Cognitive and metabolic outcomes of vildagliptin addition to the therapy in patients with type 2 diabetes mellitus: 26 week follow-up study

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ABSTRACT

Aims: Type 2 Diabetes Mellitus(DM) is a well-known risk factor for cognitive impairment. Recent evidences suggest that Dipeptidyl peptidase-4(DPP-4) inhibitors might have neuroprotective effects. Therefore, this study aimed to investigate vildagliptin, a DPP-4 inhibitor, effects on cognitive function in older patients with DM.
Materials and Methods: A retrospective longitudinal clinical trial was carried out on total 130 subjects with type 2 DM. Patients underwent comprehensive geriatric assessment twice within six months interval. The patients were divided into three groups according to antidiabetic treatment: untreated control group (patients achieve individual goal HbA1c without antidiabetic medication), vildagliptin(+) group(patients using vildagliptin alone or combination) and the vildagliptin(–) group.
Results: The mean age was 75.72 ± 7.46 years. The control group was older, of a lighter weight and also had a higher female gender ratio(p ≤ 0.01). When sex, age, educational level and metabolic profile were adjusted, there was only change in copying subdomain of Mini Mental State Examination between vildagliptin(+) and other groups at the end of 6 months. Vildagliptin also resulted in reduction of HbA1c and weight(p < 0.05).
Conclusion: The addition of vildagliptin to treatment improved the copying subdomain of cognitive function and metabolic control of the older patients with type 2 DM within 6 months.

1. Introduction

As the global population is getting older, the prevalence of diabetes mellitus (DM) and Alzheimer Disease (AD) increase (Isik, Soysal, Yay, & Usarel, 2017). AD is the most common type of dementia in older adults, and despite a large body of detailed clinical and experimental literature, there is no effective treatment to prevent disease progression, in contrast to DM (Isik, 2010). Moreover, DM is a well-recognized risk factor for AD and vascular dementia (VAD). Conditions related to insulin dysregulation, such as obesity, cardiovascular disease, and hypertension, have been commonly observed in patients with AD, raising concerns about their role in development of dementia (Isik & Bozoglu, 2009). In the Rotterdam Study, a large-sample prospective cohort study, patients with diabetes have been shown to have almost a 2-fold increase in the risk for developing AD (Ott et al., 1999). Therefore, management of DM may also reduce the risk of cognitive impairment (Li, Song, & Leng, 2015).

Additionally, Type 2 DM shares several pathophysiological mechanisms with AD, such as glucotoxicity, amyloid aggregation, insulin resistance, inflammation, mitochondrial dysfunction and oxidative stress (Ninomiya, 2014). It is reported that insulin and insulin receptors have a crucial function in neuroprotection, neurotrophy, neuromodulation, affecting learning and memory. Insulin resistance and defective insulin signaling promote accumulation of amyloid β and neurofibrillary tangles (Craft & Watson, 2004; Isik et al., 2007). Insulin receptor dysfunction, abnormally higher activity of glycogen synthase kinase-3 (GSK-3) and the subsequent dysregulated protein phosphorylation have been commonly detected among both AD and Type 2 DM patients. Biochemical studies demonstrate insulin signaling in the brain is desensitized in AD patients, similar to the changes in the periphery in patients with diabetes (Talbot et al., 2012). Moreover, insulin improves brain functions such as attention and memory formation in humans (Stockhorst, de Fries, Steingrueber, & Scherbaum, 2004). Due to the close relationship between the two diseases, AD has been termed as

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'Type 3 Diabetes' (Li et al., 2015).

Additionally, recent evidences suggest some antidiabetic medications including intranasal insulin administration, glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors may improve cognitive performance (Angelopoulou & Piperi, 2018). Among these medications GLP-1 analogs and DPP-4 inhibitors, called incretin-based drugs, are remarkable. GLP-1 has neuroprotective effects inducing cell growth, regeneration, and inhibits apoptosis, inflammation (Holscher, 2014), which is degraded rapidly by dipeptidyl peptidase-4 (DPP-4) enzyme, leading to a very short half-life less than 2 minutes. In addition to GLP-1 agonists, DPP-4 inhibitors such as sitagliptin, saxagliptin, linagliptin and vildagliptin prolong plasma half-life of GLP-1 and are potential therapeutic agents for type 2 DM. Although studies researching the effects of glucose-lowering agents on dementia reported contradictive results, some of them pointed out DPP-4 inhibitors may be beneficial on cognitive functions. Isik et al. reported that 6-month sitagliptin therapy was associated with improvement in cognitive functions in the older patients with diabetes and AD (Isik et al., 2017).

Consequently, the aim of this study was to show the effect of vildagliptin on cognitive functions in older adults with type 2 DM with or without AD. The second purpose of the study was to investigate the impact of vildagliptin on metabolic parameters including body weight, body mass index (BMI), HbA1c, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and Triglyceride (TG) in the same patients.

2. Materials and methods

2.1. