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Vildagliptin efficacy in combination with metformin among Jordanian patients with type 2 diabetes mellitus inadequately controlled with metformin

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ABSTRACT

Objective: To assess the efficacy and safety of vildagliptin added to metformin in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin monotherapy.

Methods: This was a 12-week prospective observational study where vildagliptin 50 mg twice daily was added to patients with T2DM inadequately controlled (glycosylated hemoglobin type A1c (Hba1c) 7–10%) by a daily dose of metformin ≥1700 mg between June 2012 and May 2013. Efficacy was assessed by change in Hba1c and fasting plasma glucose (FPG) levels, and safety was assessed by reported adverse events (AEs).

Results: A total of 58 patients were enrolled in this study. Their age ranged between 39.0 and 71.0 years, with a mean of 52.6 years, and a standard deviation (SD) of 7.8. The average duration of diabetes mellitus (DM) was 4.0 years (SD 3.0) and half of the patients have had DM for more than three years. The mean baseline levels of Hba1c and FPG were 8% and 10.8 mmol/L, respectively. Patients treated with vildagliptin achieved clinically significant reductions in Hba1c of 1.1% (p value <.005) and reduction in FPG of 1.8 mmol/L (p value <.005) from baseline. Overall, 62.1% had achieved the target of Hba1c of <7% after vildagliptin use. Greater reductions in Hba1c were linked to higher baseline levels as well as to the daily frequency of metformin use. Mild AEs were reported by 16 patients. There was no incidence of hypoglycemia and there were no significant changes in body weight after treatment.

Conclusions: Vildagliptin as add-on therapy to metformin improved glycemic control and was highly tolerable in T2DM patients who were inadequately controlled by metformin monotherapy.

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic disorders in adults, and constitutes a major global and growing public health problem particularly in developing countries.[1] It is expected that the number of diabetes mellitus (DM) patients will rise from 366 million in the year 2011 to 552 million by 2030.[2]

Metformin is recommended by most guidelines as first line therapy for T2DM.[3,4] However, due to the progressive nature of T2DM, inevitable combination therapies are often required if glycemic targets cannot be maintained by metformin monotherapy.[3–5] Insulin resistance and pancreatic cell dysfunction are the two main pathophysiological features of T2DM,[6,7] hence, proper treatment for such disease should target both these defects.

Vildagliptin is a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4) that improves glycemic control in T2DM by enhancing α-and β-cell response to glucose.[8–10]

Several recent clinical trials have reported that vildagliptin improves glycemic control in patients with T2DM when given as monotherapy,[11,12] in combination with metformin,[13–15] in combination with other antidiabetic agents,[16,17] or with insulin [18]. At the same time, treatment with vildagliptin has proven to be well tolerated, weight neutral, with low incidence of hypoglycemia,[10,14,15,19,20] and a good overall safety profile. Additionally, vildagliptin is as effective as a sulfonylurea or pioglitazone in lowering Hba1c but with a lower incidence of hypoglycemia.[19]

Several recent clinical trials have reported the effectiveness of other DPP-4 inhibitors on Hba1c reduction, and their neutral effect on body weight [13,21]. Furthermore, their use may contribute to a reduction in blood pressure (BP) as well [22].

Adding vildagliptin to metformin is a promising therapeutic combination in patients with T2DM as metformin addresses insulin resistance [23] and vildagliptin addresses β-cell dysfunction [10], the two main mechanisms of disease

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in T2DM. This 12-week study was conducted to assess the efficacy and tolerability of vildagliptin 50 mg twice daily as add on therapy for T2DM patients inadequately controlled with metformin monotherapy.

Methods

Study design

This was a 12-week study conducted at the diabetic outpatient clinic at Jordan University of Science and Technology Health Center (JUST Health Center) in Jordan between June 2012 and May 2013. JUST Health Center is accredited by the Health Care Accreditation Council (HCAC) and the clinic is run by a family physician and a diabetic nurse, and it provides close follow up, group counseling and continuing care for DM patients.

Patients with T2DM inadequately controlled with metformin monotherapy attended one screening visit (visit 1) during which inclusion and exclusion criteria were assessed besides demographic and clinical characteristics. All eligible patients (visit 2) received vildagliptin 50 mg twice daily in addition to the same dose of metformin they were already on (1700–2550 mg/day). Efficacy and tolerability were assessed during three additional visits at weeks 4, 8 and 12.

