Changes in Prandial Glucagon Levels After a 2-Year Treatment With Vildagliptin or Glimepiride in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy

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OBJECTIVE — To determine if the dipeptidyl peptidase-4 inhibitor vildagliptin more effectively inhibits glucagon levels than the sulfonylurea glimepiride during a meal.

RESEARCH DESIGN AND METHODS — Glucagon responses to a standard meal were measured at baseline and study end point (mean 1.8 years) in a trial evaluating add-on therapy to metformin with 50 mg vildagliptin b.i.d. compared with glimepiride up to 6 mg q.d. in type 2 diabetes (baseline A1C $7.3 \pm 0.6\%$).

RESULTS — A1C and prandial glucose area under the curve $(AUC)_{0-2\ h}$ were reduced similarly in both groups, whereas prandial insulin $AUC_{0-2\ h}$ increased to a greater extent by glimepiride. Prandial glucagon $AUC_{0-2\ h}$ (baseline 66.6 ± 2.3 pmol$\cdot$h$^{-1}\cdot$l^{-1}) decreased by 3.4 ± 1.6 pmol$\cdot$h$^{-1}\cdot$l^{-1} by vildagliptin ($n = 137$) and increased by 3.8 ± 1.7 pmol$\cdot$h$^{-1}\cdot$l^{-1} by glimepiride ($n = 121$). The between-group difference was 7.3 ± 2.1 pmol$\cdot$h$^{-1}\cdot$l^{-1} ($P < 0.001$).

CONCLUSIONS — Vildagliptin therapy but not glimepiride improves postprandial α-cell function, which persists for at least 2 years.

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G lucagon levels are increased in type 2 diabetes because of impaired glucose-mediated suppression of glucagon secretion resulting in increased hepatic glucose output with subsequent hyperglycemia (1). Improved glycemia by the dipeptidyl peptidase-4 inhibitor, vildagliptin (2), is mediated primarily by improved β- and α-cell sensitivity to glucose (3). As an add-on to metformin, vildagliptin displays equal efficacy as glimepiride, with the added benefits of a much lower risk of hypoglycemia and no weight gain (4). Here we report prandial assessments of glucagon levels and insulin secretion rates after up to ~2 years of therapy with the two drugs.

RESEARCH DESIGN AND METHODS — The study was an extension to 2 years of a previously described study (4). Standard meal challenge was performed in selected centers at last treatment visit after administration of a morning dose of metformin plus 50 mg vildagliptin or up to 6 mg glimepiride (mean treatment period 1.8 years). Doses were selected to achieve comparable improvements in glycemia. After an overnight fast, a mixed meal was served (orange juice [180 ml], two slices [60 g] of white bread, 30 g jam, 15 g butter or margarine, 120 ml whole milk [3–4% fat] or equivalent amount of cheese plus 120 ml water, and, if desired, decaffeinated coffee or tea; 510 kcal, with 50% from carbohydrate, 38% from fat, and 12% from protein). Blood samples were taken before the meal and at 15, 30, 60, 90, 120, 180, and 240 min.

Analytical determinations
Plasma glucose concentration was determined by the glucose oxidase method (Beckman Glucose Analyzer II; Beckman Instruments, Fullerton, CA). Plasma insulin, C-peptide, and glucagon concentrations were determined by radioimmunoassay (Diagnostics Products, Los Angeles, CA). Plasma intact glucagon-like peptide (GLP)-1 concentration was measured by ELISA using an NH_2-terminal–specific antibody (Linco Research, St. Charles, MO) by Novartis.

Calculations
Insulin secretory rate was determined as described previously (5). The absolute and incremental/decremental areas under the curve (AUCs) for time 0–2 h after the meal were calculated using the trapezoidal method. End point changes from baseline were assessed using ANCOVA.

Ethics
The study was conducted in accordance with the Declaration of Helsinki. It was reviewed by an independent ethics committee or institutional review board for each center. Written informed consent was obtained from each subject.

