Improved Meal-Related β-Cell Function and Insulin Sensitivity by the Dipeptidyl Peptidase-IV Inhibitor Vildagliptin in Metformin-Treated Patients With Type 2 Diabetes Over 1 Year

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OBJECTIVE — To examine the effects of dipeptidyl peptidase-IV (DPP-4) inhibition on meal-related β-cell function and insulin sensitivity over 52 weeks in type 2 diabetes.

RESEARCH DESIGN AND METHODS — In a 12-week core study, placebo ($n = 51$) or vildagliptin ($n = 56$; 50 mg OD) was added to metformin treatment (1.5–3.0 mg/day). A 40-week extension followed in 71 patients. Meal tests were performed at 0, 12, 24, and 52 weeks; glucose, insulin, and C-peptide were evaluated.

RESULTS — In subjects completing 52 weeks with participation in all meal tests ($n = 57$), HbA_{1c} (A1C) decreased in the vildagliptin/metformin group (VM group, $n = 31$) but increased in the placebo/metformin group (PM group, $n = 26$; between-group difference $-1.0 \pm 0.2\%$; $P < 0.001$; baseline of all subjects combined $7.7 \pm 0.1\%$). Also, fasting glucose decreased in the VM group but increased in the PM group (difference -0.9 ± 0.3 mmol/l, $P = 0.016$; baseline 9.8 ± 0.3 mmol/l). Insulin secretion (postmeal suprabasal area under the 0- to 30-min C-peptide curve divided by the 30-min increase in glucose) was increased in the VM group but was reduced in the PM group (difference $+0.011 \pm 0.03$ pmol/l 30 min/mmol/l, $P = 0.018$; baseline 0.036 ± 0.02). Insulin sensitivity during meal ingestion (oral glucose insulin sensitivity) increased in the VM group but was not altered in the PM group (difference $+27 \pm 4$ ml · min^{-1} · m^{-2}, $P = 0.036$; baseline 246 ± 6). Insulin secretion related to insulin sensitivity (adaptation index) increased in the VM group but decreased in the PM group (difference $+3.2 \pm 1.0$, $P = 0.040$; baseline 9.1 ± 0.5). The change in adaptation index correlated to the change in A1C ($r = -0.39$, $P = 0.004$).

CONCLUSIONS — This study presents evidence that DPP-4 inhibition by vildagliptin when added to metformin in type 2 diabetes over 52 weeks improves β-cell function along with improved postmeal insulin sensitivity.

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The enzyme dipeptidyl peptidase-IV (DPP-4) inactivates glucagon-like peptide-1 (GLP-1) (1). Since GLP-1 has antidiabetic actions (2), prevention of its inactivation by DPP-4 inhibition is currently explored as a novel approach for treatment of type 2 diabetes (3). DPP-4 inhibition thereby shows antidiabetic action both in animal models of diabetes (4–6) and in patients with type 2 diabetes (7–9).

One of the DPP-4 inhibitors in clinical development is vildagliptin (previously called LAF237) (10). Vildagliptin has thus been shown to inhibit plasma DPP-4 activity, increase circulating levels of intact GLP-1, and improve glycemic control in diabetic patients (8,9). Although several mechanisms may contribute to the improved metabolic control by DPP-4 inhibition, in comparison to the actions of GLP-1 (2), previous studies have indicated the importance of increased insulin secretion. Thus, a standardized meal test performed before and after 28 days of treatment with the DPP-4 inhibitors NVPDPP728 and vildagliptin showed sustained insulin levels in the presence of reduced circulating glycemia in drug-naïve patients (7,8). Similar results were recently reported in a 52-week study with the DPP-4 inhibitor vildagliptin in metformin-treated patients with type 2 diabetes (9). The aim of the present study was to explore β-cell function and insulin sensitivity in the 52-week study after treatment with vildagliptin in metformin-treated patients (9) by examining insulin secretion as judged from C-peptide data obtained during the standardized meals. Because insulin secretion needs to be assessed in relation to insulin sensitivity (11), we also determined insulin sensitivity after meal ingestion by assessing the oral glucose insulin sensitivity (OGIS) (12).

