-Cell Function and Insulin Sensitivity in Subjects With Impaired Fasting Glucose

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OBJECTIVE — To evaluate the effect of treatment with the dipeptidyl peptidase (DPP)-4 inhibitor vildagliptin on insulin sensitivity and β-cell function in subjects with impaired fasting glucose (IFG).

RESEARCH DESIGN AND METHODS — A total of 22 subjects with IFG (11 female and 11 male, mean ± SD age 59.6 ± 11.5 years) were treated orally with 100 mg vildagliptin once daily in a single-blind study. Subjects received placebo for 2 weeks (run-in) followed by vildagliptin for 6 weeks (treatment) and then placebo for 2 weeks (washout). A frequently sampled intravenous glucose tolerance test (FSIGT), followed by a 2-h meal tolerance test (MTT), was performed at 2, 8, and 10 weeks. From the FSIGT, the acute insulin response to glucose (AIR_g) and insulin sensitivity index (S_I) were determined and used to compute the disposition index ($AIR_g \times S_I$) as a measure of β-cell function.

RESULTS — Fasting plasma glucose did not change after 6 weeks of vildagliptin treatment. With treatment, mean ± SEM AIR_g increased from 224 ± 44 to 286 ± 52 pmol/l ($P < 0.05$), and S_I improved from 2.8 ± 0.5 to 3.5 ± 0.5 × $10^{-5} \cdot min^{-1} \cdot pmol^{-1} \cdot l$ ($P < 0.01$), resulting in an increase in the disposition index from 688 ± 180 to 1,164 ± 318 × 10^{-5}/min ($P < 0.05$). These effects were not sustained after washout. During the MTT, the incremental area under the glucose curve was significantly decreased after treatment (240 ± 15 vs. 191 ± 14 mmol $\cdot l^{-1} \cdot min^{-1}$; $P = 0.002$), but this effect was not sustained after washout.

CONCLUSIONS — The DPP-4 inhibitor vildagliptin improves insulin sensitivity and β-cell function, leading to improved postprandial glycemia in subjects with IFG, who are known to have β-cell dysfunction. Thus, vildagliptin may prevent progression to diabetes in high-risk subjects.

Diabetes Care 31:108–113, 2008

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The prevalence of type 2 diabetes will more than double during the first three decades of this century (1). Impaired fasting glucose (IFG) is a risk factor for progression to diabetes (2–4) and, as in type 2 diabetes, is associated with β-cell dysfunction (5,6). Further, abnormalities in β-cell function have even been shown at fasting plasma glucose (FPG) levels within what is considered the normal range (5,7). With the importance of β-cell dysfunction in the pathogenesis of IFG and the increased risk of diabetes in individuals with IFG, interventions that improve β-cell function may be effective at preventing or delaying progression to diabetes.

Recently, a new therapeutic approach for treatment of type 2 diabetes that targets the incretin hormones has been developed. These peptide hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released from the intestine after a meal and stimulate insulin secretion in a glucose-dependent fashion. However, their action is limited by rapid inactivation by the enzyme dipeptidyl peptidase-(DPP)-4.

Vildagliptin is a new oral agent that inhibits DPP-4, thereby increasing levels of active GLP-1 and GIP (8) and simultaneously improving glycemic control in subjects with type 2 diabetes (8–11). Treatment of subjects with type 2 diabetes with vildagliptin for 28 days resulted in enhanced β-cell function during an oral glucose tolerance test (8). Since incretins are stimulated during an oral challenge, whether improvement in insulin secretion and β-cell function was related to prolongation of the endogenous incretin response to the oral challenge or to more direct effects on β-cell function is not clear. Due to the long half-life of DDP-4 inhibitors, elevated basal levels of active GIP and GLP-1 could also be playing a role.

