DIABETES TECHNOLOGY & THERAPEUTICS
Volume 14, Number 6, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2011.0278

DTT
Diabetes Technology & Therapeutics

ORIGINAL ARTICLE

Vildagliptin Added to Metformin on β-Cell Function After a Euglycemic Hyperinsulinemic and Hyperglycemic Clamp in Type 2 Diabetes Patients

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Abstract

Background: This study evaluated the effect of vildagliptin + metformin on glycemic control and β-cell function in type 2 diabetes patients.
Subjects and Methods: One hundred seventy-one type 2 diabetes patients, naive to antidiabetes therapy and with poor glycemic control, were instructed to take metformin for 8 ± 2 months up to a mean dosage of 2,500 ± 500 mg/day; then they were randomly assigned to add vildaglipin 50 mg twice a day or placebo for 12 months. We evaluated at 3, 6, 9, and 12 months: body mass index, glycemic control, fasting plasma insulin, homeostasis model assessment insulin resistance index (HOMA-IR), homeostasis model assessment β-cell function index (HOMA-β), fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, C-peptide, glucagon, adiponectin, and high-sensitivity C-reactive protein. Before and at 12 months after the addition of vildagliptin, patients underwent a combined euglycemic hyperinsulinemic and hyperglycemic clamp, with subsequent arginine stimulation, to assess insulin sensitivity and insulin secretion.
Results: After 12 months of treatment, vildagliptin + metformin gave a better decrease of body weight, glycemic control, HOMA-IR, and glucagon and a better increase of HOMA-β compared with placebo + metformin. Regarding the measures of β-cell function, treatment-induced changes in M-value, first- and second-phase C-peptide response to glucose, and C-peptide response to arginine were significantly higher in the vildagliptin+ metformin group compared with the placebo + metformin group.
Conclusion: The addition of vildagliptin to metformin gave a better improvement of glycemic control, insulin resistance, and β-cell function compared with metformin alone.

Introduction

Recent breakthroughs in the understanding of incretin-based therapies have provided additional options for the treatment of type 2 diabetes mellitus. Incretins are secreted by intestinal L-cells, mainly in response to food intake; the most important incretin, glucagon-like peptide-1 (GLP-1), has several actions, including stimulation of insulin secretion and reduction of glucagon secretion, both in a glucose-dependent manner, resulting in reduced hepatic glucose production.[1–3] GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), which limits GLP-1's time of action in the blood.[4] Actually, two classes of drugs based on the incretin system are available: GLP-1 receptor agonists, such as exenatide and liraglutide, resistant to DPP-4 cleavage,[5] and DPP-4 inhibitors, which delay endogenous degradation of GLP-1 inhibiting DPP-4.[6] DPP-4 inhibitors that are currently available include sitagliptin, vildagliptin, saxagliptin, and linagliptin; in particular, vildagliptin is licensed at the recommended dose of 50 mg twice daily in combination with either metformin or pioglitazone and at the recommended dose of 50 mg once daily in combination with sulfonylureas in patients poorly controlled on the maximum doses of these drugs.[6] Compared with the other DPP-4 inhibitors, vildagliptin is actually the only one that proved to be effective and well tolerated in type 2 diabetes patients ≥75 years, as reported by Schweizer et al.[7]

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On the other hand, metformin is the most commonly used oral antihyperglycemic agent, both as monotherapy and in combination with other agents such as sulfonylureas,[8] thiazolidinediones,[9,10] GLP-1 receptor agonist,[11,12] or DPP-4 inhibitors.[13,14] Metformin reduces elevated blood glucose levels by reducing hepatic glucose output and also by enhancing peripheral glucose uptake, improving insulin resistance.[15]

To better understand the mechanism of action of vildagliptin, we wanted to estimate the effect of vildagliptin compared with placebo added to metformin not only on glycemic control and insulin resistance, but also its effect on insulin sensitivity and insulin secretion after an euglycemic hyperinsulinemic and hyperglycemic clamp with subsequent arginine stimulation.

Subjects and Methods

Study design

This multicenter, randomized, double-blind, placebo-controlled study was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy, at the Diabetes Care Unit, S. Carlo Hospital, Milan, Italy, at the Hospital Center of Diabetes, Sant'Angelo Lodigiano, Lodi, Italy, and at the Aging and Kidney Diseases, "G. Descovich" Atherosclerosis Study Center, University of Bologna, Bologna, Italy.

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki and its amendments. Suitable subjects, identified from review of case notes and/or computerized clinic registers, were contacted personally or by telephone. All eligible candidates had to provide signed informed consent before enrolling in the study.

Patients

We enrolled 171 white type 2 diabetes patients >18 years of age of either sex (Table 1) according to the European Society of Cardiology and European Association for the Study of Diabetes guidelines criteria,[16] naive to antidiabetes therapy and with poor glycemic control, expressed as glycated hemoglobin (HbA_{1c}) level >8.0%, but <11%, who were overweight (body mass index [BMI] $\geq 25\,kg/m^2$ but $<30\,kg/m^2$).

Patients were excluded if they had a history of ketoacidosis or had rapidly progressive diabetic retinopathy (defined by the presence of cotton wool spots on the retina on ophthalmic examination), nephropathy (defined by onset of albumin excretion >300 mg/24 h or an albumin excretion rate >200 μg/min over a 6-month period), or neuropathy (diagnosed both clinically and with electrophysiologic testing), impaired hepatic function (defined as plasma aminotransferase and/or γ-glutamyltransferase level three times higher than the upper limit of normal for age and sex), impaired renal function (defined as serum creatinine level higher than the upper limit of normal for age and sex), or severe anemia (defined as hemoglobin level <8 g/dL). Patients with serious cardiovascular disease, New York Heart Association class I–IV congestive heart failure, or a history of myocardial infarction or stroke or cerebrovascular conditions (ischemic stroke, hemorrhagic stroke, or transient ischemic attack) within 6 months before study enrollment also were excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

Table 1. Subjects' Characteristics Before Metformin Therapy and at Randomization

	Before metformin	*At randomization*
n	171	167
Sex (male/female)	86/85	85/82
Age (years)	53.7±7.9	53.2±7.8
Smoking status (male/female)	20/22	19/21
Diabetes duration (months)	6.3±3.9	6.2±3.8
Height (m)	1.67±0.05	1.67±0.05
Weight (kg)	78.1±6.4	77.8±6.3
BMI (kg/m^2)	28.0±1.6	27.9±1.5
HbA_{1c} (%)	8.7±0.9	8.2±0.7
FPG (mg/dL)	145±18	140±16
PPG (mg/dL)	184±23	178±21
FPI (μU/mL)	18.1±4.3	17.7±4.1
HOMA-IR	6.53±2.26	6.17±2.18
HOMA-β	78.4±64.2	81.7±65.1
FPPr (pmol/L)	37.9±27.6	37.5±27.1
Pr/FPI ratio	0.31±1.20	0.32±1.22
C-peptide (nmol/L)	2.17±0.86	2.18±0.88
Glucagon (pmol/L)	57.4±8.7	56.8±7.9
ADN (μg/mL)	5.3±1.1	5.3±1.1
Hs-CRP (mg/L)	1.8±0.9	1.8±0.9

Data are mean±SD values.

ADN, adiponectin; BMI, body mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; FPPr, fasting plasma proinsulin; HbA_{1c}, glycated hemoglobin; HOMA-β, homeostasis model assessment β-cell function index; HOMA-IR index, homeostasis model assessment insulin resistance index; Hs-CRP, high-sensitivity C-reactive protein; PPG, postprandial plasma glucose; Pr/FPI ratio, proinsulin/fasting plasma insulin ratio.

Treatments

Patients were assigned to receive an unblinded treatment with metformin gradually titrated until a mean dosage of 2,500±500 mg/day for 8±2 months. After the run-in period, patients were randomly assigned to take, in addition to the previously taken metformin dosage, vildagliptin 50 mg twice a day or placebo for 12 months in a randomized, double-blind, placebo-controlled study (Fig. 1). Both vildagliptin and placebo were supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study. Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

Diet and exercise

Subjects began a controlled-energy diet (near 600 Kcal daily deficit) based on American Heart Association recommendations that included 50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and fiber of

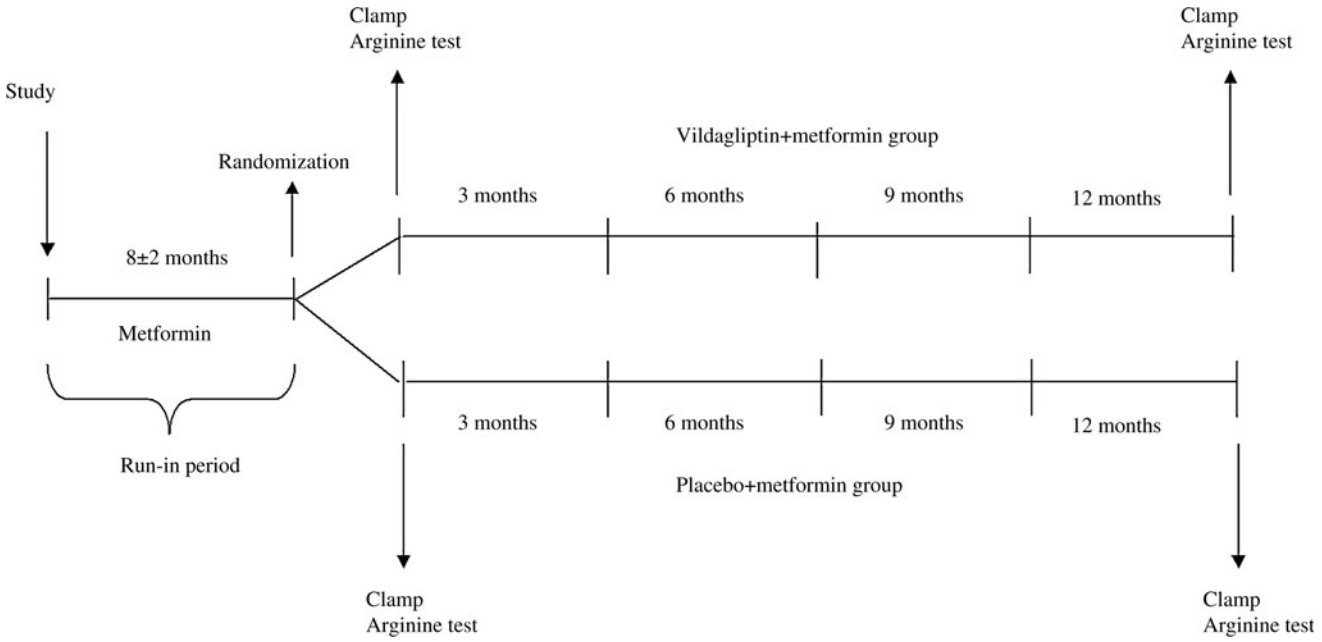

FIG. 1. Study design. Clamp, euglycemic hyperinsulinemic and hyperglycemic clamp.