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Abbreviations: AUC, area under the curve; DPP-4, dipeptidyl peptidase-IV; GLP-1, glucagon-like peptide-1; HOMA-IR, homeostasis model assessment of insulin resistance; OGIS, oral glucose insulin sensitivity; PM, placebo/metformin; VM, vildagliptin/metformin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of patients participating in the study*

	VM	PM
n	31	26
Age (years)	57.5 ± 9.2	55.9 ± 10.0
Sex (number of men)	22	20
BMI (kg/m^2)	29.3 ± 3.6	29.8 ± 3.5
Duration of diabetes (years)	5.6 ± 4.2	5.5 ± 3.7
Duration of previous metformin treatment (months)	28.2 ± 24.6	29.1 ± 29.2
A1C (%)	7.6 ± 0.6	7.8 ± 0.7
Fasting plasma glucose (mmol/l)	9.6 ± 1.7	10.1 ± 1.8

Data are means ± SD unless otherwise indicated.

RESEARCH DESIGN AND METHODS

— This was a multicenter, randomized, double-blind, placebo-controlled study that compared the effects of 52-week treatment with vildagliptin (50 mg once daily) and placebo in patients with type 2 diabetes continuing a stable dosage of metformin (1,500–3,000 mg/day). Male or infertile female patients aged ≥30 years diagnosed with type 2 diabetes at least 6 months before enrollment and treated with a stable dosage of metformin for ≥3 months could be included. Prerandomization A1C while on metformin monotherapy was required to be between 7.0 and 9.5%, inclusive, and baseline BMI was to be between 20 and 35 kg/m^2, inclusive. Patients were excluded if they had a history of type 1 or secondary forms of diabetes, significant diabetes complications, clinically significant cardiovascular abnormalities or other diseases affecting carbohydrate metabolism. Patients were also excluded if they had fasting triglyceride levels >5.1 mmol/l or were treated with any drug considered possibly able to affect results or their interpretation. A total of 107 patients were included in the study. They were randomized to vildagliptin (50 mg once daily)/metformin (VM, $n = 56$) or placebo/metformin (PM, $n = 51$). After a 12-week core study, patients and study sites were asked to continue throughout a 40-week extension period. Forty-two VM and 29 PM patients participated in this extension. The treatment with vildagliptin versus placebo was masked both in the core study and in the extension phase. The patient disposition of the study population and the reasons for drop outs have been reported previously (9). A total of 57 patients completed the 52-week study period with all tests (31 in the VM group and 26 in the PM group). Table 1 shows the clinical characteristics of these patients.

Before randomization and at 12, 24, and 52 weeks after randomization, a standardized meal test was given. The patients thereby fasted overnight and study drug was administered 30 min before consumption of a standardized 465-kcal breakfast meal. The meal was consumed within 15 min, and samples were obtained at specific time points. Here we report the insulin and C-peptide responses to the breakfast ingestion. The clinical results, including A1C data and results on insulinogenic index, along with safety and tolerability data have been published previously (9).

All samples were analyzed at a central laboratory (Medical Research Laboratories International, Zaventem, Belgium) using standardized procedures. Insulin and C-peptide were measured by radioimmunoassay (Boehringer Mannheim, Mannheim, Germany) and glucose was measured with a glucose oxidase technique.

Data handling and statistical analysis

Areas under the concentration curves (AUC) of glucose, insulin, and C-peptide during the standardized meal tests were calculated with the trapezoidal rule. Prehepatic insulin delivery was estimated as the suprabasal 30-min AUC of C-peptide divided by the 30-min increase in circulating glucose. Insulin sensitivity was estimated from a model of glucose clearance, which provides OGIS, a validated index of insulin sensitivity (12). The adaptation index, which gives a figure of the ability of the β-cell to adapt insulin secretion to the ambient insulin sensitivity (13), was calculated as the product between prehepatic insulin delivery and OGIS. We also determined the conventional homeostasis model assessment of insulin resistance (HOMA-IR) from the fasting levels of glucose and insulin (14). Data and results are reported as means ± SE and statistically evaluated with ANOVA; comparisons were performed both within the respective groups before versus after 52 weeks of treatment and between the two groups. The relationship between change in insulin secretion and change in A1C after 52 weeks of treatment was assessed using the Spearman correlation coefficient.

Written informed consent was obtained from all patients and renewed before participation in the extension. The institutional review board/independent ethics committee at each site approved the protocol. The study was conducted with good clinical practice in accordance with the Declaration of Helsinki.

RESULTS

— A1C decreased in the VM group from 7.6 ± 0.1 to 7.1 ± 0.1% ($P = 0.004$) and increased in the PM group from 7.7 ± 0.1 to 8.3 ± 0.2% ($P = 0.012$), the between-group difference being −1.0 ± 0.2% ($P < 0.001$). In 7 of the 31 patients in the VM group, A1C reached the target of 6.5% (23%) after 52 weeks, whereas A1C did not reach 6.5% in any patient in the PM group after 52 weeks. Fasting glucose was reduced after 52 weeks in the VM group from 9.6 ± 0.3 to 9.1 ± 0.3 mmol/l ($P = 0.012$). In the PM group, fasting glucose was 10.1 ± 0.4 mmol/l before treatment and 10.4 ± 0.5 mmol/l after 52 weeks (NS), the between-group difference being −0.9 ± 0.3 mmol/l ($P = 0.016$). In contrast, fasting insulin or C-peptide levels did not change significantly in any of the two groups. Thus in the VM group, fasting insulin was 71 ± 8 pmol/l before treatment and 72 ± 8 pmol/l after 52 weeks (NS) and in the PM group, fasting insulin was 84 ± 10 pmol/l before treatment and 71 ± 6 pmol/l after 52 weeks (NS). Based on fasting glucose and insulin levels in the VM group, HOMA-IR was 30.9 ± 4.2 mmol/l glucose × pmol/l insulin before treatment and 29.1 ± 3.7 mmol/l glucose × pmol/l insulin after treatment (NS) and the corresponding values in the PM group were 39.4 ± 5.7 before treatment and 33.4 ± 3.3 mmol/l glucose × pmol/l insulin after 52 weeks (NS). Further, in the VM group, fasting C-peptide was 0.29 ± 0.02 nmol/l