Study population

The study enrolled patients with T2DM who had been treated with metformin monotherapy for at least three months and who had been on a total daily dose of $\geq$1700 mg for a minimum of four weeks before visit 1. Eligibility criteria were male and female patients, non-fertile, not using a medically approved birth control method, aged $\geq$18 years with a Hba1c $>$ 7% but less than 10%.

Patients were excluded if they had a history of type 1 diabetes mellitus (T1DM), or secondary DM, or had a history of acute metabolic diabetes complications in the last six months before the study. Other exclusion criteria were patients with congestive heart failure (CHF), unstable angina, myocardial infarction (MI) or a history of coronary artery bypass surgery in the last six months. Patients with cirrhosis or chronic active hepatitis were also excluded as well as patients with renal disease or renal dysfunction (serum creatinine $\geq$132 umol/L for males and $\geq$123 umol/L for females). Written informed consent was signed by each participant. The study protocol was approved by the Institutional Review Board (IRB) in King Abdullah University Hospital and was conducted in accordance with the Declaration of Helsinki, using good clinical practice.

Study assessment

Urea and creatinine and liver enzymes (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) were measured at screening visit. Fasting blood glucose (FPG), Hba1c as well as body weight, height and BP were measured at screening visit and 12 weeks.

Body weight and height were measured with the patients wearing light clothing and with no shoes. Using a standardized mercury sphygmomanometer, two readings of systolic and diastolic BP were measured from the left arm (at the heart level) after the patient rests for at least 5 min. The mean of two readings was taken as the individuals BP.

All adverse events (AEs) were recorded and assessed by the investigator for their possible relationship to study medication. Patients were provided with glucose monitoring devices and supplies and instructed on their use by the diabetic nurse. Hypoglycemia was defined as symptoms suggestive of low blood glucose confirmed by self-measurement of plasma glucose level of $<$3.1 mmol/L. Severe hypoglycemia was defined as any episodes requiring assistance of another party. All biochemical measurements were carried out by the same team of laboratory technicians at JUST Health center lab. Hba1c was analyzed using DiaSys one HbA1c FS (particle-enhanced immunoturbidimetric test) (DiaSys Diagnostic Systems, Wixom, MI) which is a specific immunoassay for human Hba1c. FPG, total cholesterol (TC), and serum triglyceride (TG) were analyzed by the use of AU480 (Beckman Coulter, Brea, CA).

Definitions of variables

Body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in meters) squared and categorized according to the World Health Organization guidelines as normal "BMI $<$25 kg/m^2", overweight "25 $\leq$ BMI $<$30 kg/m^2" and obesity "BMI $\geq$30 kg/m^2".[24] Hypertension was defined as systolic BP $\geq$140 mmHg and or diastolic BP $\geq$90 mmHg or being treated for hypertension.[25] Current smoker was defined as those who smoked part or all of a tobacco product in the past 30 days.[26] High TC was defined as TC $\geq$200 mg/dl (5.2 mmol/L) and hypertriglyceridemia was defined as serum (TG) level $\geq$150 mmol/dl (1.69 mmol/L).[27] Diabetic neuropathy was defined as the presence of symptoms and or signs of neurological dysfunction in patients with DM after exclusion of other causes.[28] Coronary heart disease (CHD) was defined as a history of stable angina or history of MI for more than six months from participating in the study. The presence or absence of retinopathy was based on ophthalmologist report at King Abdullah University Hospital (KAUH) where our DM patients are referred for annual screening.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 15 (SPSS Inc., Chicago, IL) was used to analyze the data. Categorical variables were described using percentages and the continuous variables were described using means and standard deviation (SD). The changes in the studied parameters between the baseline and after 3 months of using vildagliptin were analyzed and tested for statistical significance using paired t test after testing for normality assumption. The variables that represent the changes in the studied parameters between the baseline and after 3 months were

checked for normality using Shapiro–Wilk Test. All variables met the normality assumption. Multivariate analysis using the general linear model (GLM) was used to determine factors associated with HbA1c changes after three months of vildagliptin use. A p value of less than 0.05 was considered statistically significant.

Results

A total of 58 patients were enrolled in this study. Their age ranged between 39.0 and 71.0 years with a mean of 52.6 years (SD 7.8). Two-thirds of patients aged 50 years and above and 60.3% of patients were males. The average duration of DM was 4.0 years (SD 3.0). Half of patients had DM for more than 3 years. About 55.2% had a baseline Hba1c <8% (27.6%) had a baseline Hba1c between 8 and <9% and 17.2% had a baseline Hba1c of ≥9%. About half of patients (53.4%) were hypertensive, 44.8% had hyperlipidemia, and 20.7% were current smokers. Other demographic and clinical characteristics of patients at the baseline are shown in Table 1.