Given the underlying β-cell dysfunction and increased risk of developing diabetes in individuals with IFG, we sought
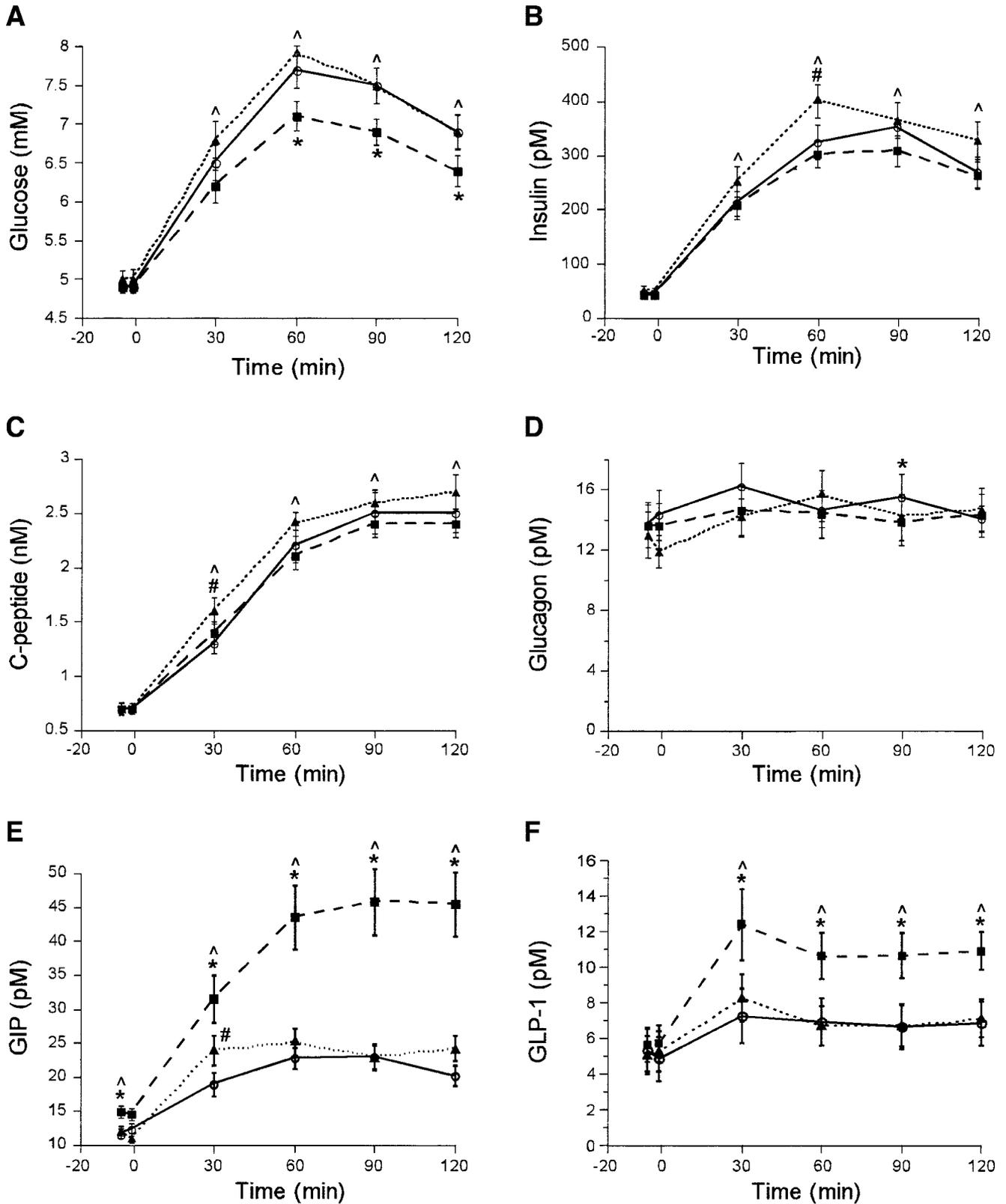
Figure 1—*Glucose (A), insulin (B), C-peptide (C), glucagon (D), intact GIP (E), and intact GLP-1 (F) levels during the MTT after placebo run-in (day 14 [○]), vildagliptin treatment (day 56 [■]), and washout (day 70 [▲]). Significant differences (P < 0.05): *day 14 vs. day 56, ∧day 56 vs. day 70, #day 14 vs. day 70.*

to determine whether treatment with the DDP-4 inhibitor vildagliptin would improve β-cell function in these subjects. We assessed β-cell function during an intravenous glucose tolerance test, when incretin levels would be expected to be low, and during a meal tolerance test (MTT), when incretin levels would be increased. To evaluate for sustained treatment effect, we repeated the tests after a 2-week washout period.