35 g/day.[17] Patients were not treated with vitamins or mineral preparations during the study.

Standard diet advice was given by a dietitian and/or specialist doctor. The dietitian and/or specialist doctor periodically provided instruction on dietary intake recording procedures as part of a behavior modification program and then later used the subject's food diaries for counciling. Individuals were also encouraged to increase their physical activity by walking briskly for 20–30 min, three to five times per week, or by cycling. The recommended changes in physical activity throughout the study were not assessed.

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, a 12-lead electrocardiogram, and measurements of BMI, HbA_{1c}, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR), homeostasis model assessment β-cell function index (HOMA-β), fasting plasma proinsulin (FPPr), proinsulin/FPI ratio (Pr/FPI ratio), C-peptide, glucagon, adiponectin (ADN), and high-sensitivity C-reactive protein (Hs-CRP). We measured these parameters at baseline and at 3, 6, 9, and 12 months after addition of vildagliptin. Before and at 12 months after addition of vildagliptin, patients underwent a combined euglycemic hyperinsulinemic and hyperglycemic clamp, with subsequent arginine stimulation, to assess insulin sensitivity and insulin secretion.

In order to evaluate the tolerability assessments, all adverse events were recorded. All plasma parameters were determined after a 12-h overnight fast, with the exception of PPG, which was determined 2 h after a standardized meal. Venous blood samples were taken for all patients between 0800 and 0900 h. We used plasma obtained by addition of disodium EDTA (1 mg/mL) and centrifuged at 3,000 *g* for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at −80°C for no more than 3 months. All measurements were performed in a central laboratory.

BMI was calculated as weight (in kg) divided by the square of the height (in m). HbA_{1c} level was measured by a high-performance liquid chromatography method (Diamat™, Bio-Rad, Hercules, CA) (normal values, 4.2–6.2%), with intra- and interassay coefficients of variation (CVs) of <2%.[18]

Plasma glucose was assayed by the glucose oxidase method (Roche Diagnostics, Mannheim, Germany) with intra- and interassay CVs of <2%.[19] Plasma insulin was assayed with the Phadiaseph insulin radioimmunoassay (Pharmacia, Uppsala, Sweden) by using a second antibody to separate the free and antibody-bound ^{125}I-insulin (intra- and interassay CVs of 4.6% and 7.3%, respectively).[20]

The HOMA-IR was calculated as the product of basal glucose (in mmol/L) and insulin (in μU/mL) levels divided by 22.5.[21,22] The HOMA-β was calculated as the product of 20 and basal insulin levels (in μU/mL) divided by the value of basal glucose concentrations (in mmol/L) minus 3.5; this formula has been proposed to be a good measure of β-cell function.[22]

Proinsulin was determined using an enzyme-linked immunosorbent assay (Mercodia, Uppsala). The intra- and interassay CVs were 2.4% and 8.9%, respectively.[23]

C-peptide levels were measured with the automated immunochemiluminometric method (ADVIA Centaur®, Siemens Medical Solutions Diagnostics, Deerfield, IL). The smallest detectable level is 0.02 nmol/L. The intra- and interassay CVs were 3.7% and 8.3%, respectively. The normal range for fasting C-peptide levels is 0.3–0.9 nmol/L. There is no significant cross-reaction with proinsulin.[24]

Pancreatic glucagon concentrations were measured using porcine antibody 4305 (supplied by Novo Research Institute, Bagsværd, Denmark) in ethanol-extracted plasma. The detection limit was less than 1 pmol/L. The intra- and interassay CVs were 6.7% and 16%, respectively.[25]

ADN levels were determined using enzyme-linked immunosorbent assay kits (B-bridge International, Sunnyvale, CA); intraassay CVs were 3.6% for low- and 3.3% for high-control samples, whereas interassay CVs were 3.2% for low- and 7.3% for high-control samples, respectively.[26]

Hs-CRP was measured with use of latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Newark, DE). The intra- and interassay CVs were 5.7% and 1.3%, respectively.[27]

Glucose clamp technique

A combined euglycemic hyperinsulinemic and hyperglycemic clamp, with subsequent arginine stimulation, was performed to assess insulin sensitivity[28] and insulin secretion.[29] Arginine was administered during a hyperglycemic clamp to measure maximum insulin secretory capacity at a steady-state glucose concentration of 270 mg/dL.[30]

Clamps were performed before randomization and at 12 months, at the end of the study. At 0900 h, after the patients had fasted for 12 h overnight, an indwelling cannula (18-gauge polyethylene; Venflon, Viggo, Helsingborg, Sweden) was placed into an antecubital vein for infusion of glucose and insulin. To obtain arterialized venous blood samples, an indwelling cannula was inserted in a retrograde fashion into a dorsal hand or wrist vein and maintained in a heated box at 70°C. In the contralateral arm, a second cannula was introduced anterogradely in an antecubital vein of the forearm for the variable infusion of 20% glucose (model 560 pump; IVAC, San Diego, CA) and insulin (1 mU/min/kg; Humulin® R, Eli Lilly and Co., Indianapolis, IN) using a Harvard microinfusion pump (Plato BV, Diemen, The Netherlands). Arterialized blood samples were collected every 5 min to determine glucose concentration (model EML 105 electrolyte analyzer, Radiometer, Copenhagen, Denmark). The amount of glucose infused was adjusted to maintain euglycemia at 90 mg/dL. After the euglyemic hyperinsulinemic part of the clamp ($t = 120$ min) insulin infusion was discontinued for 60 min, while glucose was maintained at 90 mg/dL. After the euglycemic hyperinsulinemic clamp, a hyperglycemic clamp was performed. To quantify insulin secretion, the blood glucose concentration was rapidly raised to 270 mg/dL by administering a 50% glucose bolus in 2 min (adjusted for body weight) followed by a variable 20% glucose infusion to maintain 270 mg/dL blood glucose for the next 110 min. At 80 min after induction of hyperglycemia, 5 g of arginine dissolved in 50 mL was infused over 45 s to measure maximum insulin secretory capacity ($t = 260$ min), while the glucose concentration was maintained at 270 mg/dL.

First- and second-phase C-peptide secretion during the hyperglycemic clamp was calculated as area under the curve (AUC) ($AUC_{180–190min}$ and $AUC_{190–260min}$, respectively. Arginine-stimulated C-peptide secretion (AIR_{arg}) was calculated as the incremental $AUC_{260–270min}$ above the fasting C-peptide concentration. During the euglycemic hyperinsulinemic clamp, the M-value was calculated based on the last 30 min (steady state) and after adjustments for steady-state insulin concentration. The disposition index was determined by multiplying arginine-stimulated insulin secretion by the M-value.

Statistical analysis

A sample size of 85 patients per group was required to provide 90% power to detect a significant between-group difference in AIR_{arg}. All patients randomized with at least one post-randomization measure were analyzed (i.e., intent-to-treat). Continuous variables were evaluated using analysis of variance tests. Intervention effects were adjusted for the presence of potential confounding variables using analysis of covariance. Analysis of variance was also used to assess the significance of difference in variables within and between groups. The statistical significance of the independent effects of treatments on the other variables was determined using analysis of covariance. The dependent variable used in the model is the change from pretreatment for the β-cell function variables (AIR_{arg}, first phase, second phase). For all other end points the dependent value used is the mean at the corresponding visit. Integration (AUC) was carried out using the trapezoidal rule. Integrated incremental responses describe changes above baseline. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS Inc., Chicago, IL). All inferential statistical tests were conducted at a significance level of 0.05 (two sided). Data are presented as mean ± SD values.[31]

Results

Study sample

In total, 171 patients were enrolled in the study, and 167 patients completed the run-in period; at randomization 84 (50.3%) were allocated to the vildagliptin + metformin group and 83 (49.7%) to the placebo + metformin group. There were 11 patients (five men and six women) who did not complete the study, and the reasons for premature withdrawal included side effects such as diarrhea (one male and one female at randomization and one male at 6 months in the placebo + metformin group), nausea (one female at randomization and one female at 9 months in the vildagliptin + metformin group), vomiting (one female at randomization and one female at 12 months in the vildagliptin + metformin group), gastrointestinal discomfort (one male at 3 months and one male at 9 months in the placebo + metformin group), and lost to follow-up (one female at 3 months in the placebo + metformin group and one male at 12 months in the vildagliptin + metformin group). No patients had hypoglycemia (FPG < 60 mg/dL).

The characteristics of the patients at baseline and after the run-in period are shown in Table 1; no statistically significant differences were observed before and after the run-in period. The characteristics of the patients at randomization are reported in Table 2; the two groups did not differ at randomization.

Body weight and BMI

Both placebo + metformin and vildagliptin + metformin gave a decrease of body weight and BMI after 9 ($P < 0.05$ for both) and 12 ($P < 0.01$ for both) months compared with baseline, although vildagliptin + metformin gave a greater decrease of body weight compared with placebo + metformin at 9 and 12 months ($P < 0.05$ for both) (Tables 3 and 4).

Table 2. Subjects' Characteristics at Randomization

	Placebo + metformin	*Vildagliptin + metformin*
n	83	84
Sex (male/female)	43/40	42/42
Age (years)	52.4 ± 7.1	54.2 ± 8.3
Smoking status (male/female)	11/10	8/11
Diabetes duration (months)	6.3 ± 3.9	6.1 ± 3.7
Height (m)	1.68 ± 0.06	1.66 ± 0.04
Weight (kg)	78.5 ± 6.4	76.9 ± 5.8
BMI (kg/m^2)	27.8 ± 1.4	27.9 ± 1.5
HbA_{1c} (%)	8.2 ± 0.7	8.1 ± 0.6
FPG (mg/dL)	139 ± 14	141 ± 15
PPG (mg/dL)	179 ± 23	177 ± 20
FPI (μU/mL)	17.3 ± 3.9	17.9 ± 4.2
HOMA-IR	5.99 ± 1.97	6.28 ± 2.13
HOMA-β	80.8 ± 64.2	81.9 ± 65.1
FPPr (pmol/L)	36.2 ± 26.8	38.4 ± 27.7
Pr/FPI ratio	0.31 ± 1.19	0.32 ± 1.25
C-peptide (nmol/L)	2.15 ± 0.79	2.20 ± 0.94
Glucagon (pmol/L)	56.3 ± 7.7	57.2 ± 8.6
ADN (μg/mL)	5.4 ± 1.2	5.2 ± 1.0
Hs-CRP (mg/L)	1.7 ± 0.8	1.9 ± 2.0

Data are mean ± SD values.

