Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

The effects of sitagliptin, a DPP-4 inhibitor, on cognitive functions in elderly diabetic patients with or without Alzheimer's disease

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ARTICLE INFO

Article history:
Received 30 August 2016
Accepted 8 December 2016
Available online 21 December 2016

Keywords:
Sitagliptin
Cognitive function
Alzheimer disease
Dementia
Elderly

ABSTRACT

Aims: The present study aimed to evaluate effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4I), on cognitive functions in elderly diabetic patients with and without cognitive impairment.

Methods: 253 elderly patients with type 2 DM, were enrolled in this prospective and observational study. After comprehensive geriatric assessment, the patients were divided into either sitagliptin or non-sitagliptin group.

Results: A total of 205 patients who completed the study (52 with Alzheimer's Disease (AD)) were re-evaluated 6 months later. Sixth-month evaluation revealed no difference between sitagliptin and non-sitagliptin groups in terms of weight, body mass index, and HbA1c ($p > 0.05$). However, the number of patients that required reduced insulin dose was significantly higher in the sitagliptin group ($p = 0.01$). Sitagliptin therapy was associated with an increase in the Mini-Mental State Examination (MMSE) scores ($p = 0.034$); patients without AD receiving only sitagliptin or insulin showed higher MMSE scores as compared to the patients receiving metformin alone ($p = 0.024$). Likewise, the change in MMSE scores in AD patients receiving sitagliptin was significant and indicated improvement as compared to the patients receiving metformin ($p = 0.047$).

Conclusion: Besides its effects similar to those of insulin and metformin in glycemic control and in reducing need for insulin, 6-month sitagliptin therapy may also associated with improvement of cognitive function in elderly diabetic patients with and without AD. Further randomized controlled trials are needed to support these results.

1. Introduction

The prevalence of diabetes mellitus (DM) and dementia, particularly Alzheimer Disease (AD), increases with age all over the world. There is a growing body of evidence indicating the role of DM in cognitive functions in the elderly; epidemiological evidence suggest that DM is associated with 2-fold increased risk of developing AD independent from vascular risk factors as compared to healthy controls [1–3]. Although the molecular interaction between both diseases has not been

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http://dx.doi.org/10.1016/j.diabres.2016.12.010
0168-8227/

completely understood yet, it is known that physiopathological mechanisms in AD including molecular, biochemical and signal transduction abnormalities are some similarities to those in DM. Decreased insulin signaling dysfunction in the brain due to insulin dysfunction might be the primary mechanism shared in both diseases [4]. Therefore, "brain insulin resistant state" has been suggested, to better characterize the nature of AD [5,6]. Chronic peripheral hyperinsulinemia and insulin resistance are the major characteristics of DM, and chronic peripheral hyperglycemia is suggested to be the cause of cognitive impairment in elderly patients with DM [4,7]. On the other hand, insulin signaling has been desensitized in the brains of AD patients even though they did not have diabetes [8,9]. In addition, chronic peripheral hyperinsulinemia could cause brain insulin-resistance and defective insulin receptor activity by impairing Blood Brain Barrier and insulin transport into the brain [10]. Consequently, impaired brain insulin signaling could be one of the underlying mechanisms in neurodegenerative disorders, and brain activity is rapidly affected by progressively impaired learning, memory and cognition [11–13].

Moreover, recent studies' suggestion that some antidiabetics improve cognitive functions in addition to glycemic regulation has been promising for AD, for which no curative therapy has been developed until today. Glucagon-like peptide-1 (GLP-1) analogues are one of these anti-diabetic agents dwelled on recently. GLP-1 is mainly secreted by intestinal endocrine epithelial L-cells. Physiological levels of GLP-1 enhance glucose-induced insulin secretion, delay gastric emptying, restore peripheral insulin sensitivity and regulate blood glucose level. Besides, it was demonstrated that GLP-1 influences brain metabolism, stimulates neuritic growth in the brain, and has neuroprotective effect against oxidative stress and cell death [14,15]. It was also demonstrated that GLP-1 is cytoprotective and can prevent cognitive decline by improving learning ability in the experimental rat model of AD [11]. It is therefore clear that GLP-1 receptor agonists represent an important class of anti-diabetic agents that may also offer a potential to treat cognitive decline [16].