RESULTS — Baseline characteristics were as follows: patient demographics of the subpopulation who participated in the meal challenge ($n = 259$) were essentially the same as reported previously (4). Mean baseline A1C was $7.3 \pm 0.6\%$.

A1C, glucose, and insulin
At the follow-up meal test (up to 2 years after start; mean 1.8 years), A1C was reduced by $-0.1 \pm 0.9\%$ in the vildagliptin group ($n = 137$) versus $-0.2 \pm 0.8\%$ in the glimepiride group ($n = 121$). Prandial glucose $AUC_{0-2\,h}$ was similarly reduced in both groups (-1.7 mmol $\cdot$ h$^{-1} \cdot$ l^{-1} for vildagliptin vs. -2.1 mmol $\cdot$ h$^{-1} \cdot$ l^{-1} for glimepiride), whereas prandial insulin 1 $AUC_{0-2\,h}$ increased to a greater extent in the glimepiride group (33 ± 18 pmol $\cdot$ h$^{-1} \cdot$ l^{-1} for vildagliptin vs. 91 ± 19 pmol $\cdot$ h$^{-1} \cdot$ l^{-1} for glimepiride) ($P = 0.017$).

Glucagon, GLP-1, and insulin secretion
Prandial glucagon $AUC_{0-2\,h}$ decreased from baseline with vildagliptin treatment but increased with glimepiride (-3.4 ± 1.6 pmol $\cdot$ h$^{-1} \cdot$ l^{-1} for vildagliptin vs. 3.8 ± 1.7 pmol $\cdot$ h$^{-1} \cdot$ l^{-1} for glimepiride; $P < 0.001$; Fig. 1*A*). Prandial intact GLP-1 $AUC_{0-2\,h}$ increased in both groups but was much larger after vildagliptin (18.8 ± 1.8 pmol $\cdot$ h$^{-1} \cdot$ l^{-1} for vildagliptin vs. 1.6 ± 1.7 pmol $\cdot$ h$^{-1} \cdot$ l^{-1} for glimepiride; Fig. 1*B*). Insulin secretion rate relative to glucose ($0-2$ h) increased in both groups (4.3 ± 0.9 pmol/min/m^2/mmol/l for glimepiride vs. 1.6 ± 0.9 pmol/min/m^2/mmol/l for vildagliptin; $P = 0.022$; Fig. 1*C*). Prandial insulin-to-glucagon ratio ($AUC_{0-2\,h}$ for insulin/$AUC_{0-2\,h}$ for glucagon) changed by -1.1 ± 9.3 (baseline 7.4 ± 0.4) pmol insulin/pmol glucagon in the vildagliptin group versus -7.3 ± 9.8 (baseline 7.1 ± 0.4) pmol insulin/pmol glucagon in the glimepiride group ($P = 0.62$).

Insulin resistance
Fasting insulin (15.2 ± 1.6 pmol/l for glimepiride vs. 5.7 ± 1.6 pmol/l for vildagliptin; $P < 0.001$) and HOMA-IR (0.11 ± 0.10 for vildagliptin vs. 0.63 ± 0.10 for glimepiride; $P < 0.001$; Fig. 1*D*) increased in both treatment groups with larger increases with glimepiride.