ADN, adiponectin; BMI, body mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; FPPr, fasting plasma proinsulin; HbA_{1c}, glycated hemoglobin; HOMA-β, homeostasis model assessment β-cell function index; HOMA-IR index, homeostasis model assessment insulin resistance index; Hs-CRP, high-sensitivity C-reactive protein; PPG, postprandial plasma glucose; Pr/FPI ratio, proinsulin/fasting plasma insulin ratio.

Glycemic control

We observed an improvement of HbA_{1c} and PPG with both treatments compared with baseline: after 9 ($P < 0.05$) and 12 ($P < 0.01$) months with placebo + metformin and after 6 ($P < 0.05$), 9 ($P < 0.01$), and 12 ($P < 0.001$) months with vildagliptin + metformin, but with vildagliptin + metformin patients reached better HbA_{1c} and PPG values relative to placebo + metformin at 12 months ($P < 0.05$ for both) (Tables 3 and 4).

Similarly, there was an improvement of FPG compared with baseline at 6 ($P < 0.05$), 9 ($P < 0.01$), and 12 ($P < 0.001$) months with both treatments, even if patients treated with vildagliptin + metformin reached a better FPG value at 12 months compared with placebo + metformin ($P < 0.05$) (Tables 3 and 4).

Insulin resistance and β-cell function parameters

FPI and HOMA-IR were both reduced by placebo + metformin at 12 months compared with baseline ($P < 0.05$) and at 9 ($P < 0.05$) and 12 ($P < 0.01$) months with vildagliptin + metformin; moreover, vildagliptin + metformin were superior to placebo + metformin in improving HOMA-IR at 12 months ($P < 0.05$) (Tables 3 and 4).

HOMA-β was increased by vildagliptin + metformin after 9 ($P < 0.05$) and 12 ($P < 0.01$) months compared with baseline, whereas no variations were observed with placebo + metformin. Furthermore, the HOMA-β value recorded with vildagliptin + metformin was higher than the value obtained with placebo + metformin at 12 months ($P < 0.05$) (Tables 3 and 4).

FPPr and Pr/FPI ratio were both reduced compared with baseline with vildagliptin + metformin after 9 ($P < 0.05$) and 12 ($P < 0.01$) months, whereas no effects were produced by

Table 3. Patients' Data During the Study in the Placebo + Metformin Group

	Placebo + metformin group			
	3 months	*6 months*	*9 months*	*12 months*
n	81	80	79	79
Sex (male/female)	42/39	41/39	40/39	40/39
Smoking status (male/female)	10/10	10/10	9/10	9/10
Weight (kg)	77.9 ± 6.2	77.1 ± 5.9	75.6 ± 5.1[a]	73.4 ± 4.3[b]
BMI (kg/m^2)	27.6 ± 1.2	27.3 ± 1.1	26.8 ± 0.9[a]	26.0 ± 0.6[b]
HbA_{1c} (%)	8.0 ± 0.6	7.8 ± 0.5	7.7 ± 0.4[a]	7.4 ± 0.2[b]
FPG (mg/dL)	133 ± 12	127 ± 10[a]	122 ± 8[b]	117 ± 6[c]
PPG (mg/dL)	172 ± 17	166 ± 14	155 ± 12[a]	148 ± 10[b]
FPI (μU/mL)	17.1 ± 3.7	16.7 ± 3.4	16.5 ± 3.2	16.1 ± 3.1[a]
HOMA-IR	5.66 ± 1.91	5.28 ± 1.83	5.01 ± 1.72	4.72 ± 1.61[a]
HOMA-β	86.6 ± 68.3	92.5 ± 72.6	99.1 ± 77.2	105.6 ± 85.2
FPPr (pmol/L)	35.2 ± 23.8	31.4 ± 20.2	28.7 ± 18.5	27.3 ± 17.8
FPPr/FPI ratio	0.31 ± 1.17	0.28 ± 1.14	0.26 ± 1.12	0.25 ± 1.11
C-peptide (nmol/L)	2.43 ± 0.88	2.64 ± 0.96	2.78 ± 1.13	2.84 ± 1.21
Glucagon (pmol/L)	51.4 ± 6.8	49.2 ± 6.2	47.8 ± 5.6	45.2 ± 5.4[a]
ADN (μg/mL)	5.8 ± 1.4	6.1 ± 1.7	6.2 ± 1.9	6.5 ± 2.1[a]
Hs-CRP (mg/L)	1.6 ± 0.7	1.6 ± 0.7	1.4 ± 0.6	1.3 ± 0.5

Data are mean ± SD values.

[a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$ versus baseline.