In addition to GLP-1 agonists, augmentation of GLP-1 by oral DPP-4 inhibitors such as sitagliptin is now being used to treat patients with DM. Sitagliptin prevents degradation of endogenous incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide and improves glycemic control, stimulates insulin secretion, and suppresses glucagon secretion [17,18]. It was reported that DPP-4 inhibition improves neuronal insulin receptor function and brain mitochondrial function and can delay some forms of AD-like pathology [19]. It was demonstrated that sitagliptin not only could improve cognitive impairment but also play a role in improved insulin sensitivity, increased hippocampal neurogenesis and reduced oxidative stress in an experimental study performed in high-fat-fed mice [20]. It was recently reported that DPP-4 inhibitors improve glucose control and stabilize cognitive functions in elderly diabetic patients with mild cognitive impairment [20]. Furthermore, the fact that DPP-4 inhibitors improve glycemic control without associated hypoglycemia in older adult patients with diabetes [21] is also important to be able to prevent hypoglycemia to reduce the risk of cognitive decline [22].

The present study was aimed to evaluate whether sitagliptin therapy was associated with improvement of cognitive functions in the diabetic older adults with or without AD. On the other hand, to evaluate the advantages such as decreased risk for hypoglycemia, limiting insulin dose, effectiveness and tolerability of sitagliptin in these patients were secondary end-points of this study.

2. Materials and methods

A total of 253 elderly patients with type 2 DM, who admitted to the department of geriatric medicine in Dokuz Eylul University hospital between January 2012 and March 2015, were included in this prospective and observational study.

2.1. *Patients*

The type 2 DM was diagnosed based on the plasma glucose criteria, either the fasting plasma glucose or the 2-h plasma glucose value after a 75-g oral glucose tolerance test or the A1C criteria [22]. Seventy-seven of the patients had been diagnosed with AD based on the "National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association" criteria and the patients have been receiving standard AchEI and/or memantine therapy for AD. The patients, who are intolerant to or have medical ontraindications for metformin, were treated with sitagliptin, and sitagliptin were added to insulin and/or metformin therapy in those patients who had poor glycemic control. Subsequently, the patients were divided into either sitagliptin or non-sitagliptin group in addition to their current therapies. The group receiving sitagliptin (100 mg/day) was defined as the case group and the patients not receiving sitagliptin were defined as the control group. Over the course of study period, 48 patients were excluded due to the reasons illustrated in Fig. 1. After 6-month follow-up period, glycemic status and comprehensive geriatric assessment were repeated in 205 patients, of whom 52 had AD, and the study was finalized.

The study was carried out in accordance with the Declaration of Helsinki and was approved by The Central Ethical Committee of the Ministry of Health. The written consents were provided from patients or their guardians.

2.2. *Exclusion criteria*

Diabetic patients who have been currently receiving antidiabetic agents other than metformin and/or insulin were not included in the study. Patients with type 1 DM, active liver disease, recent history of cardiovascular disease (acute coronary syndrome, coronary artery intervention, New York Heart Association Class III/IV heart failure, stroke, transient ischemic neurologic event, or new/worsening symptoms of coronary heart disease or cerebrovascular disease), inadequately controlled hypertension, severe peripheral vascular disease, triglyceride levels $\geqslant$600 mg/dL, history of HIV infection, pancreatitis, malignancy or clinically important hematologic disorder, and an estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal

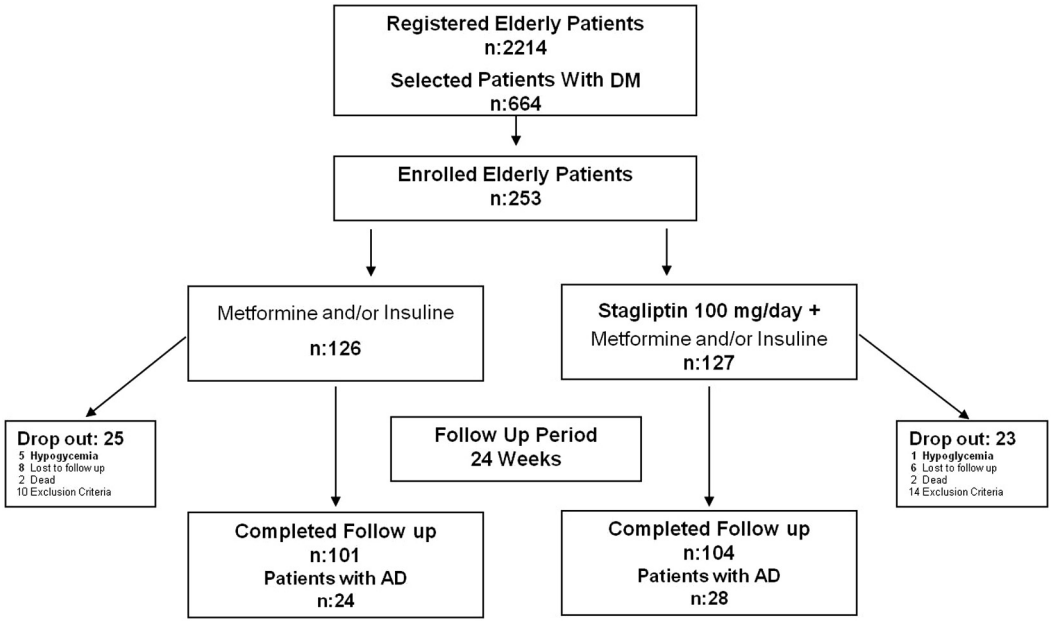

Fig. 1 – Study flow sheet.

Disease formula) less than 30 mL/min/1.73 m^2 were also excluded. Moreover, patients with dementia other than AD, that were in delirium status during evaluation period, patients with psychotic disease (schizoaffective disorder, etc.), treatment-resistant major depressive disorder and alcohol and substance addiction were not enrolled in the study. Patients receiving DPP-4 inhibitor other than sitagliptin or GLP-1 agonists, those with intolerance to sitagliptin, as well as those who have been receiving or needed to receive diabetogenic drugs or the drugs that are likely to affect cognitive functions such as corticosteroids, benzodiazepines and antipsychotics were excluded.

2.3. *Comprehensive geriatric assessment (CGA)*

Age, gender, duration of DM (year), number of drugs used, weight, body mass index (BMI) and comorbidities such as hypertension, coronary artery disease, congestive heart failure, peripheral vascular disease, hyperlipidemia, cerebrovascular disease, chronic obstructive pulmonary disease and depression were recorded. Cognitive functions of the patients were evaluated by Mini-Mental State Examination (MMSE). In addition, scores of the Geriatric Depression Scale (GDS), Mini Nutritional Assessment-Short Form (MNA-SF), and basic and instrumental Activities of Daily Living (BADL and IADL, respectively) indexes were also recorded for each patient [23]. To calculate body mass index (BMI), height was measured to the nearest centimeter (cm) and weight was measured to the nearest half-kilogram (kg) with the same stadiometer.

2.4. *Laboratory findings*

Certain laboratory tests such as complete blood count, fasting blood glucose, HbA1c, renal and hepatic functions, albumin, cholesterol, thyroid stimulating hormone (TSH), vitamin B12 and folic acid levels were done to assess biochemical, metabolic and glycemic status of the patients in our geriatrics clinic. All of these biochemical tests were done using Diagnostic Modular Systems auto-analyzer (Roche E170 and P-800).

2.5. *Follow-up*

Patients' glycemic status was evaluated at the 3th and 6th months, whereas CGA was re-performed at the 6th month.

2.6. *Statistical analysis*

Continuous variables were expressed as mean ± standard deviation. Kolmogorov–Smirnov test was used to analyze continuous variables in terms of suitability for normal distribution. Continuous variables with normal distribution were analyzed by Independent Sample *t*-test, whereas continuous variables without normal distribution were analyzed by Mann–Whitney *U* test. Differences in proportions were analyzed using chi-square test. Probabilities <0.05 were considered significant. All statistical analyses were done using SPSS 15.0 (SPSS Inc.). Changes between the visits were calculated by the [after treatment–before treatment] formula. The relation of metformin, sitagliptin and insulin use with the changes between visits was assessed by Kruskal–Wallis Test. Paired *t* test was used for the comparison of the values between baseline and 6th-month visit in each drug group.

3. Results

Demographic, anthropometric, comorbidity and laboratory data of sitagliptin (104) and non-sitagliptin (101) groups are demonstrated in Table 1.

Baseline and 6th-month evaluations revealed no difference between the groups in terms of weight, BMI, HbA1c,

Table 1 – Comparison of socio-demographic, clinical and laboratory features of patients's groups.

	Sitagliptin (–) (n:101)	Sitagliptin (+) (n:104)	*P value*
Age	76.12 ± 8.20	74.75 ± 8.72	0.246
Sex (female%)	65.3	54.8	0.124
Duration of diabetes	13.48 ± 5.42	14.91 ± 7.58	0.123
Number of drugs	7.24 ± 3.69	7.78 ± 3.44	0.240
Weight (kg)	72.78 ± 13.82	76.59 ± 14.34	0.084
BMI (kg/m^2)	29.57 ± 5.31	30.65 ± 5.42	0.177
Comorbidities%			
HT	85.1	79.8	0.315
CAD	31.7	26.9	0.454
HL	19.8	26.9	0.229
CHF	12.9	12.5	0.936
COPD	9.9	11.5	0.705
CVD	7.9	5.8	0.541
PVD	5.9	8.7	0.456
Dementia	23.8	27.2	0.575
Depression	21.5	37.8	0.142
Laboratory data			
Hgb (g/L)	12.78 ± 1.70	12.73 ± 1.71	0.818
Albumin (g/l)	4.06 ± 0.36	4.08 ± 0.31	0.715
LDL cholesterol (mg/dL)	122.16 ± 43.46	118.76 ± 37.07	0.578
Triglyceride (mg/dL)	138.40 ± 68.33	153.92 ± 75.05	0.154
HDL cholesterol (mg/dL)	51.57 ± 15.18	49.10 ± 12.91	0.259
TSH (uIU/mL)	1.71 ± 1.40	2.35 ± 3.81	0.126
Folic acid (ng/mL)	9.48 ± 5.71	8.70 ± 4.48	0.345
Vitamin B12 (pmol/L)	557.05 ± 388.33	497.38 ± 317.59	0.262

BMI: body mass index; CAD: coronary artery disease; CHF: congestive heart failure; CVD: cerebrovascular disease; DM: diabetes mellitus; HDL: high density lipoprotein; HL: hyperlipidemia; HT: hypertension; LDL: low density lipoprotein; PVD: peripheral vascular disease; TSH: thyroid stimulating hormone.

nutritional status, cognition, mood, and functionality ($p > 0.05$). The number of patients receiving and not receiving sitagliptin was 101 and 104 respectively among type 2 diabetic patients. There was also no difference between the groups in terms of the changes between the visits ($p > 0.05$). The number of patients that decreased in insulin requirement was higher in the sitagliptin group ($p < 0.02$) (Table 2). Insulin therapy could be stopped in 6 patients receiving sitagliptin because of no longer need for insulin. In addition, the number of patients who was excluded the follow up due to the hypoglycemia episode was 1 in sitagliptin group; whereas, this was 5 in those treated without sitagliptin.

Baseline characteristic of the patients without AD treated with metformin, sitagliptin or insulin monotherapy were summarized in the Table 3, and at the end of 6 months MMSE scores of the patients were 23.34 ± 5.43, 23.65 ± 5.50 and 24.50

Table 2 – Comparison of baseline and 6-month clinical features of the patients.

Parameters	Sitagliptin (–) (n:101)		Sitagliptin (+) (n:104)		*p*	
	Baseline	6 months	Baseline	6 months	p_1	p_2
Fasting blood glucose (mg/dl)	132.36 ± 49.47	133.20 ± 49.84	159.35 ± 73.43	143.50 ± 51.87	<0.01	<0.05
HbA1c	7.36 ± 1.60	7.11 ± 1.36	7.62 ± 1.63	7.16 ± 1.09	0.10	0.79
Weight (kg)	72.78 ± 13.82	72.11 ± 13.07	76.59 ± 14.34	75.14 ± 16.64	0.08	0.21
BMI (kg/m^2)	29.57 ± 5.31	29.23 ± 4.84	30.65 ± 5.42	30.57 ± 5.59	0.17	0.17
MMSE	23.12 ± 5.38	23.12 ± 5.38	23.48 ± 5.13	24.18 ± 5.02	0.64	0.26
GDS	4.54 ± 3.92	3.60 ± 3.71	4.88 ± 3.76	4.35 ± 3.50	0.42	0.10
BADL	92.16 ± 11.82	92.22 ± 11.57	88.72 ± 16.42	88.87 ± 16.34	0.06	0.29
IADL	10.81 ± 4.75	10.16 ± 4.70	10.52 ± 4.82	10.36 ± 5.26	0.64	0.58
MNA	11.31 ± 2.34	11.51 ± 1.99	10.96 ± 2.21	11.33 ± 2.28	0.17	0.90
Decrease in insulin requirement, n(%)	4 (3.96)		18 (17.30)		<.02	

p_1 for baseline comparisons; p_2 for control comparisons.

BADL: basic activities of daily living (0 [worst]–100 [best]), CDR: clinical dementia rating (0 [best]–3 [worst]); GDS: geriatric depression scale: (0 [worst]–15 [best]); IADL: instrumental activities of daily living (0 [worst]–17 [best]); MMSE: Mini-Mental State Examination (0 [worst]–30 [best]); MNA: Mini Nutritional Assessment-Short Form (0 [worst]–14 [best]).

Table 3 – Characteristics of the patients without AD treated with metformin, sitagliptin or insulin monotherapy.

	Metformin n:69	Sitagliptin n:43	Insulin n:22	P
Baseline Characteristics				
Age	77.12 ± 7.87	77.05 ± 8.50	77.61 ± 9.40	.758
Duration of Diabetes	12.95 ± 4.99	13.38 ± 8.5	15.66 ± 6.97	.309
HbA1c	6.90 ± 1.29	7.29 ± 1.49	7.50 ± 1.19	.022
BMI (kg/m^2)	29.78 ± 4.71	28.86 ± 4.21	28.33 ± 5.24	.335
BADL	89.73 ± 17.25	90.41 ± 13.45	93.71 ± 10.39	.482
IADL	11.11 ± 4.70	10.03 ± 4.63	11.82 ± 4.31	.261
GDS	4.87 ± 4.21	5.40 ± 3.82	3.28 ± 3.25	.134
MMSE	23.55 ± 5.38	22.73 ± 5.64	23.50 ± 4.03	.794
Changes from Baseline				
cHbA1c*	−0.30 ± 0.88	−0.30 ± 0.98	0.11 ± 0.82	.244
cMMSE*	−2.50 ± 3.03	0.95 ± 2.17	0.94 ± 1.89	.024
cIADL*	−1.06 ± 2.65	−0.17 ± 1.35	−1.00 ± 1.88	.094
cBADL*	−0.48 ± 7.18	−1.05 ± 5.25	−3.78 ± 5.79	.126

BADL: basic activities of daily living (0 [worst]–100 [best]); BMI: body mass index; GDS: geriatric depression scale: (0 [worst]–15 [best]); IADL: instrumental activities of daily living (0 [worst]–17 [best]); MMSE: Mini-Mental State Examination (0 [worst]–30 [best]).
* Mean changes from baseline.

± 4.39, respectively. There were significant increase in the MMSE scores of the patients receiving sitagliptin or insulin ($p = 0.034$, $p = 0.039$; respectively when compared the baseline. Comparing the patients receiving metformin, sitagliptin or insulin in terms of mean change from baseline in glycemic status, cognitive functions and daily living activities, there were significant increase in MMSE scores in the patients receiving sitagliptin or insulin ($p = 0.024$).

The number of AD patients receiving only metformin, sitagliptin or insulin was 17, 11 and 3, respectively. Because of limited number of patients receiving insulin, the comparison was done between the patients receiving only metformin and only sitagliptin and an increase was determined in MMSE scores in the patients receiving sitagliptin ($p = 0.047$) (Fig. 2).

4. Discussion

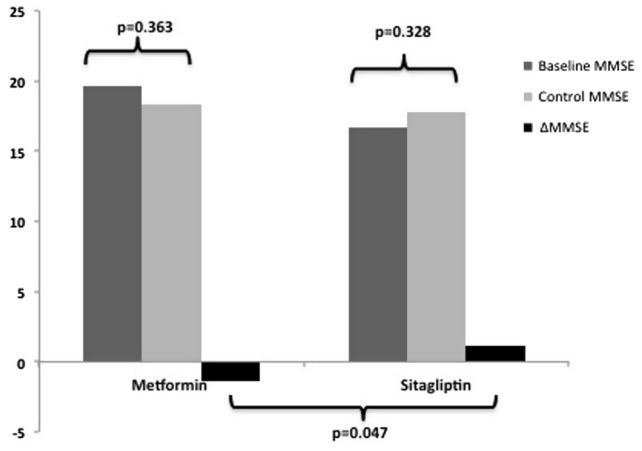

Fig. 2 – Comparison of MMSE scores and mean changes from baseline in MMSE scores in the patients with AD treated with metformin or sitagliptin monotherapy.

This prospective observational study demonstrated that 6-month sitagliptin therapy was associated with increased cognitive functions in the elderly diabetic patients with and without AD. Furthermore, it was also demonstrated that the need for insulin was lower in those treated with sitagliptin.