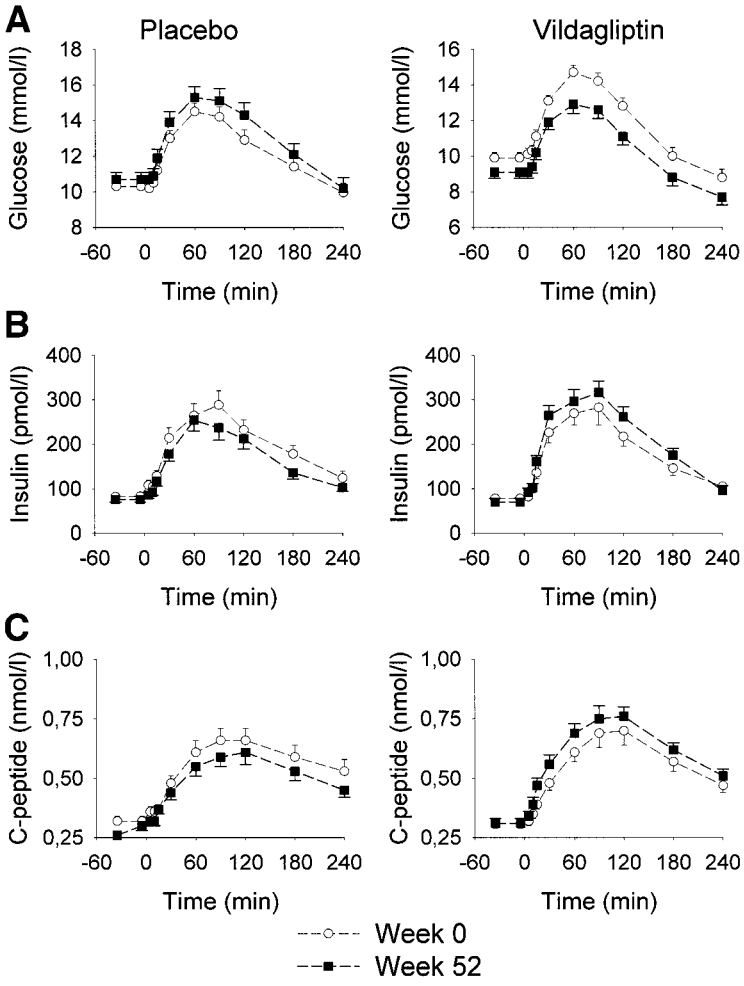

Figure 1—*Plasma levels (means ± SE) of glucose* (A)*, insulin* (B)*, and C-peptide* (C) *before and after ingestion of a standardized 465-kcal breakfast at baseline (week 0) and after 52 weeks of treatment with vildagliptin (50 mg once daily,* n = *31) or placebo* (n = *26) in metformin-treated type 2 diabetic subjects.*

before treatment and 0.31 ± 0.02 nmol/l after 52 weeks (NS) and in the PM group, fasting C-peptide was 0.30 ± 0.02 nmol/l before treatment and 0.28 ± 0.02 nmol/l after 52 weeks (NS).

Glucose, insulin, and C-peptide responses to standardized breakfast

Figure 1 shows the glucose, insulin, and C-peptide responses during the standardized breakfast at baseline and after 52 weeks of treatment in the VM and PM groups, respectively. $AUC_{glucose}$ was reduced in the VM group from 557 ± 68 to 372 ± 77 mmol/l 240 min after 52 weeks ($P < 0.001$), whereas $AUC_{glucose}$ was increased in the PM group from 539 ± 79 to 610 ± 89 mmol/l 240 min ($P < 0.001$). The between-group difference in $AUC_{glucose}$ was −256 ± 23 mmol/l 240 min ($P < 0.001$). $AUC_{insulin}$ was increased in the VM group (from 26.2 ± 2.8 to 30.3 ± 2.8 pmol/l 240 min, $P = 0.016$) but reduced in the PM group (from 28.7 ± 3.6 to 24.3 ± 3.0 pmol/l 240 min, $P = 0.036$); the between-group difference was 8.5 ± 2.6 pmol/l 240 min ($P = 0.018$). Similarly, $AUC_{C\text{-}peptide}$ was increased in the VM group (from 60.8 ± 5.4 to 71.6 ± 5.6 pmol/l 240 min, $P = 0.015$) and reduced in the PM group (from 59.6 ± 8.0 to 40.2 ± 4.9 pmol/l 240 min, $P = 0.021$); the between-group difference was 30.2 ± 7.7 pmol/l 240 min ($P = 0.019$).

Meal-related β-cell function, insulin sensitivity, and adaptation index

Figure 2 shows meal-related β-cell function, insulin sensitivity, and adaptation index at baseline and after 12, 24, and 52 weeks of treatment with VM or PM. Insulin secretion from the suprabasal 30-min AUC of C-peptide after breakfast divided by the 30-min increase in glucose was increased in the VM group from 0.036 ± 0.02 to 0.042 ± 0.003 (pmol/l 30 min)/(mmol/l) after 52 weeks ($P = 0.012$) but decreased in the PM group from 0.037 ± 0.002 to 0.032 ± 0.002 (pmol/l 30 min)/(mmol/l) ($P = 0.036$). The between-group difference in 52-week change in insulin secretion was 0.011 ± 0.03 (pmol/l 30 min)/(mmol/l) ($P = 0.018$). Also, the OGIS was increased in the VM group (from 248 ± 10 to 279 ± 9 ml · min^{-1} · m^{-2} after 52 weeks ($P = 0.012$) but was not significantly altered in the PM group (from 242 ± 7 to 237 ± 8 ml · min^{-1} · m^{-2}, NS). The between-group difference in 52-week change in insulin sensitivity was 27 ± 4 ml · min^{-1} · m^{-2} ($P = 0.036$). Adaptation index (insulin secretion × insulin sensitivity) increased in the VM group from 9.3 ± 0.6 to 11.4 ± 0.8 after 52 weeks ($P = 0.003$) and decreased in the PM group from 8.8 ± 0.5 to 7.3 ± 0.6 after 52 weeks ($P = 0.017$); the between-group difference in 52-week change in adaptation index was 3.2 ± 0.1 ($P = 0.040$). The change in adaptation index across the entire study group showed a negative correlation with change in A1C ($r = -0.39$, $P = 0.04$; Fig. 2), i.e., the highest increase in insulin secretion showed the highest reduction in A1C.