RESEARCH DESIGN AND METHODS

The study employed a single-blind, single-treatment design, with 2 weeks of placebo treatment before (run-in) and after (washout) 6 weeks of active treatment. During active treatment, subjects with IFG orally ingested 100 mg vildagliptin daily. Study procedures were performed on days 14, 56, and 70 after commencing study medication, which corresponded with the ends of the run-in, treatment, and washout periods, respectively.

The primary outcome was β-cell function determined after 6 weeks of treatment. Secondary outcomes included effects of treatment on α-cell function, insulin sensitivity, glucose tolerance, and intact GLP-1 and GIP levels following a standardized MTT. The durability of treatment on these measures was determined following the 2-week washout period.

Eligible subjects had an average FPG between 5.56 and 6.39 mmol/l (100 and 115 mg/dl), determined by two measurements made within 19 days of each other, with neither measure outside the range of 5.28–6.94 mmol/l (95–125 mg/dl). Additional inclusion criteria included A1C between 5.5 and 7.0%, BMI 22–40 kg/m^2, stable weight ($\pm$2.5 kg) for the past 6 months, and no evidence of significant renal, liver, gastrointestinal, endocrine, or hematological disease. Exclusion criteria included pregnancy or lactation, history or diagnosis of diabetes, or history of cardiac disease in the prior 6 months. Subjects taking class Ia, Ib, Ic, or III antiarrhythmics, glucose-lowering medications, corticosteroids, or HIV protease inhibitors were ineligible. The Human Subjects Review Committee at the University of Washington approved the study, and all subjects gave written informed consent.

Subjects arrived at the study center after a fast of at least 10 h. Intravenous catheters were inserted into arm veins, one for blood sampling and the other for administration of glucose and insulin as part of the insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT). The blood-sampling arm was heated to arterialize the blood. Subjects took a dose of study medication 30 min before intravenous glucose administration.

The insulin-modified FSIGT was performed using a standardized protocol. Briefly, following basal sampling, glucose (11.4 g/m^2 body surface area) was injected intravenously over 60 s starting at time zero, and insulin (0.03 units/kg) was infused over 5 min starting 20 min after glucose administration. Blood samples were obtained at 36 time points over 240 min.

An MTT was performed 30 min after completion of the FSIGT. Subjects received a standardized lunch (550 kcal: 28% protein, 26% fat, and 46% carbohydrate) and consumed the meal within 30 min. Blood samples were drawn at −10, −5, −1, 30, 60, 90, and 120 min relative to commencing the meal.

Assays

Plasma glucose was determined by the hexokinase method. Insulin and C-peptide levels were measured using a two-site immunoenzymometric method based on specific monoclonal antibodies. Samples for glucagon were collected with aprotinin and assayed by radioimmunoassay (Linco, St. Louis, MO). Fructosamine was assayed using a colorimetric test (Pointe, Canton, MI).

Intact GIP and GLP-1 levels were measured on EDTA plasma with diprotin A added. COOH-terminal GIP immunoreactivity was measured using the COOH-terminally directed antiserum R65, which reacts fully with intact GIP and the NH$_2$-terminally truncated metabolite GIP$_{3–42}$. In this assay, addition of synthetic human peptides to plasma before ethanol extraction gives a recovery of 85% for GIP$_{1–42}$ and 81% for GIP$_{3–42}$. The assay has a detection limit of <2 pmol/l and intra-assay variation of 6%.