There is a growing body of evidence about the role of DM on cognitive functions in elderly and, according to the current evidence, cognitive impairment in elderly diabetic patients is considered to be the direct consequence of chronic hyperglycemia. Therefore, effects of anti-DM agents on cognitive functions have become the subject of interest. In the recent days, however, emphasis has been put on the effects of GLP-1-based therapies, one of the anti-DM therapies, on cognitive functions due to their potential effects on central nervous system. It was reported that the neuroprotective effects of sitagliptin may be attributable to increased plasma GLP-1 levels which cause an increase in the available endogenous GLP-1 crossing the blood–brain barrier and increase brain GLP-1 levels. Besides, it was also reported that sitagliptin therapy may be also associated with improved insulin sensitivity, enhanced hippocampal neurogenesis and reduced oxidative stress [18]. Experimental studies reported that such therapeutic agents act by preventing either Aβ accumulation or hyperphosphorylation of AD-associated tau protein [11,16]. The number of relevant clinical studies is quite less. In one of these, a retrospective longitudinal study evaluated effects of DPP- IV inhibitors (sitagliptin, vildagliptin or saxagliptin) + metformin therapy and sulfonylurea + metformin therapy on glycemic control and cognitive functions in 240 diabetic elderly patients with MCI (mild cognitive impairment). At the end of two years, it was determined that glycemic control was better and cognitive functions were less impaired in the patients receiving DPP-IV inhibitor. In the above-mentioned study, however, DPP- IV inhibitors have not been evaluated individually by subgroup analysis; the diagnosis of MCI was made based only on patient records, and it could not be identified whether MCI stands for amnes-

tic MCI [20]. In the present study, we determined that prospectively added sitagliptin into the current therapy has no significant effect on cognitive functions, daily activities, weight, and BMI in the elderly diabetic patients. Nevertheless, evaluation of the patients receiving sitagliptin, insulin or metformin alone revealed significant increase in MMSE scores as compared to the baseline in the patients receiving sitagliptin therapy and this increase was significantly higher as compared to those receiving metformin, and sitagliptin provided a glycemic control similar to that of the other two agents. The fact this significant increase is more prominent in AD patients receiving sitagliptin versus metformin is of particular importance. Besides, this increase brought our mind that sitagliptin might be a cognitive enhancer as well as anti-diabetic properties. Furthermore, we determined increase in MMSE scores also in those receiving only insulin, which is consistent with the literature [24,26]. These results are similar to the results of the study conducted by Rizo et al. [20]. However, the reason for this favorable effect of sitagliptin becoming more striking in the present study might have been the result of likely neutral/negative effect of metformin on cognitive functions. Accordingly, it could be reason why possible cognitive enhancer effect of sitagliptin could have been demonstrated in the patients receiving sitagliptin alone.

As well as glycemic control, DPP-IV inhibitors are also associated with low risk of hypoglycemia, neutral effect on body weight, and potential improvement in quality of life in older patients [17,20]. Consistent with the literature, not only the number of patients that developed hypoglycemia was lower, but also decrease in blood glucose levels was more significant in the cases receiving sitagliptin. In addition, insulin need significantly decreased in the patients receiving sitagliptin. Hypoglycemia episodes can cause serious complications such as cardiovascular events, arrhythmia, stroke and falls in addition to cognitive impairment in elderly [25]. Multiple comorbid condition, cognitive decline, visual disorders, and loss of hand skills such as tremor may limit insulin use or necessitate someone's help in elderly [25]. For these reasons, lowering the risk of hypoglycemia and reducing insulin need have been propounded in the present study as two advantages of sitagliptin for elderly in which treatment of diabetes has particular importance.

This observational and prospective study has few limitations; number of cases is inadequate for subgroup analysis, which would evaluate effects of monotherapies and combined therapies. Six months may be short to clearly expose the efficacy of the sitagliptin and metformin treatment, and prolonged study duration may be an appropriate approach. Finally, the number of AD patients in the groups was limited. The powerful aspects of the present study are the facts that it is prospective and is one of the pioneer studies that evaluate effects of sitagliptin on cognitive functions and daily activities in elderly diabetic patients with and without AD.

In conclusion, 6-month sitagliptin therapy shows similar effect to that of metformin and insulin on glycemic control in elderly diabetic patients with and without AD. On the other hand, different from the metformin, sitagliptin therapy may also associated with increased cognitive functions. Further randomized controlled trials are needed to support these results.

Conflicts of interest

None.

Funding of source

None.

Acknowledgment

The authors thanks to Hulya ELLIDOKUZ for statistical analysis.

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