CONCLUSIONS — We have previously shown that when added to metformin treatment, vildagliptin (previously LAF237) is effective at improving glycemic control for 52 weeks in patients with type 2 diabetes in association with favorable tolerability and safety (9). Since DPP-4 inhibition prevents the inactivation of GLP-1, enhanced prandial levels of active GLP-1 during DPP-4 inhibition are seen in subjects with type 2 diabetes (8). This would suggest that effects of GLP-1 might underlie the antidiabetic actions of DPP-4 inhibition. However, the mechanisms of the improved glycemic control after long-term DPP-4 inhibition remain to be established. In this study, we explored whether vildagliptin during 52-week treatment, when added to metformin, affects β-cell function and insulin sensitivity.

We previously demonstrated that the so-called insulinogenic index (relating

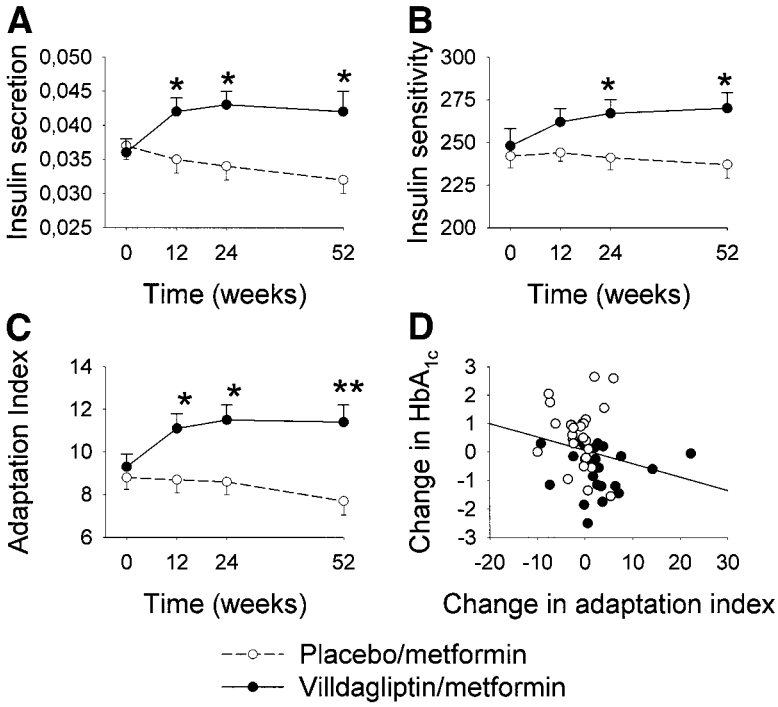

Figure 2—*Means ± SE time courses of insulin secretion (pmol/l 30 min)/(mmol/l) (*A*), dynamic insulin sensitivity (OGIS, ml · min^{-1} · m^{-2}) (*B*), and adaptation index (nmol$_{C\text{-}peptide}$ · mmol$_{glucose}^{-1}$ · ml^{-1} · m^{-2}) (*C*) at baseline (week 0) and after 12, 24, and 52 weeks of treatment with vildagliptin (50 mg once daily, n = 31) or placebo (n = 26) in metformin-treated type 2 diabetic subjects.* D: *Regression between change in adaptation index and change in A1C after 52 weeks of treatment with vildagliptin (●) or placebo (○). Asterisks indicate probability level of random difference between groups: *P < 0.05, **P < 0.01.*