NH$_2$-terminal GIP immunoreactivity was measured using the specific antiserum 98171, which cross-reacts <0.1% with GIP$_{3–42}$ or with structurally related GLP peptides or glucagon. Addition of synthetic GIP$_{1–42}$ to plasma before extraction gives a recovery of 85%. The assay has a detection limit of 5 pmol/l and intra-assay variation <6%.

Intact GLP-1 levels were measured using a GLP-1 (active) enzyme-linked immunosorbent assay kit (Linco). The assay detects GLP-1 at a minimum concentration of 2 pmol/l.

DPP-4 activity was assessed before administration of study medication on days 14 and 56 and 1 min before glucose administration for the FSIGT on day 56. DPP-4 was assayed enzymatically using the H-Gly-Pro–7-AMC (amino-4-methylcoumarin substrate), which, when cleaved by DPP-4, produces fluorescent AMC. The lower limit of quantification for DPP-4 activity was 0.24 mU/ml × min.

Calculations

From the FSIGT, the following measures were calculated: the acute insulin response to glucose (AIR$_g$) and acute C-peptide response to glucose (ACR$_g$) as the mean incremental responses from 0 to 10 min and the glucose disappearance constant (K_g) as the slope of the regression line relating the natural log of the glucose concentration from 10 to 19 min. The insulin sensitivity index (S_I) and glucose effectiveness at basal insulin (S_g) were quantified using Bergman's minimal model (12). The disposition index provides a measure of β-cell function and was calculated as AIR$_g$ × S_I (13). From the MTT, incremental areas under the curves (AUCs) for glucose, insulin, C-peptide, and glucagon were determined using the trapezoidal method.

Table 1—*Fasting measures before, during, and after treatment with vildagliptin*

	Day 14 (baseline)	Day 56 (treatment)	Day 70 (washout)	*P* day 14 vs. 56	*P* day 14 vs. 70	*P* day 56 vs. 70
Weight (kg)	85.85 ± 3.93	85.66 ± 3.98	85.90 ± 3.97	NS	NS	NS
FPG (mmol/l)	5.90 ± 0.07	5.84 ± 0.08	6.00 ± 0.08	NS	0.08	0.038
A1C (%)	6.02 ± 0.1	5.90 ± 0.09	5.94 ± 0.09	0.056	NS	NS
Fructosamine (mmol/l)	2.01 ± 0.08	1.92 ± 0.05	1.99 ± 0.05	NS	NS	NS

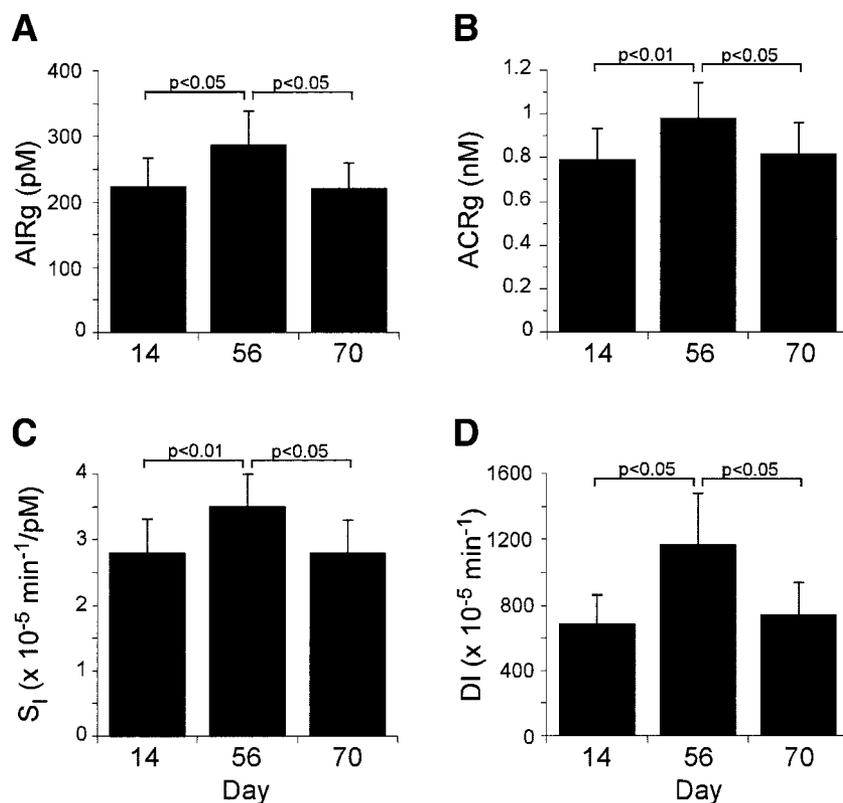Data are means ± SEM unless otherwise indicated. NS, not significant.