ADN, adiponectin; BMI, body mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; FPPr, fasting plasma proinsulin; HbA_{1c}, glycated hemoglobin; HOMA-β, homeostasis model assessment β-cell function index; HOMA-IR index, homeostasis model assessment insulin resistance index; Hs-CRP, high-sensitivity C-reactive protein; PPG, postprandial plasma glucose; Pr/FPI ratio, proinsulin/fasting plasma insulin ratio.

Table 4. Patients' Data During the Study in the Vildagliptin + Metformin Group

	Vildagliptin + metformin group			
	3 months	*6 months*	*9 months*	*12 months*
n	84	84	83	81
Sex (male/female)	42/42	42/42	42/41	41/40
Smoking status (male/female)	8/11	8/11	8/10	8/10
Weight (kg)	75.8 ± 5.4	74.7 ± 4.8	72.7 ± 4.0[ad]	71.1 ± 3.6[bd]
BMI (kg/m^2)	27.5 ± 1.1	27.1 ± 1.0	26.4 ± 0.8[a]	25.8 ± 0.5[b]
HbA_{1c} (%)	7.8 ± 0.5	7.6 ± 0.3[a]	7.4 ± 0.2[b]	6.9 ± 0.1[cd]
FPG (mg/dL)	129 ± 11	125 ± 9[a]	111 ± 7[b]	106 ± 4[cd]
PPG (mg/dL)	164 ± 15	153 ± 13[a]	145 ± 9[b]	132 ± 8[cd]
FPI (μU/mL)	17.3 ± 3.9	16.8 ± 3.5	16.1 ± 3.0[a]	15.2 ± 2.4[b]
HOMA-IR	5.55 ± 1.87	5.23 ± 1.80	4.45 ± 1.53[a]	4.01 ± 1.22[bd]
HOMA-β	93.0 ± 74.2	96.0 ± 77.3	118.4 ± 94.8[a]	124.6 ± 97.7[bd]
FPPr (pmol/L)	35.1 ± 22.4	31.6 ± 19.8	27.3 ± 17.1[a]	21.9 ± 14.6[b]
FPPr/FPI ratio	0.30 ± 1.16	0.28 ± 1.14	0.25 ± 1.11[a]	0.22 ± 1.04[b]
C-peptide (nmol/L)	2.66 ± 0.99	2.99 ± 1.38	3.08 ± 1.47	3.29 ± 1.56[a]
Glucagon (pmol/L)	52.8 ± 8.1	45.7 ± 7.2	38.9 ± 5.8[a]	33.2 ± 4.9[bd]
ADN (μg/mL)	5.9 ± 1.5	6.4 ± 2.0	6.7 ± 2.2[a]	7.1 ± 2.4[b]
Hs-CRP (mg/L)	1.6 ± 0.7	1.4 ± 0.6	1.2 ± 0.5	1.1 ± 0.4[a]

Data are mean ± SD values.
[a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$ versus baseline; [d]$P < 0.05$ versus placebo + metformin.
ADN, adiponectin; BMI, body mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; FPPr, fasting plasma proinsulin; HbA_{1c}, glycated hemoglobin; HOMA-β, homeostasis model assessment β-cell function index; HOMA-IR index, homeostasis model assessment insulin resistance index; Hs-CRP, high-sensitivity C-reactive protein; PPG, postprandial plasma glucose; Pr/FPI ratio, proinsulin/fasting plasma insulin ratio.

placebo + metformin, even if no differences were noted between the two groups (Tables 3 and 4).

C-peptide did not change during the study in the placebo + metformin group, whereas it increased in the vildagliptin + metformin group after 12 months ($P < 0.05$) compared with baseline, but not compared with placebo + metformin (Tables 3 and 4).

Glucagon was reduced by placebo + metformin after 12 months ($P < 0.05$) and by vildagliptin + metformin after 9 ($P < 0.05$) and 12 ($P < 0.01$) months compared with baseline, with a lower value obtained with vildagliptin + metformin after 12 months ($P < 0.05$) (Tables 3 and 4).

Inflammatory parameters

There was an increase of ADN compared with baseline after 12 months ($P < 0.05$) with placebo + metformin ($P < 0.05$) and after 9 and 12 months ($P < 0.05$ and $P < 0.01$, respectively) with vildagliptin + metformin, without differences between the two groups (Tables 3 and 4).

Vildagliptin + metformin reduced Hs-CRP after 12 months of treatment compared with baseline ($P < 0.05$), whereas no changes were observed with placebo + metformin; no variations were noted between the two treatments (Tables 3 and 4).

Euglycemic and hyperglycemic clamp-derived measures of β-cell function

The treatment-induced change in the M-value was +1.20 ± 1.03 μmol/min/kg ($P < 0.05$ vs. baseline) and +2.10 ± 1.57 μmol/min/kg ($P < 0.01$ vs. baseline) for placebo + metformin and vildagliptin + metformin, respectively. The difference was also significant between the groups: + 0.90 ± 0.99 μmol/min/kg ($P < 0.05$ vs. placebo + metformin) (Table 5 and Fig. 2A).