the increase in insulin to the increase in glucose after meal ingestion) was improved after 52-week treatment with vildagliptin in metformin-treated patients with type 2 diabetes (9). In the present study, we proceeded by estimating insulin secretion by determining the C-peptide responses to meal ingestion in relation to the increase in glucose. We found that meal-related insulin secretion was augmented in the VM group compared with the PM group. The most pronounced action of vildagliptin was seen during the first 12 weeks of treatment. However, the increase in insulin secretion was sustained throughout the study period. This suggests that vildagliptin improves β-cell function when added to metformin in subjects with type 2 diabetes. This would be similar as the action of GLP-1 to increase insulin secretion under a variety of conditions (2). An important fact that has been discovered during recent years is that insulin secretion has to be judged in relation to insulin sensitivity because there is an inverse relation between these variables (11). To accomplish this, we also evaluated insulin sensitivity by estimating glucose clearance in relation to the prevailing insulin levels during the meal challenge. This was performed by calculating the OGIS index of insulin sensitivity (12). Its validity has been confirmed both against the hyperinsulinemic-euglycemic clamp in healthy, obese, and type 2 diabetic subjects (12) and against insulin sensitivity assessed with the intravenous glucose test (15,16). OGIS has already been used in several other studies (17,18). In the present study, OGIS was significantly increased in the VM group, showing improved insulin sensitivity by the DPP-4 inhibition. It has previously been proposed that short-term GLP-1 administration does not improve insulin sensitivity in healthy subjects (19) or in subjects with type 2 diabetes (20). On the other hand, long-term (6 weeks) subcutaneous administration of GLP-1 has been shown to enhance insulin sensitivity as judged by the hyperinsulinemic-euglycemic clamp technique in subjects with type 2 diabetes along with the improved glucose metabolism (21). Similarly, it has also been shown that long-term (12 weeks) DPP-4 inhibition improves insulin sensitivity in a diabetes model in rats (22). Our findings suggest that DPP-4 inhibition improves insulin sensitivity after long-term treatment in patients with type 2 diabetes. However, it cannot be ruled out that this may be an indirect action through improvement of the glycemia. It may be of interest that in spite of improved OGIS in the VM group, fasting insulin or HOMA-IR did not change significantly. This may suggest that DPP-4 inhibition more readily improves the dynamic insulin sensitivity in relation to meal intake than fasting (static) insulin sensitivity.

Considering further the inverse relation between insulin sensitivity and insulin secretion (11), an index relating the changes in posthepatic insulin levels to insulin sensitivity by multiplying the two variables was introduced by Bergman et al. (23) in the early 1980s and later explored in detail by Kahn et al. (24). This so-called disposition index is a valid index to understand the relation of the posthepatic insulin response to insulin sensitivity and has been demonstrated to be reduced in diabetic subjects (11). However, a more appropriate descriptor characterizing the relation between insulin secretion and insulin sensitivity requires a more direct measurement of prehepatic insulin secretion based on C-peptide. We have previously introduced such an index, called the adaptation index, by multiplying the sensitivity of glucose of C-peptide response by insulin sensitivity (13). The adaptation index thus displays the direct adjustment of the β-cell function to changes of insulin sensitivity and has been shown to be reduced in subjects with impaired glucose tolerance (13). Here we show that the adaptation index was augmented in the VM group when compared with the PM group, suggesting that vildagliptin augments β-cell function independent from changes in insulin sensitivity.

In conclusion, this study demonstrates amelioration of the β-cell function in type 2 diabetic subjects after vildagliptin. The main effect was observed already within the initial 12-week treatment and was sustained throughout the 52-week study period. The correspondingly ameliorated glucose tolerance and the correlation between change in adaptation index and change in A1C after 52 weeks

suggests that an important mechanism underlying the improved glycemic control following 52-week treatment with vildagliptin is improved action of the β-cell.