Figure 2—*Treatment with vildagliptin (day 56) significantly increased AIR$_g$ (A), ACR$_g$ (B), S$_I$ (C), and disposition index (DI) (D) compared with placebo run-in (day 14), but these effects were not sustained after the washout (day 70).*

Statistics

The statistical approach was determined a priori with paired *t* tests to compare the results of interest: day 14 (end of run-in) versus day 56 (end of treatment) for treatment effect and day 14 versus day 70 (washout) to test for durability of response. Secondary comparisons were performed between days 56 and 70. Statistical analyses were performed using SAS, version 8.2. Data are presented as mean ± SEM unless otherwise specified. Variables were log transformed as necessary to achieve normal distribution. A $P < 0.05$ was considered significant.

RESULTS

Subject characteristics, compliance, and medication tolerability

A total of 22 subjects (11 men and 11 women) met eligibility criteria and were enrolled in the study, and all completed the study. Subjects had a mean ± SD age of 59.6 ± 11.5 years (range 32–75), BMI 29.7 ± 4.5 kg/m^2 (22.6–40.5), and FPG at screening 5.96 ± 0.26 mmol/l (5.56–6.31). Compliance with medication, assessed by pill counts at days 14, 28, 56, and 70, was >80%. The drug was well tolerated, and there were no serious adverse events.

Effect of vildagliptin treatment on DPP-4 activity and GIP and GLP-1 levels

After 6 weeks on vildagliptin, DPP-4 activity immediately before administration of active drug was inhibited by 67.9% (3.1 ± 0.5 mU · ml^{-1} · min^{-1} for day 56 basal vs. 9.5 ± 0.4 mU · ml^{-1} · min^{-1} for day 14). DPP-4 activity was inhibited further (96.3% relative to day 14) when assessed 30 min after administration of vildagliptin on day 56 (0.3 ± 0.03 mU · ml^{-1} · min^{-1}).

Treatment resulted in a slight increase in fasting GIP but not GLP-1 levels and marked increases in both AUC intact GIP and GLP-1 levels during the MTT (Fig. 1*E* and *F*).

Effect of vildagliptin treatment on parameters of glucose metabolism, insulin sensitivity, and β-cell function

Vildagliptin treatment for 6 weeks did not result in significant changes in weight, FPG, A1C, or fructosamine (Table 1). AIR$_g$ and ACR$_g$ measured over the first 10 min following intravenous glucose administration were both enhanced with vildagliptin treatment, increasing by 27 and 24%, respectively (Fig. 2*A* and *B*). In addition, 6 weeks of treatment resulted in a significant 25% increase in insulin sensitivity. With the improvements in both AIR$_g$ and S$_I$, the disposition index increased by 69% (Fig. 2*C* and *D*). These changes were not accompanied by significant changes in either S$_g$ (1.61 ± 0.09, 1.61 ± 0.09, and 1.73 ± 0.07 × 10^{-2}/min on days 14, 56, and 70, respectively) or K$_g$ (1.40 ± 0.12, 1.55 ± 0.13, and 1.40 ± 0.08% per min on days 14, 56, and 70, respectively).