First- and second-phase secretions were also improved after 12 months of vildagliptin + metformin treatment (+ 0.75 ± 0.59 nmol/L × min [$P < 0.05$ vs. baseline] and +10.70 ± 3.98 nmol/L × min [$P < 0.05$ vs. baseline], respectively). The difference was also significant between the groups: + 0.61

Table 5. Measures of Insulin Resistance and β-Cell Secretory Function During Euglycemic and Hyperglycemic Clamp at Randomization, After Metformin Therapy, and After the Randomization to Placebo or Vildagliptin

Measurement	*Randomization*	*Placebo + metformin*	*Vildagliptin + metformin*
M-value (μmol/min/kg)	5.3 ± 2.8	6.5 ± 3.8[a]	7.4 ± 4.3[bc]
First phase (nmol/L × min)	2.60 ± 1.36	2.74 ± 1.48	3.35 ± 1.89[ac]
Second phase (nmol/L × min)	30.8 ± 4.94	36.7 ± 5.37	41.5 ± 6.86[ac]
AIR_{arg} (nmol/L × min)	33.4 ± 5.18	36.8 ± 5.84	43.2 ± 7.44[ac]
DI (nmol/L · μmol/kg)	174.92 ± 38.5	226.38 ± 49.7[a]	288.92 ± 58.4[bc]

Data are mean ± SD values.
[a]$P < 0.05$, [b]$P < 0.01$ versus baseline; [c]$P < 0.05$ versus placebo + metformin.
First phase, first-phase C-peptide response to glucose (nmol/L × min); second phase, second phase C-peptide response to glucose (nmol/L × min); AIR_{arg}, C-peptide response to arginine at 270 mg/dL glucose concentration (nmol/L × min); DI, disposition index (AIR_{arg} × M-value).

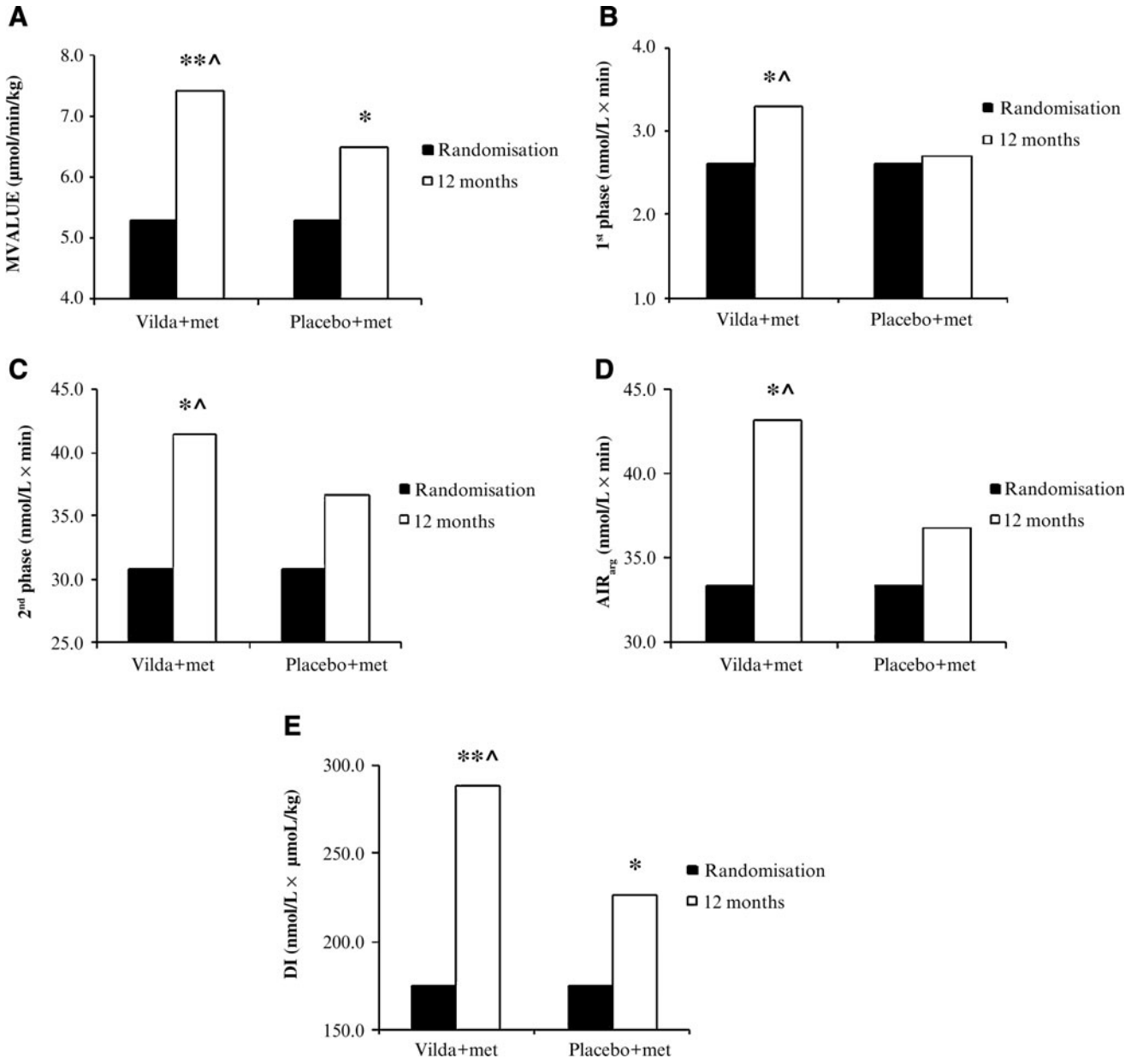

FIG. 2. Measures of insulin resistance and β-cell secretory function during euglycemic and hyperglycemic clamp: **(A)** M-value, **(B)** first-phase C-peptide response to glucose, **(C)** second-phase C-peptide response to glucose, **(D)** C-peptide response to arginine at 270 mg/dL glucose (AIR_{arg}), and **(E)** disposition index (DI) ($AIR_{arg} \times$ M-value). $^{*}P < 0.05$, $^{**}P < 0.01$ versus baseline; $\hat{}P < 0.05$ versus placebo + metformin (met). Vilda, vildagliptin.

