

# Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes

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Received: 6 March 2006 / Accepted: 10 May 2006 / Published online: 1 July 2006  
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## Abstract

**Aims/hypothesis** We assessed the effects of vildagliptin, a novel dipeptidyl peptidase IV inhibitor, on postprandial lipid and lipoprotein metabolism in patients with type 2 diabetes.

**Subjects, materials and methods** This was a single-centre, randomised, double-blind study in drug-naive patients with type 2 diabetes. Patients received vildagliptin (50 mg twice daily,  $n=15$ ) or placebo ( $n=16$ ) for 4 weeks. Triglyceride, cholesterol, lipoprotein, glucose, insulin, glucagon and glucagon-like peptide-1 (GLP-1) responses to a fat-rich mixed meal were determined for 8 h postprandially before and after 4 weeks of treatment.

**Results** Relative to placebo, 4 weeks of treatment with vildagliptin decreased the  $AUC_{0-8h}$  for total triglyceride by  $22\pm 11\%$  ( $p=0.037$ ), the incremental  $AUC_{0-8h}$  ( $IAUC_{0-8h}$ )

for total triglyceride by  $85\pm 47\%$  ( $p=0.065$ ), the  $AUC_{0-8h}$  for chylomicron triglyceride by  $65\pm 19\%$  ( $p=0.001$ ) and the  $IAUC_{0-8h}$  for chylomicron triglyceride by  $91\pm 28\%$  ( $p=0.002$ ). This was associated with a decrease in chylomicron apolipoprotein B-48 ( $AUC_{0-8h}$ ,  $-1.0\pm 0.5$  mg  $\Gamma^{-1}$  h,  $p=0.037$ ) and chylomicron cholesterol ( $AUC_{0-8h}$ ,  $-0.14\pm 0.07$  mmol  $\Gamma^{-1}$  h,  $p=0.046$ ). Consistent with previous studies, 4 weeks of treatment with vildagliptin also increased intact GLP-1, suppressed inappropriate glucagon secretion, decreased fasting and postprandial glucose, and decreased HbA<sub>1c</sub> from a baseline of 6.7% (change,  $-0.4\pm 0.1\%$ ,  $p<0.001$ ), all relative to placebo.

**Conclusions/interpretation** Treatment with vildagliptin for 4 weeks improves postprandial plasma triglyceride and apolipoprotein B-48-containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal. The mechanisms underlying the effects of this dipeptidyl peptidase IV inhibitor on postprandial lipid metabolism remain to be explored.

**Keywords** Apo B-48 · Dipeptidyl peptidase IV inhibitors · Postprandial lipids · Triglyceride-rich lipoproteins · Type 2 diabetes · Vildagliptin

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## Abbreviations

AMΔ	adjusted mean change
ANCOVA	analysis of covariance
apo	apolipoprotein
DPP-4	dipeptidyl peptidase IV
FPG	fasting plasma glucose
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
IAUC	incremental AUC
IDL	intermediate-density lipoprotein
ISI	insulin sensitivity index

Sf	Svedberg flotation rate
TG	triglyceride
TRL	triglyceride-rich lipoprotein

## Introduction

Vildagliptin is a potent and selective inhibitor of dipeptidyl peptidase IV (DPP-4), and has been shown to reduce fasting and postprandial glucose levels in patients with type 2 diabetes primarily through incretin hormone-mediated improvements in islet function [1, 2]. Although clinical studies to date indicate that fasting lipid levels are minimally affected by vildagliptin treatment, animal studies suggest that glucagon-like peptide-1 (GLP-1) reduces intestinal triglyceride (TG) absorption and apolipoprotein (apo) production [3] and that glucose-dependent insulinotropic peptide (GIP) increases chylomicron clearance [4] and reduces post-load TG levels [5]. Because vildagliptin increases plasma levels of the active forms of both GLP-1 and GIP in diabetic patients [1], the present study was performed to assess the effects of vildagliptin on postprandial lipaemia.

Postprandial hypertriglyceridaemia is an important metabolic abnormality in many patients with type 2 diabetes [6]. Because partially catabolised TG-rich lipoprotein (TRL) remnants are highly atherogenic [7, 8], a possible reduction of postprandial TRL levels by vildagliptin would add to the therapeutic utility of this DPP-4 inhibitor and suggest the potential to reduce cardiovascular risk in patients with type 2 diabetes.

## Subjects, materials and methods

### Subjects and study design

This was a 4-week, single-centre, randomised, double-blind, placebo-controlled, parallel-group study of 31 drug-naive patients with type 2 diabetes. The Ethics Committee of the Helsinki University Hospital approved the study protocol and all study subjects gave their informed consent. Subjects were recruited from community hospital diabetes clinics and by newspaper advertisements.

Each subject fulfilled the following inclusion and exclusion criteria assessed at two screening visits during a 4-week run-in period. Patients with type 2 diabetes (male and non-fertile females and females of childbearing potential who were using a medically approved birth control method) were eligible to participate provided they were aged at least 30 years, had a BMI of 25–40 kg/m<sup>2</sup> inclusive, and had a baseline (mean of weeks –4 and –2)

HbA<sub>1c</sub> ≥6.5 and ≤10.0%, baseline fasting plasma glucose (FPG) ≤13.3 mmol/l and mean fasting serum TG levels of 1.7–3.5 mmol/l inclusive. Participants were required to have the apo E3/3 or E3/4 phenotype and to be drug-naive, defined as never having received an oral antidiabetic drug or not having received any oral antidiabetic drug within 3 months prior to week –4, or not having received a sulphonylurea within 6 months of week –4 or not having been treated with a sulphonylurea for longer than 3 months. The subjects agreed to maintain their previous diet and exercise regimen during the full course of the study.

Patients were excluded if they had a history of type 1 diabetes or secondary forms of diabetes; acute metabolic diabetic complications; major cardiac, hepatic or renal disease; or a fasting cholesterol level at baseline greater than 6.5 mmol/l. Patients receiving lipid-lowering therapy were also excluded.

Following confirmation of eligibility, patients were randomised at week 0 to receive vildagliptin (50 mg twice daily) or placebo. Fasting plasma glucose levels were measured and safety laboratory assessments were made at screening and at three biweekly study visits (weeks 0, 2 and 4). Fasting plasma levels of insulin, glucagon, GLP-1 and NEFA and total serum TG and cholesterol were measured at weeks 0 and 4 prior to the oral fat tolerance tests described below.

### Oral fat tolerance tests

Patients abstained from alcohol ingestion for 3 days and from strenuous exercise for 24 h prior to the standardised fat-rich meal tests (performed after an overnight fast). No study medication was given before the meal test at week 0; study medication was taken with 200 ml water 30 min prior to the meal test at week 4. The fat-rich test meal consisted of bread, butter, cheese, sliced sausage, a boiled egg, fresh paprika, soured whole milk, orange juice and coffee. It contained 1,000 kcal, 72 g fat (saturated fat 64.5%, monounsaturated fat 30.4%, polyunsaturated fat 5.1%) with a polyunsaturated:saturated fat ratio of 0.08, 490 mg cholesterol, 50 g carbohydrate and 35 g protein. Blood samples were drawn from a catheter placed in an antecubital vein at the following time-points: 35 and 5 min before starting the meal and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h after the meal (which was provided at time 0 and ingested within 10 min). The patients were allowed to drink only water until the last blood sample had been collected.

Total serum TG, total cholesterol, apo B-100 and apo B-48 were assessed in samples obtained at times –35 and –5 min and at hourly intervals after meal ingestion. Plasma glucose, insulin and NEFA levels were measured in samples obtained at times –35 and –5 min and 0.25, 0.5, 1, 2, 3, 4, 6 and 8 h

after the meal. Plasma glucagon and GLP-1 were measured in samples obtained at times  $-35$  and  $-5$  min and 0.25, 0.5, 1, 2, 4, 6 and 8 h after the meal.

### Biochemical analyses

Plasma glucose, insulin, glucagon, NEFA and HbA<sub>1c</sub> were analysed at a central laboratory (Medical Research Laboratories International, Zaventem, Belgium) by standardised and validated procedures according to good laboratory practice [9]. Plasma levels of intact GLP-1 were determined by ELISA at Novartis Pharma (Basel, Switzerland) using an N-terminally directed antibody (Linco Research, St Charles, MO, USA). Samples for analysis of GLP-1 and glucagon were taken in EDTA tubes with the addition of diprotin A to prevent proteolytic degradation.

Lipids and lipoproteins were measured at the Biomedicum, Helsinki, Finland. Plasma lipoprotein fractions were separated by density gradient ultracentrifugation as described previously [10]. Triglyceride and cholesterol concentrations were analysed in total plasma and both chylomicron (Svedberg flotation rate [Sf]  $>400$ ) and VLDL/intermediate-density lipoprotein (IDL) (Sf 12–400) fractions by automated enzymatic methods (Cobas Mira S Analyzer; Hoffman-La Roche, Basel, Switzerland). Apo B was quantified in serum using immunoturbidimetric kits (Orion Diagnostics, Espoo, Finland). Concentrations of apo B-48 and apo B-100 were measured in chylomicron and VLDL/IDL fractions using SDS-PAGE [11]. The bands represented by apo B-48 and apo B-100 were analysed with ImageMaster 1D software (Amersham Pharmacia Biotech, Newcastle upon Tyne, UK). Apo E phenotyping was performed in serum by isoelectric focusing [12].

All adverse events were recorded and assessed as to their severity and possible relationship to the study medication. Patients were provided with glucose monitoring devices and supplies and instructed on their use. Symptoms suggestive of hypoglycaemia that reversed with carbohydrate ingestion (regardless of glucose level) as well as asymptomatic events with self-monitored plasma glucose equivalent 3.7 mmol/l or less were defined as hypoglycaemia.

### Data analysis

Unless otherwise specified, data are presented as mean  $\pm$  SE. For glucose, insulin, glucagon, GLP-1 and each lipid parameter measured, the AUC and incremental AUC (IAUC) were calculated using the trapezoidal rule. For all parameters, the change from baseline to end-point was calculated and for all lipid parameters the percentage change from baseline was also calculated. The corrected insulin response at peak glucose (CIR<sub>GluPeak</sub>) was calculated as a dynamic index of beta cell function [13] and the

insulin sensitivity index (ISI) was calculated as a dynamic measure of insulin sensitivity [14].

The comparability of baseline variables between treatment groups was assessed with the Cochran–Mantel–Haenszel  $\chi^2$  test for qualitative variables and with the *t*-test for quantitative variables. Between-treatment comparisons of fasting parameters, AUC, IAUC and percentage changes from baseline were made with an analysis of covariance (ANCOVA) model including terms for treatment, baseline value, and treatment  $\times$  baseline interaction. Thus, the model adjusted for any potential influence of differences in baseline value on the response to treatment. Analyses were conducted using two-sided tests and a significance level of 0.05.

## Results

### Patient disposition and baseline characteristics

Table 1 reports the demographic and baseline metabolic characteristics of the randomised population together with patient disposition. Patients randomised to placebo were on average somewhat older, more overweight and had a longer disease duration than those randomised to vildagliptin. The majority of participants were male and all were Caucasian. The groups were well matched with regard to HbA<sub>1c</sub> and FPG. One patient randomised to vildagliptin discontinued prematurely because of an adverse event (haematuria). This event occurred on day 14 and was not suspected to be related to study medication.

### Lipids and lipoproteins

Table 2 reports fasting lipid parameters before and after treatment with vildagliptin. Although fasting levels of TG, cholesterol and total apo B at baseline tended to be higher in patients who subsequently received vildagliptin than in those who received placebo, the differences were not statistically significant. Four weeks of treatment with vildagliptin 50 mg twice daily had no significant effect on fasting total TG, total cholesterol or serum apo B relative to placebo.

In patients randomised to placebo, postprandial lipid and lipoprotein levels during the standard fat-rich meal test were either superimposable at weeks 0 and 4 or tended to increase from weeks 0 to 4. Therefore, data from the placebo group are not depicted, although the integrated measures are reported in the tables and the significance of the effects of vildagliptin was assessed relative to placebo. Figure 1 depicts total plasma TG concentrations (panel a), chylomicron TG (panel b), chylomicron apo B-48 (panel c) and chylomicron cholesterol levels (panel d) before and

**Table 1** Baseline characteristics and patient disposition

Mean±SD or <i>n</i> (%)	Vildagliptin ( <i>n</i> =15)	Placebo ( <i>n</i> =16)
Age (years)	53.5±8.8	56.9±8.7
Sex		
Male	11 (73.3)	11 (68.8)
Female	4 (26.7)	5 (31.3)
BMI (kg/m <sup>2</sup> )	30.8±5.0	34.1±4.7
HbA <sub>1c</sub> (%)	6.8±0.7	7.0±0.8
FPG (mmol/l)	8.3±1.1	8.5±1.9
Duration of type 2 DM (years)	4.2±5.4	6.0±5.6
Apo E phenotype		
E3/3	11 (73.3)	11 (68.8)
E3/4	4 (26.7)	4 (25.0)
Other	0	1 (6.2)
Completed study	14 (93.3)	16 (100)
Discontinued study	1 (6.7)	0
Discontinued because of adverse event	1 (6.7)	0

DM diabetes mellitus

after 4 weeks of treatment with vildagliptin (50 mg twice daily). Vildagliptin treatment elicited a substantial decrease in total plasma TGs and chylomicron TG and decreased apo B-48 and cholesterol in the chylomicron subfraction. However, 4 weeks of treatment with vildagliptin did not significantly affect the fasting concentrations of lipids or total apo B, apo B-48 or apo B-100 in the chylomicron or the VLDL/IDL subfractions (data not shown).

The total and incremental AUCs for postprandial lipid and lipoprotein concentrations before and after 4 weeks of treatment with vildagliptin 50 mg twice daily and placebo were calculated and compared by ANCOVA. Table 3 reports incremental AUCs. Consistent with Fig. 1, vildagliptin significantly decreased the AUC for total plasma TG relative to placebo when expressed as the percentage change from baseline (between-group difference=−22±11%,  $p=0.037$ ; data not shown), as well as the incremental

AUC when expressed in absolute terms. Vildagliptin also significantly decreased the AUC (data not shown) and the incremental AUC for chylomicron TG relative to placebo, whether expressed in absolute terms or as a percentage change from baseline (between-group difference=−91±28%,  $p=0.002$ ).

Relative to placebo, vildagliptin did not significantly affect VLDL/IDL TG concentrations, although there was a trend towards a reduction in the incremental AUC of VLDL/IDL TG during vildagliptin treatment and a minor increase in placebo-treated patients, such that when expressed as percentage change from baseline relative to placebo there was a 46% reduction ( $p=0.129$ ). Vildagliptin also significantly decreased the AUC (data not shown) and incremental AUC for chylomicron cholesterol relative to placebo, whether expressed in absolute terms or as the percentage change from baseline (data not shown). Vildagliptin did not significantly affect total cholesterol or cholesterol concentrations in the VLDL/IDL subfraction.

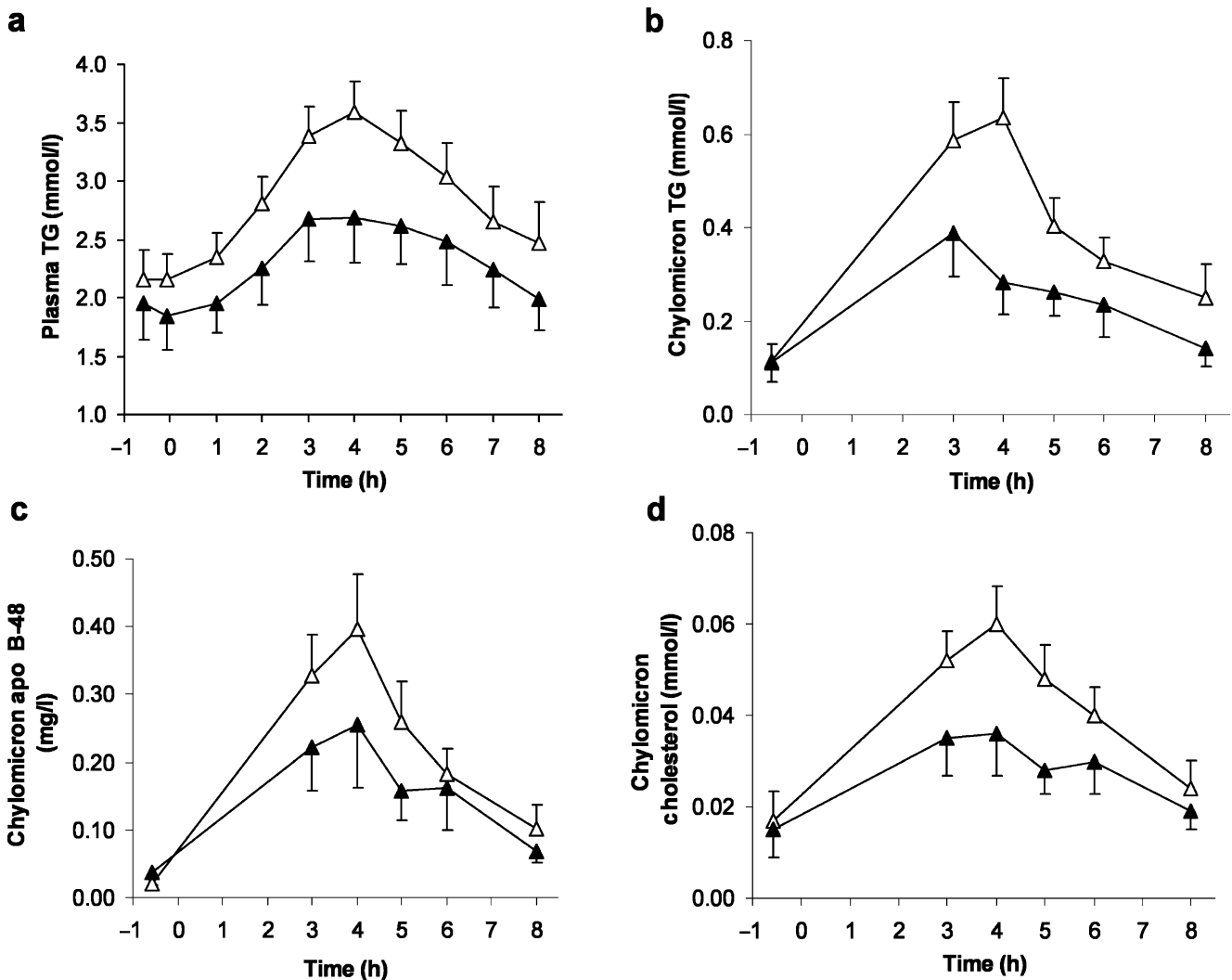
Table 4 summarises the statistical comparisons of apolipoprotein levels in patients receiving placebo or vildagliptin. Vildagliptin did not significantly affect total plasma apo B, VLDL/IDL apo B-48 or apo B-100 in the chylomicron or the VLDL/IDL subfractions. However, as also illustrated in Fig. 1, there was a statistically significant decrease in both the AUC (data not shown) and the incremental AUC for chylomicron apo B-48.

#### Non-esterified fatty acids and non-lipid parameters

Four weeks of treatment with vildagliptin 50 mg twice daily had no effect on fasting or postprandial concentrations of NEFA. Baseline fasting NEFA averaged 0.58±0.04 mmol/l in patients randomised to placebo and 0.53±0.04 mmol/l in those randomised to vildagliptin. Fasting NEFA concentrations did not change in either group, and the between-group difference in the adjusted mean change (AMΔ) was −0.03±0.05 mmol/l ( $p=0.466$ ). The ratio of the nadir to pre-meal

**Table 2** Between-group comparisons of fasting lipid parameters

	<i>n</i>	Baseline	End-point (week 4)	Adjusted mean change ± SE	Between-group difference	<i>p</i>
Fasting total triglycerides (mmol/l)						
Placebo	16	1.8±0.3	1.7±0.1	−0.3±0.2		
Vildagliptin	14	2.2±0.2	1.8±0.3	−0.3±0.2	−0.0±0.3	0.930
Fasting total cholesterol (mmol/l)						
Placebo	16	5.0±0.3	5.2±0.2	−0.0±0.0		
Vildagliptin	14	5.6±0.2	5.5±0.2	−0.2±0.1	−0.2±0.2	0.298
Fasting total apo B (g/l)						
Placebo	16	1.13±0.05	1.12±0.04	−0.02±0.03		
Vildagliptin	14	1.20±0.05	1.13±0.07	−0.08±0.04	−0.06±0.05	0.231



**Fig. 1** Total plasma TG (**a**), chylomicron TG (**b**), chylomicron apo B-48 (**c**) and chylomicron cholesterol (**d**) during fat-rich meal tests performed before (week 0, *open triangles*) and after 4 weeks of

treatment with vildagliptin (50 mg twice daily, *closed triangles*) in patients with type 2 diabetes. Mean $\pm$ SE,  $n=15$

NEFA concentration was calculated as an index of lipolysis. This was also unaffected by vildagliptin treatment (data not shown).

In patients receiving placebo, the postprandial profiles of intact GLP-1, glucose, glucagon and insulin were essentially superimposable at weeks 0 and 4. These data are not depicted graphically, but, as for the lipid and lipoprotein parameters, the significance of the effects of vildagliptin were assessed relative to placebo. Figure 2 depicts plasma levels of intact GLP-1 (panel a), glucose (panel b), glucagon (panel c) and insulin (panel d) before and after 4 weeks of treatment with vildagliptin 50 mg twice daily. Vildagliptin greatly increased both fasting and postprandial plasma GLP-1 levels. The between-group difference in the AM $\Delta$  in the GLP-1 AUC $_{0-8h}$  was  $59\pm 5$  pmol  $\Gamma^{-1}$  h ( $p<0.001$ ).

Vildagliptin also significantly decreased FPG as well as postprandial glucose levels. In patients randomised to placebo and vildagliptin, FPG at baseline averaged  $8.5\pm 0.5$  and  $8.4\pm 0.3$  mmol/l, respectively. FPG increased modestly in patients receiving placebo (AM $\Delta=0.4\pm 0.2$  mmol/l) and decreased substantially in those receiving vildagliptin (AM $\Delta=-0.9\pm 0.2$  mmol/l). The between-group difference in AM $\Delta$  FPG was  $-1.3\pm 0.3$  mmol/l ( $p<0.001$ ). Similarly, the AUC $_{0-8h}$  for glucose in patients randomised to placebo and vildagliptin averaged  $63.2\pm 3.4$  and  $62.0\pm 2.5$  mmol  $\Gamma^{-1}$  h, respectively. This increased modestly in patients receiving placebo (AM $\Delta=3.6\pm 1.6$  mmol  $\Gamma^{-1}$  h) and decreased substantially in vildagliptin-treated patients (AM $\Delta=-5.8\pm 1.7$  mmol  $\Gamma^{-1}$  h). The between-group difference in the AM $\Delta$  glucose AUC $_{0-8}$  was  $-9.4\pm 2.5$  mmol  $\Gamma^{-1}$  h ( $p<0.001$ ). The between-group



**Table 3** Between-group comparisons of integrated postprandial lipid parameters (incremental AUCs)

	<i>n</i>	Baseline	End-point (week 4)	Adjusted mean change ± SE	Between-group difference	<i>p</i>
Total plasma TG IAU <sub>C</sub> <sub>0–8h</sub> (mmol l <sup>-1</sup> h)						
Placebo	16	6.2±0.6	7.2±0.8	1.0±0.8		
Vildagliptin	14	6.1±1.1	4.1±0.8	-2.0±0.8	-3.1±1.2	0.011
Chylomicron TG IAU <sub>C</sub> <sub>0–8h</sub> (mmol l <sup>-1</sup> h)						
Placebo	16	1.9±0.3	2.4±0.5	0.5±0.2		
Vildagliptin	14	2.4±0.5	1.2±0.2	-1.0±0.3	-1.5±0.4	<0.001
VLDL/IDL TG IAU <sub>C</sub> <sub>0–8h</sub> (mmol l <sup>-1</sup> h)						
Placebo	16	3.8±0.3	4.0±0.7	0.3±0.6		
Vildagliptin	14	2.9±0.6	2.4±0.5	-0.8±0.6	-1.1±0.9	0.215
Total plasma cholesterol IAU <sub>C</sub> <sub>0–8h</sub> (mmol l <sup>-1</sup> h)						
Placebo	16	1.3±0.4	1.0±0.2	-0.1±0.2		
Vildagliptin	14	1.0±0.3	0.9±0.2	-0.3±0.2	-0.2±0.3	0.517
Chylomicron cholesterol IAU <sub>C</sub> <sub>0–8h</sub> (mmol l <sup>-1</sup> h)						
Placebo	16	0.22±0.05	0.25±0.05	0.03±0.04		
Vildagliptin	14	0.20±0.06	0.11±0.05	-0.10±0.04	-0.13±0.05	0.020
VLDL/IDL cholesterol IAU <sub>C</sub> <sub>0–8h</sub> (mmol l <sup>-1</sup> h)						
Placebo	16	0.39±0.09	0.38±0.2	-0.03±0.18		
Vildagliptin	14	0.26±0.17	0.06±0.16	-0.26±0.19	-0.22±0.28	0.409

difference in the AMΔ 2-h postprandial glucose level was  $-1.5\pm 0.4$  mmol/l ( $p<0.001$ ).

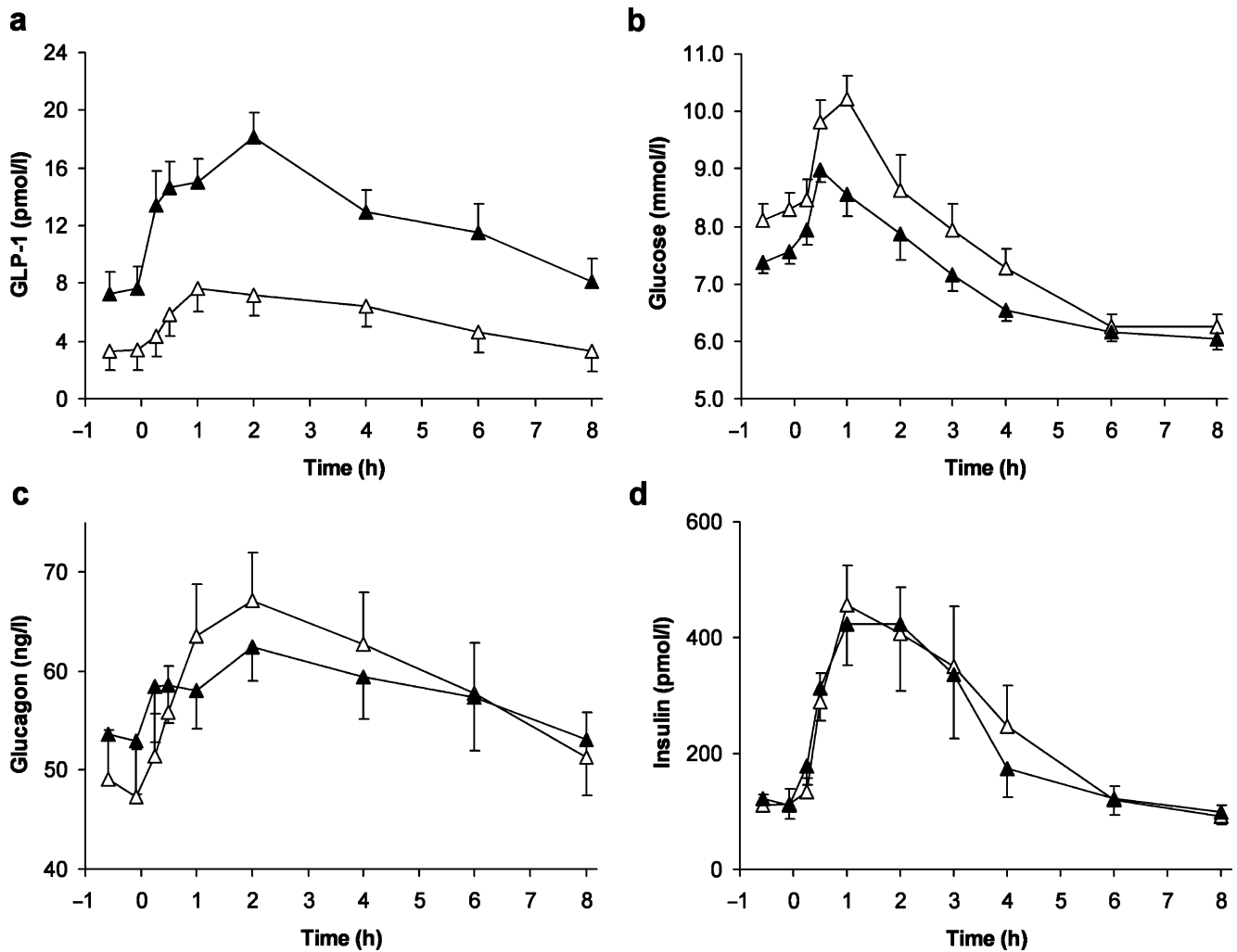
Postprandial plasma glucagon levels were also significantly decreased after 4 weeks of treatment with vildagliptin relative to placebo. The between-group difference in the AMΔ glucagon IAU<sub>C</sub><sub>0–2h</sub> was  $-14\pm 5$  ng l<sup>-1</sup> h ( $p=0.009$ ) and the between-group difference in the AMΔ glucagon IAU<sub>C</sub><sub>0–8h</sub> was  $-55\pm 25$  ng l<sup>-1</sup> h ( $p=0.031$ ). Because the fasting plasma glucagon levels tended to increase in vildagliptin-treated patients (AMΔ= $5\pm 3$  ng/l), the reductions in total AUC<sub>0–2h</sub> and AUC<sub>0–8h</sub> for glucagon (AMΔ= $-5\pm 4$  and  $-19\pm 15$ , respectively) were not statistically significant relative to placebo. As shown in Fig. 2, vildagliptin did not affect fasting or postprandial plasma insulin levels.

During the meal test, the CIR<sub>GluPeak</sub> increased in patients receiving vildagliptin (AMΔ= $0.13\pm 0.05$ ) and did not change in patients who received placebo (AMΔ= $0.00\pm 0.05$ ). The between-group difference was  $0.13\pm 0.07$  ( $p=0.071$ ). Although vildagliptin did not affect fasting insulin levels, the ISI during meal tests increased significantly relative to placebo. In patients receiving vildagliptin the ISI increased (AMΔ= $1.1\pm 0.5$ ) and in patients receiving placebo it decreased (AMΔ= $0.9\pm 0.4$ ). The between-group difference in the AMΔ ISI was  $2.0\pm 0.7$  ( $p=0.003$ ).

At baseline, body weight averaged  $94.4\pm 5.9$  and  $101.0\pm 4.3$  kg in patients randomised to vildagliptin and placebo, respectively. The AMΔ for body weight was  $-0.4\pm 0.3$  kg

**Table 4** Between-group comparisons of integrated postprandial lipoprotein parameters (incremental AUCs)

	<i>n</i>	Baseline	End-point (week 4)	Adjusted mean change ± SE	Between-group difference	<i>p</i>
Chylomicron apo B-48 IAU <sub>C</sub> <sub>0–8h</sub> (mg l <sup>-1</sup> h)						
Placebo	16	1.4±0.3	1.8±0.4	0.4±0.2		
Vildagliptin	14	1.7±0.4	1.0±0.3	-0.6±0.3	-1.0±0.4	0.008
VLDL/IDL apo B-48 IAU <sub>C</sub> <sub>0–8h</sub> (mg l <sup>-1</sup> h)						
Placebo	16	37.3±5.4	41.1±7.8	1.8±8.4		
Vildagliptin	14	43.5±6.9	28.4±9.3	-12.7±9.0	-14.4±12.9	0.250
Chylomicron apo B-100 IAU <sub>C</sub> <sub>0–8h</sub> (mg l <sup>-1</sup> h)						
Placebo	16	1.7±0.4	1.6±0.8	-0.2±0.8		
Vildagliptin	14	1.9±0.6	0.2±0.6	-1.6±0.8	-1.4±1.2	0.208
VLDL/IDL apo B-100 IAU <sub>C</sub> <sub>0–8h</sub> (mg l <sup>-1</sup> h)						
Placebo	16	-21.9±95.8	-19.5±136.0	9.2±166.0		
Vildagliptin	14	-38.1±215.3	139.6±215.3	172.5±177.5	163.3±254.9	0.508



**Fig. 2** Plasma levels of intact GLP-1 (**a**), glucose (**b**), glucagon (**c**) and insulin (**d**) during fat-rich meal tests performed before (week 0, *open triangles*) and after 4 weeks of treatment with vildagliptin

(50 mg twice daily, *closed triangles*) in patients with type 2 diabetes. Mean $\pm$ SE,  $n=15$

in patients receiving vildagliptin and  $-0.2\pm 0.3$  kg in patients receiving placebo. The between-group difference was  $-0.2\pm 0.5$  kg ( $p=0.709$ ). In the patients for whom both baseline and end-point values were available, HbA<sub>1c</sub> at baseline averaged  $6.7\pm 0.2\%$  in patients randomised to vildagliptin ( $n=14$ ) and  $7.0\pm 0.2\%$  in patients randomised to placebo ( $n=16$ ). The AM $\Delta$  for HbA<sub>1c</sub> after 4 weeks of treatment with vildagliptin was  $-0.4\pm 0.1\%$ ; after 4 weeks of administration of placebo it was  $0.0\pm 0.1\%$ . The between-group difference in the AM $\Delta$  HbA<sub>1c</sub> was  $-0.4\pm 0.1\%$  ( $p<0.001$ ).

#### Tolerability

Of patients receiving vildagliptin, 4 of 15 (26.7%) experienced an adverse event, while 12 of 16 patients receiving placebo (75.0%) experienced one or more adverse

events. No serious adverse events were reported and no hypoglycaemic episodes occurred. There were no clinically meaningful changes from baseline or differences between treatment groups in haematology, biochemistry, vital signs, ECGs or faecal occult blood tests. At the study end-point, positive urine glucose test results were observed in six of 16 patients in the placebo group (four of whom had had positive results at baseline) and in no patient who received vildagliptin.

#### Discussion

This is the first report on the influence of a DPP-4 inhibitor such as vildagliptin on postprandial lipoprotein metabolism in patients with type 2 diabetes. We show in this single-centre, double-blind, randomised, placebo-controlled, par-

allel-group study that 4 weeks of treatment with vildagliptin 50 mg twice daily reduces the postprandial TRL response and that this is mainly due to a decrease in intestinally derived apo B-48-containing particles. These pilot findings suggest that vildagliptin treatment may benefit patients with type 2 diabetes by reducing postprandial atherogenic TRLs in the circulation. The study also confirms previous results establishing that vildagliptin increases active GLP-1, suppresses inappropriate glucagon release, reduces fasting and postprandial plasma glucose levels, and significantly decreases HbA<sub>1c</sub> from a low baseline after only 4 weeks of treatment [2].

There are several possible mechanisms by which vildagliptin could have improved postprandial lipaemia, although an increase in active GLP-1 (confirmed in this study) and/or GIP (not measured in the present study but demonstrated previously [1]) would underlie each of them. Most simply, the influence of vildagliptin on postprandial lipaemia could reflect incretin-mediated changes in pancreatic hormone secretion, an improved metabolic state and reduced insulin resistance secondary to improved islet function, incretin-mediated effects to slow gastric emptying, or direct effects of GLP-1 and/or GIP on lipoprotein metabolism.

Any influence of vildagliptin mediated by changes in pancreatic hormone release would involve either a peripheral effect to decrease lipolysis and thus circulating NEFA or an effect on the liver to suppress glucose production. The present observation that vildagliptin did not affect plasma NEFA levels is consistent with there being no effect on circulating insulin levels and rules out mediation by reduced NEFA flux to the liver. However, because the inappropriate glucagon response to the meal was substantially decreased and the insulin response was sustained, there was presumably an increase in the ratio of insulin to glucagon and more effective restraint of hepatic glucose production with vildagliptin treatment. This could result in decreased VLDL production (i.e. reduced availability of glucose for lipogenesis), and it has been shown that hepatic VLDL production contributes significantly to postprandial lipaemia [15]. Since a trend towards a decrease in VLDL/IDL TG was observed, we cannot rule out the possibility that one effect of vildagliptin was to reduce hepatic VLDL production, which would be secondary to improved islet function or hepatic insulin sensitivity [16]. On the other hand, improved islet function does not explain the reduction in chylomicron TGs. The observed decrease in the postprandial chylomicron response could itself reduce the competition between hepatic and intestinal lipoproteins, improving also the catabolism of VLDL particles.

Regarding the second proposed mechanism, although it has been shown that many different antihyperglycaemic agents can improve postprandial lipaemia, this is not a

universal finding. Thiazolidinediones have been reported to exert beneficial effects on postprandial TG metabolism [17–20], but these are unlikely to be mediated by reduced NEFA flux to the liver, a mechanism that is largely independent of improved glycaemia. Both metformin [21, 22] and glipizide [23] can improve postprandial lipaemia in poorly controlled patients with type 2 diabetes. This may be secondary to improved glycaemic control and reduced insulin resistance. However, in a population of patients and an experimental setting similar to those described here, we found that neither nateglinide nor glibenclamide, despite their insulinotropic action and associated improvement in metabolic control, exerted an effect on postprandial lipid metabolism [24]. Thus, in patients with less severe hyperglycaemia, reducing plasma glucose levels appears to be insufficient to overcome postprandial dyslipidaemia. In the present study there was some evidence of reduced insulin resistance (increased ISI). However, the increase in ISI did not correlate with the lipid responses and does not appear to be sufficient to explain how vildagliptin improves TRL metabolism.

Although administration of exogenous GLP-1 can slow gastric emptying in a dose-related manner [25] and endogenous GLP-1 has been proposed to function as an ‘ileal brake’ [26], the parallel peak responses of postprandial TG, apo B-48 and cholesterol before and after treatment with vildagliptin but the greatly decreased incremental AUCs suggest an improvement in TRL metabolism with vildagliptin rather than just a decreased rate of fat absorption and retarded chylomicron secretion. This situation contrasts with the recent finding in healthy volunteers that exogenous GLP-1 infusion (which increased plasma levels >10-fold) eliminated the postprandial increase in TGs [27]. In that study, the effects of much higher concentrations of GLP-1 were attributed to a marked slowing of gastric emptying and increased insulin-mediated inhibition of lipolysis. On the basis of the results of our study, rather than any of the first four proposed indirect mechanisms, we suggest that a direct effect of GLP-1 and/or GIP on lipoprotein metabolism is more likely to mediate the observed effect of vildagliptin to decrease postprandial lipaemia.

The recent demonstration that GLP-1 reduces intestinal TG absorption and apo B and apo A-IV production in rats [3] provides one potential mechanism that could be addressed in future studies. A modest decrease in TG absorption could also explain the lack of weight gain during the study, whereas there was a clear improvement in glycaemic controls. Animal studies have also shown that exogenous GIP infusion increases chylomicron clearance [4]. Thus it will be of interest to determine the degree to which decreased fat absorption and increased clearance of chylomicrons contribute to the vildagliptin-induced decrease in chylomicron TG.



Recent prospective studies with long-term follow-up demonstrate that patients with type 2 diabetes have a lifetime cardiovascular risk that is a ‘coronary heart disease equivalent’ [28]. A significant part of the risk is accounted for by abnormal lipid and glucose metabolism in the postprandial period. Clearly, there is an urgent need to target both postprandial glucose and dyslipidaemia in order to reduce cardiovascular risk. Our hypothesis-generating study demonstrated that DPP-4 inhibition by vildagliptin is associated with improvement in both postprandial lipidemia and in overall glycaemic control, as reflected by a decrease in HbA<sub>1c</sub> of 0.4% relative to placebo, from a baseline of 6.7% after 4 weeks of treatment. Although the mechanisms underlying the observed decrease in chylomicron TG and the question of whether vildagliptin also decreases hepatic VLDL production remain to be more fully explored, these promising results suggest that DPP-4 inhibition may offer a novel approach to reducing cardiovascular risk in patients with type 2 diabetes.

**Acknowledgements** We thank the subjects for participating in the study, and H. Perttunen-Nio, H. Hilden, V. Naatti and M. Savolainen for their excellent technical assistance and patient care. This study was funded by Novartis Pharma AG.

**Duality of interest** A. Schweizer, A. Ulvestad, D. Mills and J. E. Foley are employed by Novartis and own shares in the company. B. E. Dunning has been a consultant for Novartis and owns shares in the company. M.-R. Taskinen has been a consultant for Novartis.

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