With vildagliptin administration, both 2-h plasma glucose and incremental AUC glucose decreased (Fig. 1*A*, Table 2) during the MTT. The absolute incremental AUC insulin and C-peptide responses did not change significantly with treatment, but when the decrease in glucose levels was taken into account, the incremental AUC insulin–to–incremental AUC glucose and incremental AUC C-peptide–to–incremental AUC glucose ratios improved (Table 2), consistent with the FSIGT findings of increased insulin release. Fasting and AUC glucagon levels

Table 2—*Incremental AUCs from the MTT before, during, and after vildagliptin treatment*

	Day 14 (baseline)	Day 56 (treatment)	Day 70 (washout)	*P* day 14 vs. 56	*P* day 14 vs. 70	*P* day 56 vs. 70
Glucose (mmol · l^{-1} · min^{-1})	240.4 ± 15.2	190.5 ± 13.9	242.6 ± 15.8	0.002	NS	<0.001
Insulin (nmol · l$^-$ · min^{-1})	25.96 ± 2.7	24.04 ± 1.97	30.16 ± 2.21	NS	0.08	<0.001
CP (nmol · l^{-1} · min^{-1})	142.7 ± 12.9	140.5 ± 7.8	161.2 ± 9.1	NS	0.028	0.002
Insulin-to-glucose ratio (×10^{-9})	111.3 ± 10.2	140.5 ± 14.1	136.7 ± 12.7	0.013	0.011	NS
CP-to-glucose ratio (×10^{-9})	611 ± 49	807 ± 66	720 ± 55	<0.001	0.002	0.04
Glucagon (pmol · l^{-1} · min^{-1})	131.3 ± 75.4	70.7 ± 45.9	254.1 ± 88.2	NS	NS	0.03
Intact GLP-1 (pmol · l^{-1} · min^{-1})	194 ± 46	579 ± 67	217 ± 20	<0.001	NS	<0.001
Intact GIP (pmol · l^{-1} · min^{-1})	981 ± 160	2758 ± 451	1301 ± 168	0.001	0.012	0.001

Data are means ± SEM unless otherwise indicated. CP, C-peptide; NS, not significant.

during the MTT did not change significantly with treatment (Fig. 1*D*, Table 2), although there was a clear tendency for AUC glucagon to decrease following treatment.

Durability of the effect of vildagliptin on parameters of glucose metabolism, insulin sensitivity, and β-cell function

After the 2-week washout period (day 70), neither A1C nor fructosamine was significantly different compared with baseline (day 14) or treatment (day 56) (Table 1) values. FPG tended to increase after the washout compared with that at baseline (*P* = 0.08) and was significantly higher compared with treatment values (*P* < 0.05) (Table 1). After the washout, AIR$_g$, ACR$_g$, S$_I$, and the disposition index were not significantly different from those at baseline (Fig. 1).

Despite the fact that the incremental AUC insulin–to–incremental AUC glucose ratio and the incremental AUC C-peptide–to–incremental AUC glucose ratio on day 70 were improved compared with baseline values, the incremental AUC glucose during the MTT returned to baseline levels (Fig. 2*A*, Table 2). Meal incremental AUC glucagon levels were increased after washout compared with treatment levels. Both the incremental AUC intact GIP and intact GLP-1 levels decreased after washout. While incremental AUC intact GLP-1 levels returned to baseline, those for intact GIP decreased but remained elevated relative to baseline after the washout (Table 2).

CONCLUSIONS — We have demonstrated that in subjects with IFG, 6 weeks of treatment with the DPP-4 inhibitor vildagliptin increased insulin and C-peptide responses to intravenous glucose and also increased insulin sensitivity, in-

dicating that β-cell function was greatly improved. This study therefore provides evidence that reducing incretin degradation with a DPP-4 inhibitor is not only effective in modulating glucose metabolism during a meal but also improves β-cell function when no dynamic change in incretin release would be expected to occur, namely, following intravenous administration of glucose.