±0.48 nmol/L×min ($P < 0.05$ vs. placebo + metformin) and +4.80±1.76 nmol/L×min ($P < 0.05$ vs. placebo + metformin), respectively (Table 5 and Fig. 2B and C).

C-peptide response to arginine was significantly higher in the vildagliptin + metformin group compared with the placebo + metformin group (+9.8±1.87 nmol/L×min [$P < 0.05$ vs. baseline] and +3.4±0.61 nmol/L×min [P = not significant], respectively). The difference was also significant between the groups: +6.40±1.49 nmol/L×min ($P < 0.05$ vs. placebo + metformin) (Table 5 and Figure 2D).

Vildagliptin + metformin increased the disposition index by +114.0±23.1 nmol/L·µmol/kg ($P < 0.01$ vs. baseline) compared with +51.46±15.8 nmol/L·µmol/kg for placebo + metformin ($P < 0.05$ vs. baseline), and this difference was statistically significant (+62.54±19.6 nmol/L·µmol/kg, $P < 0.05$ vs. placebo + metformin) after 12 months of treatment (Table 5 and Fig. 2E).

Discussion

Several studies have been published to evaluate the efficacy and safety of vildagliptin on glycemic control, both in monotherapy[32] or in combination with other antidiabetes agents.[33–37] Regarding the glycemic control, our study confirmed what already reported in literature: vildagliptin in addition to metformin was better than placebo + metformin in improving HbA_{1c}, confirming the safety and efficacy of the vildagliptin + metformin combination. This is in line with

what was already reported by Bosi et al.[37]: they confirmed that vildagliptin + metformin provided superior efficacy to monotherapy treatments with a mean HbA_{1c} change from baseline of −1.8% versus −1.2% in our study. This mild difference in efficacy could be due to the fact that patients enrolled by Bosi et al.[37] had a higher baseline HbA_{1c} compared with our patients.

Vildagliptin + metformin also gave a better decrease of body weight compared with placebo + metformin (−5.8 kg vs. 5.1 kg); this is in line with what has been reported in the literature where a weight neutrality or weight loss of vildagliptin in multiple monotherapy and combination trials has been reported in patients with type 2 diabetes.[38] This weight decrease is important because obesity contributes to an individual's risk of type 2 diabetes, largely through its contribution to insulin resistance; chronic insulin resistance frequently results in progressive failure of pancreatic β-cell function with a worsening of glycemic control.[39,40] For this reason modern therapies for the treatment of type 2 diabetes mellitus should be aimed not only at lowering HbA_{1c} levels below 7.0% as recommended by current American Diabetes Association guidelines,[41] but also to preserve β-cell function as long as possible.

Several studies have been conducted to evaluate the effects of the various antidiabetes drugs on preservation of β-cell function. The common opinion is that pioglitazone is better than sulfonylureas and metformin alone in improving insulin sensitivity and in decreasing insulin resistance, without further stimulating insulin secretion by failing β-cells.[42–44] Regarding DPP-4 inhibitors, and in particular vildagliptin, it has already been reported that vildagliptin increased β-cell function as a result of improved sensitivity of β-cells to glucose,[45,46] and it improved the ability of α-cells and β-cells to sense and respond to glucose after treatment.[47]

In our study we observed that vildagliptin, in addition to metformin, gave a better improvement of all measures of β-cell function such as the M-value, C-peptide, and disposition index compared with placebo after a combined glucose and arginine-stimulated C-peptide secretion rate that is the established measure for assessing β-cell capacity to secrete insulin.[48] This is in line with what already reported by Foley et al.,[49] who analyzed the effects of 1 year of treatment with vildagliptin compared with placebo in antidiabetes therapy–naive type 2 diabetes patients; they also observed that vildagliptin increased β-cell secretory capacity. Regarding glucagon, vildagliptin + metformin better decreased glucagon concentration compared with placebo + metformin (−24.0 vs. −11.1 pmol/L), confirming the GLP-1-induced improvement in glucose sensitivity of the α-cells as reported by Ahrén et al.,[50] who showed that vildagliptin enhances α-cell responsiveness to both the suppressive effects of hyperglycemia and the stimulatory effects of hypoglycemia.

One limitation of our study is that we did not verify if the positive effect of vildagliptin on β-cell function continued after the suspension of the treatment, even if this was already verified by Foley et al.,[49] who performed a 12-week washout period. This effect was not maintained after the washout, indicating that this increased capacity was not a disease-modifying effect on β-cell mass and/or function, suggesting that vildagliptin increased β-cell capacity by a reversible mechanism.

Conclusion

The addition of vildagliptin to metformin gave a better improvement of glycemic control, insulin resistance, and β-cell function compared with metformin alone, confirming the protective effect of vildagliptin on β-cells.

Author Disclosure Statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was used in the production of this manuscript.

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