The changes in the studied parameters between the baseline and after three months of using vildagliptin are shown in Table 2. FBG decreased significantly from 10.8 mmol/L at the baseline to 9.0 mmol/L after the three months of vildagliptin use (p value <.005). Hba1c decreased significantly from an average of 8.0% at the baseline to 6.9% with an average reduction of 1.1% (p value <.005). Overall, 62.1% had achieved the target of Hba1c of <7% with the addition of vildagliptin.

After three months of vildagliptin use, 75% of patients who had baseline Hba1c <8%, 50% of those who had baseline Hba1c 8–<9%, and 40% who had baseline Hba1c ≥9% had achieved the target of Hba1c of <7% after vildagliptin use (Figure 1). Furthermore, the use of vildagliptin resulted in a significant decrease of systolic BP by 3.1 mmHg (p value = .016) and a significant decrease in diastolic BP by 3.7 mmHg (p value = .002). However, there was no significant change in the weight of patients after using vildagliptin (p value = .208).

In the multivariate analysis, the only factors associated with reduction in Hba1c were the baseline Hba1c level and the daily frequency of metformin use. The average reduction in Hba1c was higher for those who were taking metformin three times a day compared to two times a day (Table 3). Patients with higher Hba1c at baseline had higher decrease in Hba1c after three months of vildagliptin use. Other variables including age, BMI, and duration of T2DM were not significantly associated with the decrease in Hba1c.

The addition of vildagliptin to metformin was generally well tolerated during the 12- week treatment. AEs were reported in 16 patients (28%). The most commonly reported AEs were gastrointestinal symptoms (seven patients), three patients reported abdominal pain, two patients reported diarrhea, two reported dizziness, two reported mild upper

Table 1. The demographic and clinical characteristics of patients at the baseline.

Variable	Frequency	%
Age (years)		
<50	22	37.9
≥50	36	62.1
Duration of diabetes (years)		
≤3	29	50.0
>3	29	50.0
Baseline Hba1c (%)		
<8	32	55.2
8–<9	16	27.6
≥9	10	17.2
Sex		
Male	35	60.3
Female	23	39.7
Current smoker	12	20.7
Family history of diabetes	46	79.3
Retinopathy	3	5.2
Ischemic heart disease	5	8.6
Neuropathy	10	17.2
Hypertension	31	53.4
Angiotensin – converting enzymes inhibitors use	20	34.5
Hyperlipidemia	26	44.8
Beta blockers use	12	20.7
Calcium channel blockers use	11	19.0
Diuretics use	9	15.5
Statins use	20	34.5

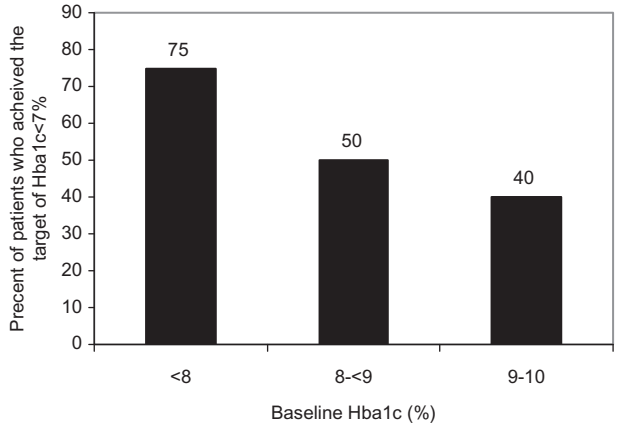

Figure 1. The effect of using vildagliptin on Hba1c.

Table 2. The changes in the studied parameters between the baseline and after 3 months of using vildagliptin.

Variables	Mean (SD)		Mean difference (SD)	p Value (paired t test)
	Baseline	After 3 months		
Fasting blood sugar	10.8 (2.9)	9.0 (2.8)	1.8 (2.9)	<.005
Hba1c (%)	8.0 (0.9)	6.9 (0.7)	1.1 (1.0)	<.005
Systolic blood pressure	129.0 (9.0)	125.9 (9.1)	3.1 (9.5)	.016
Diastolic blood pressure	83.1 (6.9)	79.4 (8.1)	3.7 (8.9)	.002
Weight (kg)	90.1 (17.0)	89.6 (17.2)	0.4 (2.7)	.208

Table 3. Variables associated with Hba1c reduction after three months of vildagliptin use.

Variables	Mean and standard deviation (SD)	p Value
Metformin frequency		.027
Two times daily	1.0 (0.9)	
Three times daily	1.4 (1.1)	
Baseline Hba1c		<.005
<8	0.7 (0.6)	
8–<9	1.3 (0.8)	
9–10	2.3 (1.1)	

Hba1c: glycosylated hemoglobin type a1c

respiratory tract symptoms, one patient reported constipation, and one reported nausea. Other non-specific symptoms were one complaint of each of insomnia, pruritus, fatigue, palpitation, and hand numbness. No episodes of hypoglycemia or other AEs were reported during the 12-week study.

Discussion

This study demonstrated that adding vildagliptin of doses of 50 mg twice daily to patients with T2DM inadequately controlled by metformin monotherapy results in clinically meaningful reduction in FPG and Hba1c without increase in the incidence of hypoglycemia or weight gain. The combination proved to be well tolerated with low incidence of AEs.

We found that both Hba1c and FPG levels were reduced at three months by 1.1% and 1.8 mmol/L, respectively. Although solid conclusions cannot be established by comparing studies performed with different design and patient's population, the observed reduction in Hba1c of 1.1% in this study is in agreement with recently published clinical trials.[10,29] A similar result was obtained from longitudinal data from general and internal practices in Germany.[21]

In China, one study of adding vildagliptin to metformin resulted in 1.05% reduction of Hba1c after 24 weeks' treatment.[30] A slightly higher Hba1c reduction of 1.25% was reported in another randomized control trial.[31]

In a recent Indian retrospective study,[32] the reduction in Hba1c was 1.9% which is compatible with another study [33] where vildagliptin combined with metformin was given in treating T2 DM naïve patients. Combination of vildagliptin therapy with metformin have also been evaluated in three double-blind controlled studies and showed statistically meaningful reduction in Hba1c of 0.7 [13] and 0.9%.[14,15] The pill burden and compliance in type-2 diabetic patients treated with vildagliptin (PROVIL) study [34] in Germany demonstrated a reduction of 0.9% in mean Hba1c after six months of the treatment by vildagliptin and metformin.

Data from large studies [35] have also demonstrated that vildagliptin reduced Hba1c by 0.65–1.1% in studies up to 52 weeks. A meta-analysis [36] of 30 randomized controlled trials showed that treatment with vildagliptin decreased Hba1c by 0.77%.

In addition to glycemic control, safety, tolerability, and effects on body weight are important considerations in selecting of antidiabetic medications. Recurrent episodes of hypoglycemia are also an important obstacle in achieving glycemic control in diabetic patients. According to the UK Prospective Diabetes Study (UKPDS),[37] the rates of hypoglycemic episodes vary between 7.9 and 25.5% with the highest incidence in patients treated with sulfonylurea and insulin. In this study, there was no single hypoglycemic event reported, a result which is consistent with data from several previous studies.[10,19,20] A result of meta-analysis [38] of 29 studies showed that the risk of hypoglycemia is the same in patients taking DPP-4 inhibitors or placebo. Our study showed that there was no significant change in body weight, a result which is consistent with data from previous studies.[10,13–15] The most frequent AEs reported in our study were mild gastrointestinal complaint experienced by only about 1 in 8 subjects. Though different studies showed varied incidence of AEs in patients treated with vildagliptin compared to placebo, a recent meta-analysis [36] summarized the AEs of vildagliptin and stated that there was no increase in overall risk of any AEs when compared to placebo.

Our research has two important limitations. First, it is not a randomized double-blinded study comparison group. However, we were interested in assessing the effectiveness and tolerability of vildagliptin in a primary care clinic so that our findings would have relevance to other community-based clinics. The second limitation is that our study lasted only 12 weeks and T2DM is a chronic disease. Clearly, additional studies with longer durations need to be undertaken in primary care settings.

Conclusion

In conclusion, vildagliptin as add-on therapy to metformin improved glycemic control and was highly tolerable in patients with T2DM who had inadequately glycemic control using metformin as monotherapy. Our findings consolidated the consistency of showing that vildagliptin as an add-on therapy to metformin is both efficacious and safe.

Transparency

Declaration of funding

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Declaration of financial/other relationships

The authors and JDA peer reviewers on this manuscript have no relevant financial relationships to disclose.

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