As expected, postprandial levels of intact GIP and intact GLP-1 increased with inhibition of DDP-4 and were associated with a decrease in postprandial glycemia in subjects with IFG. While insulin and C-peptide levels did not increase during the MTT, when related to the change in glucose levels their release was significantly enhanced, in keeping with improved β-cell responsiveness. Improvements in postprandial glycemia with vildagliptin have been documented previously in subjects with type 2 diabetes (8–11) but not IFG. Subjects with isolated IFG (5) and combined IFG and impaired glucose tolerance (IGT) (14) clearly have defective insulin release, considering their response to intravenous glucose. While it is quite likely that some of the subjects in our study had combined IFG and IGT and others may have had just isolated IFG, because of subject burden a formal oral glucose tolerance test was not performed. However, we do not believe that our findings regarding acute response to intravenous glucose would have been affected.

The improvement in β-cell function in this study may be due to the prolonged effects of DPP-4 inhibition by vildagliptin that resulted in elevated basal levels of active GIP, thereby potentiating the insulin response to intravenous glucose. Another potential mechanism is that reduction in glucose levels reduces stress on the β-cell via reduction of glucotoxicity. However, the latter would seem to be a less likely

explanation because FPG levels in this study were not significantly reduced by treatment. Another possibility is that elevated levels of GIP and GLP-1 have direct beneficial effects on β-cell function that persist for hours but are lost after a period of 2 weeks. Single-dose administration of the drug followed by an intravenous glucose tolerance test might be able to provide further insight into these different possibilities.

Animal data have suggested that GLP-1 may have beneficial effects to increase β-cell mass by reducing apoptosis as well as by differentiating endocrine precursor cells into β-cells, stimulating replication of existing β-cells and forming new islets (15). Chronic inhibition of DPP-4 with sitagliptin for 2–3 months dose-dependently increased pancreatic β-cell mass and improved islet function in the high-fat–fed streptozotocin-injected diabetic mice (16). While the animal data are encouraging, no human data exist to suggest that increasing GLP-1 levels in humans can restore or increase β-cell mass, and this would be very difficult, if not impossible, to assess with current technology. One way to address this is to demonstrate a sustained response to the intervention after withdrawal of the medication. To that end, we performed a short washout and found that the effect of active treatment with vildagliptin to improve β-cell function was not sustained after withdrawal of medication for 2 weeks. However, it is likely that our study design, incorporating a relatively short 6-week treatment period along with the 2-week washout, was insufficient to detect functional changes that would have been compatible with a sustained increase in β-cell mass.

Although the effect of vildagliptin to improve β-cell function and insulin sensitivity was not sustained after washout,

measures of β-cell responsiveness to the meal remained increased relative to baseline values. Despite the higher insulin response, glucose tolerance was not different from that at baseline. It is not clear why this occurred, given that insulin sensitivity and insulin response to intravenous glucose returned to baseline levels, although the nonsignificant increase in glucagon may have played a role.

The effects of GLP-1 on insulin sensitivity are still somewhat controversial. Acute infusions of GLP-1 in healthy humans did not result in improved insulin sensitivity (17). However, chronic infusion of GLP-1 for 6 weeks improved insulin sensitivity and β-cell function (18). In vitro data show that GLP-1 improves insulin-mediated glucose uptake by myotubes but not by adipocytes (19). Treatment of VDF Zucker (*fa/fa*) rats for 3 months with a DPP-4 inhibitor resulted in improved hepatic and peripheral insulin sensitivity (20). Ours is the first study to show improvement in insulin sensitivity in pre-diabetic subjects treated with a DPP-4 inhibitor. The combined effects of vildagliptin to improve both insulin sensitivity and insulin secretion would therefore appear to contribute to its therapeutic effects.

Subjects with IFG have abnormal β-cell function (5,6) and are at risk for progression to diabetes (2–4). In the Hoorn Study, the cumulative incidence of diabetes was 64.5% over 5.75 years in subjects with combined IFG and IGT and 33% over 6.42 years in subjects with isolated IFG (3). Based on the findings of the current study, it is therefore likely that therapeutic approaches with agents that improve β-cell function, such as DPP-4 inhibitors, could offer another option to slow or prevent the progression to diabetes. The definitive answer to this will require a long-term clinical trial.

