Changes in Prandial Glucagon Levels after 2-year Treatment with Vildagliptin or Glimepiride in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin Monotherapy

Short title: Glucagon after vildagliptin versus glimepiride

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Clinical Trial Registry No.: NCT00106340; ClinicalTrials.gov.

Submitted 8 October 2009 and accepted 27 December 2009.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
Objective — To determine if the dipeptidyl peptidase 4 inhibitor vildagliptin more effectively than the sulfonylurea glimepiride inhibits glucagon levels during meal.

Research design and methods — Glucagon responses to a standard meal were measured at baseline and study endpoint (mean 1.8 years) in a trial evaluating add-on therapy to metformin with vildagliptin 50 mg bid compared to glimepiride up to 6 mg qd in type 2 diabetes (baseline HbA1c 7.3±0.6%).

Results — HbA1c and prandial glucose AUC0-2h were reduced similarly in both groups, while prandial insulin AUC0-2h increased to a greater extent by glimepiride. Prandial glucagon AUC0–2h (baseline 66.6±2.3 pmol·h/l) decreased by 3.4±1.6 pmol·h/l by vildagliptin group (n=137) and increased by 3.8±1.7 pmol·h/l by glimepiride group (n=121). The between-group difference was 7.3±2.1 pmol·h/l (p<0.001).

Conclusion — Vildagliptin therapy but not glimepiride improves post-prandial α-cell function, which persists for at least 2 years.
Glucagon levels are increased in type 2 diabetes due to 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 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 approximately 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 morning dose of metformin plus vildagliptin 50 mg bid or glimepiride up to 6 mg (mean treatment period 1.8 years). Doses were selected to achieve comparable improvements in glycemia. After an overnight fast, a mixed meal (orange juice (180 ml), 2 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) was served. Blood samples were prior to 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 Inc., Fullerton, CA). Plasma insulin, C-peptide, and glucagon concentrations were determined by radioimmunoassay (Diagnostics Products, Los Angeles, CA). Plasma intact GLP-1 concentration was measured by ELISA using an N-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 AUCs for time 0–2 hours after meal were calculated using the trapezoidal method. Endpoint changes from baseline were assessed using analysis of covariance (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 centre. Written informed consent was obtained from each subject.

RESULTS
Baseline characteristics: Patient demographics of the subpopulation who participated in the meal challenge (n=259) were essentially the same as reported previously (4). Mean baseline HbA1c was 7.3±0.6%.

HbA1c, glucose and insulin: At the follow-up meal test (up to 2 years after start; mean 1.8 years), HbA1c was reduced by -0.1±0.9% in the vildagliptin group (n=137) vs. -0.2±0.8% after glimepiride (n=121). Prandial glucose AUC0-2h was similarly reduced in both groups (-1.7 mmol·h/l for vildagliptin vs. -2.1 mmol·h/l for glimepiride), whereas prandial insulin AUC0-2h increased to a greater extent in the glimepiride group (33±18 pmol·h/l for vildagliptin vs. 91±19 pmol·h/l for glimepiride) (p=0.017).

Glucagon, GLP-1 and insulin secretion: Prandial glucagon AUC0-2h decreased from baseline with vildagliptin treatment but increased with glimepiride (-3.4±1.6 pmol·h/l for vildagliptin vs. +3.8±1.7 pmol·h/l for glimepiride; p<0.001; Fig. 1a). Prandial intact GLP-1 AUC0-2h increased in both groups but much larger after vildagliptin (18.8±1.8 pmol·h/l for vildagliptin vs. 1.6±1.7 pmol·h/l for glimepiride; Fig. 1b). Insulin secretion
rate relative to glucose (0–2 h) increased in both groups (4.3±0.9 pmol/min/m²/mmol/l for glimepiride vs. 1.6±0.9 pmol/min/m²/mmol/l for vildagliptin; *p*=0.022; Fig. 1c). Prandial insulin to glucagon ratio (AUC0-2h for insulin/AUC0-2h for glucagon) changed by -1.1±9.3 (baseline 7.4±0.4) pmol insulin/pmol glucagon in the vildagliptin group vs. -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. 1d) increased in both treatment groups with larger increases with glimepiride.

**DISCUSSION**

Vildagliptin reduces glucagon levels following a standard mixed meal in patients with type 2 diabetes who are treated with metformin, as 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 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 HbA1c levels below 7% is associated with much less hypoglycemia than glimepiride while being associated with the same HbA1c reduction (4).

**ACKNOWLEDGEMENTS**

The authors gratefully acknowledge the investigators, those who participated in any part of the study (listed previously in Ferrannini et al, 2009), staff at the 402 participating sites, and the editorial assistance of Mr. Gali Venkateswara Prasad and Ms. Shivali Arora, PhD (both Novartis, India). This study was funded by Novartis Pharmaceuticals. DRM is a Senior Investigator of the National Institute of Health Research (NIHR), UK, and acknowledges NIHR funding support.

**Disclosure:** E. F. has received consulting fees from Novartis Pharmaceuticals. V. F. has received funding for research and consulting/speaking for Novartis as well as from other manufacturers of drugs in this class, including Merck, NovoNordisk, Eli Lilly, Takeda and Glaxo. B. Z. has received research support and consulting fees from Novartis Pharmaceuticals. B. A. has received funding and consulting fees from Novartis Pharmaceuticals. D. M. has received consulting fees from Novartis as well as from other manufacturers of drugs in this class, including NovoNordisk and MSD. He has also received lecturing honoraria from Eli Lilly and NovoNordisk. J.F. and S. D. are employees of Novartis Pharmaceuticals.
REFERENCES


Figure legends

**Figure 1.** Changes in prandial glucagon AUC$_0$-2h, prandial GLP-1 AUC$_{2h}$, insulin secretory rate relative to glucose (ISR/G) and HOMA-IR after up to 2 year (mean 1.8 years) add-on treatment with vildagliptin (50 mg bid; n=137) or glimepiride (up to 6 mg; n=121) in patients with type 2 diabetes inadequately controlled with prior metformin therapy. Means±SD are shown. Asterisks indicate $p<0.001$ (Fig. 1a), $p<0.001$ (Fig. 1b), $p=0.022$ (Fig. 1c) and $p<0.001$ (Fig. 1d) between the groups.