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References

1. Mentlein R: Dipeptidyl-peptidase IV (CD26): role in the inactivation of regulatory peptides. *Regul Pept* 85:9–24, 1999
2. Holst JJ, Gromada J: Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol* 287:E199–E206, 2004
3. Deacon CF, Ahrén B, Holst JJ: Inhibitors of dipeptidyl peptidase IV: a novel approach to prevention and treatment of type 2 diabetes. *Expert Opin Investig Drugs* 13:1091–1102, 2004
4. Pedersen RA, White HA, Schlenzig D, Pauly RP, McIntosh CHS, Dermuth HU: Improved glucose tolerance in Zucker fatty rats by oral administration of the dipeptidyl peptidase IV inhibitor isoleucine thiazolidide. *Diabetes* 47:1253–1258, 1998
5. Balkan B, Kwasnik L, Miserendino R, Holst JJ, Li X: Inhibition of dipeptidyl peptidase IV with NVP DPP728 increases plasma GLP-1 (7–36 amide) concentrations and improves oral glucose tolerance in obese Zucker rats. *Diabetologia* 42: 1324–1331, 1999
6. Kvist Reimer M, Holst JJ, Ahrén B: Long-term inhibition of dipeptidyl peptidase IV improves glucose tolerance and preserves islet function in mice. *Eur J Endocrinol* 146:717–727, 2002
7. Ahrén B, Simonsson E, Larsson H, Landin-Olsson M, Torgeirsson H, Jansson PA, Sandqvist M, Båvenholm P, Efendic S, Eriksson JW, Dickinson S, Holmes D: Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. *Diabetes Care* 25:869–875, 2002
8. Ahrén 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
9. Ahrén 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. Villhauer EB, Brinkman JA, Naderi GB, Burkey BF, Dunning BE, Prasad K, Mangold BL, Russell ME, Hughes TE: 1-[[(3-hydroxy-1-adamantyl) amino] acetyl]-2-cyano-(S)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. *J Med Chem* 46:2774–2789,2003
11. Ahrén B, Pacini G: Importance of quantifying insulin secretion in relation to insulin sensitivity to accurately assess beta cell function in clinical studies (Review). *Eur J Endocrinol* 150:97–104, 2004
12. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ: A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. *Diabetes Care* 24: 539–548, 2001
13. Ahrén B, Pacini G: Impaired adaptation of first-phase insulin secretion in postmenopausal women with glucose intolerance. *Am J Physiol* 273:E701–E707, 1997
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
15. Ludvik B, Waldhäusl W, Prager R, Kautzky-Willer A, Pacini G: Mode of action of ipomoea batatas (Caiapo) in type 2 diabetic patients. *Metabolism* 52:875–880, 2003
16. Kautzky-Willer A, Krssak M, Winzer C, Pacini G, Tura A, Farhan S, Wagner O, Brabant G, Horn R, Stingl H, Schneider B, Waldhausl W, Roden M: Increased intramyocellular lipid concentration identifies impaired glucose metabolism in women with previous gestational diabetes. *Diabetes* 52:245–251, 2003
17. Rask E, Olsson T, Söderberg S, Holst JJ, Tura A, Pacini G, Ahrén B: Insulin secretion and incretin hormones after oral glucose in non-obese subjects with impaired glucose tolerance. *Metabolism* 53:624–631, 2004
18. Kanauchi M, Yamano S, Kanauchi K, Saito Y: Homeostasis model assessment of insulin resistance, quantitative insulin sensitivity check index, and oral glucose insulin sensitivity index in nonobese nondiabetic subjects with high-normal blood pressure. *J Clin Endocrinol Metab* 88:3444–3446, 2003
19. Ørskov L, Holst JJ, Moller J, Ørskov C, Moller N, Alberti KG, Schmitz O: GLP-1 does not acutely affect insulin sensitivity in healthy man. *Diabetologia* 39:1227–1232, 1996
20. Ahrén B, Larsson H, Holst JJ: Effects of glucagon-like peptide-1 on islet function and insulin sensitivity in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 82:473–478, 1997
21. Zander M, Madsbad S, Madsen JL, Holst JJ: Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 359:824–830, 2002
22. Pospisilik JA, Stafford SG, Demuth Hul, McIntosh CHS, Pederson RA: Long-term treatment with dipeptidyl peptidase IV inhibitor improves hepatic peripheral insulin sensitivity in the VDF Zucker rat: a euglycemic-hyperinsulinemic clamp study. *Diabetes* 51:2677–2683, 2003
23. Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man. *J Clin Invest* 68: 1456–1467, 1981
24. Kahn SE, Prigeon ERL, McCulloch DK, EJ Boyko, RN Bergman, MW Schwartz, JL Neifing, WK Ward, JC Beard, JP Palmer, et al.: Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993