References
1. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053, 2004
2. Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R: The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. *Diabetes* 52:1475–1484, 2003
3. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. *JAMA* 285:2109–2113, 2001
4. Lyssenko V, Almgren P, Anevski D, Perfekt R, Lahti K, Nissen M, Isomaa B, Forsen B, Homstrom N, Saloranta C, Taskinen MR, Groop L, Tuomi T: Predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. *Diabetes* 54:166–174, 2005
5. Utzschneider KM, Prigeon RL, Carr DB, Hull RL, Tong J, Shofer JB, Retzlaff BM, Knopp RH, Kahn SE: Impact of differences in fasting glucose and glucose tolerance on the hyperbolic relationship between insulin sensitivity and insulin responses. *Diabetes Care* 29:356–362, 2006
6. van Haeften TW, Pimenta W, Mitrakou A, Korytkowski M, Jenssen T, Yki-Jarvinen H, Gerich JE: Disturbances in β-cell function in impaired fasting glycemia. *Diabetes* 51 (Suppl. 1):S265–S270, 2002
7. Godsland IF, Jeffs JA, Johnston DG: Loss of β-cell function as fasting glucose increases in the non-diabetic range. *Diabetologia* 47:1157–1166, 2004
8. Mari A, Sallas WM, He YL, Watson C, Ligueros-Saylan M, Dunning BE, Deacon CF, Holst JJ, Foley JE: Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed β-cell function in patients with type 2 diabetes. *J Clin Endocrinol Metab* 90:4888–4894, 2005
9. Ahren B, Gomis R, Standl E, Mills D, Schweizer A: Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. *Diabetes Care* 27:2874–2880, 2004
10. Ahren B, Landin-Olsson M, Jansson PA, Svensson M, Holmes D, Schweizer A: Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. *J Clin Endocrinol Metab* 89:2078–2084, 2004
11. Ristic S, Byiers S, Foley J, Holmes D: Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. *Diabetes Obes Metab* 7:692–698, 2005
12. Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 236:E667–E677, 1979
13. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D Jr: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
14. Festa A, D'Agostino R Jr, Hanley AJ, Karter AJ, Saad MF, Haffner SM: Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. *Diabetes* 53:1549–1555, 2004
15. Nauck MA, Meier JJ: Glucagon-like peptide 1 and its derivatives in the treatment of diabetes. *Regul Pept* 128:135–148, 2005
16. Mu J, Woods J, Zhou YP, Roy RS, Li Z, Zycband E, Feng Y, Zhu L, Li C, Howard AD, Moller DE, Thornberry NA, Zhang BB: Chronic inhibition of dipeptidyl peptidase-4 with a sitagliptin analog preserves pancreatic β-cell mass and function in a rodent model of type 2 diabetes. *Diabetes* 55:1695–1704, 2006
17. D'Alessio DA, Kahn SE, Leusner CR, Ensinck JW: Glucagon-like peptide 1 enhances glucose tolerance both by stimulation of insulin release and by increasing insulin-independent glucose disposal. *J Clin Invest* 93:2263–2266, 1994
18. Zander M, Madsbad S, Madsen JL, Holst JJ: Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β-cell function in type 2 diabetes: a parallel-group study. *Lancet* 359:824–830, 2002
19. Idris I, Patiag D, Gray S, Donnelly R: Exendin-4 increases insulin sensitivity via a PI-3-kinase-dependent mechanism: contrasting effects of GLP-1. *Biochem Pharmacol* 63:993–996, 2002
20. Pospisilik JA, Stafford SG, Demuth HU, McIntosh CH, Pederson RA: Long-term treatment with dipeptidyl peptidase IV inhibitor improves hepatic and peripheral insulin sensitivity in the VDF Zucker rat: a euglycemic-hyperinsulinemic clamp study. *Diabetes* 51:2677–2683, 2002