CONCLUSIONS — Vildagliptin reduces glucagon levels after a standard mixed meal in patients with type 2 diabetes who are treated with metformin, as
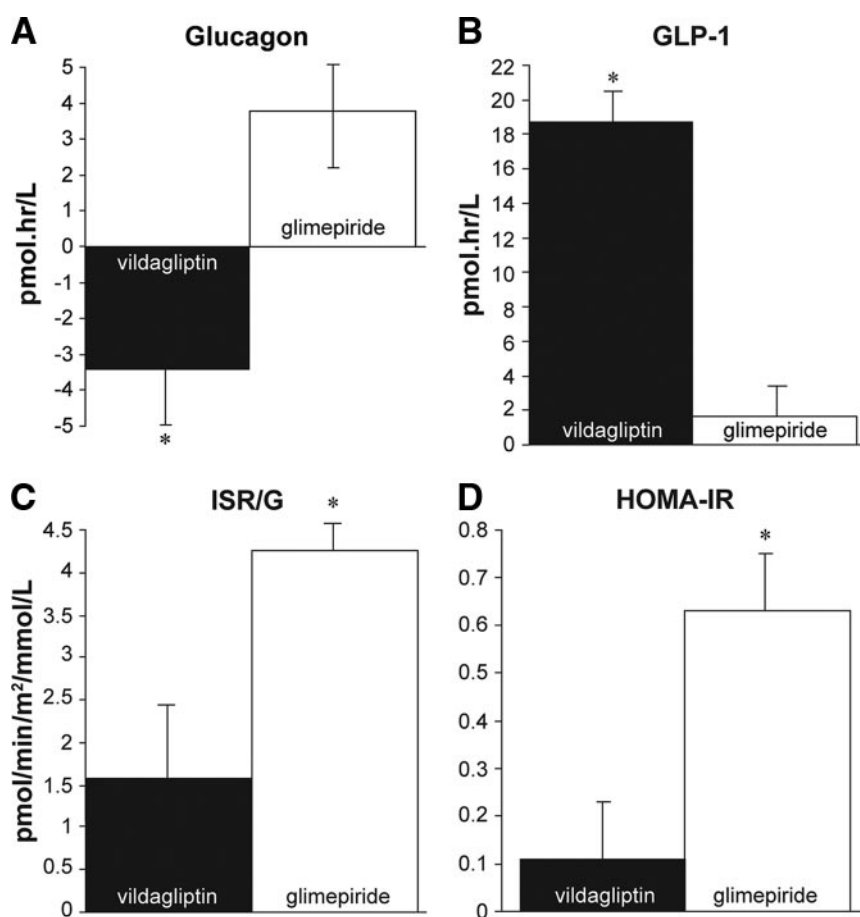

Figure 1—*Changes in prandial glucagon $AUC_{0-2\,h}$, prandial GLP-1 $AUC_{2\,h}$, insulin secretory rate relative to glucose (ISR/G), and HOMA-IR after up to a 2-year (mean 1.8 years) add-on treatment with vildagliptin (50 mg b.i.d.; n = 137) or glimepiride (up to 6 mg; n = 121) in patients with type 2 diabetes inadequately controlled with prior metformin therapy. Means $\pm$ SD are shown. The asterisk indicates P < 0.001 (A), P < 0.001 (B), P = 0.022 (C), and P < 0.001 (D) between the groups.*

was previously demonstrated in individuals with IGT (6), IFG (7), and type 1 diabetes (8). This effect appears to be the result of a GLP-1–induced improvement in glucose sensitivity of the α-cells (3,9). In contrast, glimepiride increases glucagon levels, which may be the result of attenuation of the glucose sensitivity of the α-cells with uncoupling of glucose dependency (10).

With respect to β-cell function, vildagliptin increases glucose sensitivity (11), whereas indirect data suggest that sulfonylurea uncouples the glucose dependency of the β-cells, which attenuates glucose sensitivity (10). In this study, this resulted in increased insulin secretion by both treatments, although vildagliptin did not increase the insulin secretion rate as much as glimepiride. The greater insulin secretion rate in the glimepiride group was balanced by less insulin resistance in the vildagliptin

group, as reflected by HOMA-IR and lower postprandial glucagon levels resulting in similar glucose levels.

In summary, prandial glucagon is increased by glimepiride but reduced by vildagliptin. Hence, vildagliptin effectively targets glucagon secretion in the treatment of diabetes. This together with the lesser increase in insulin by vildagliptin than by glimepiride may provide a pathophysiological explanation for the observation that vildagliptin's effect of reducing A1C levels below 7% is associated with much less hypoglycemia than glimepiride while being associated with the same A1C reduction (4).

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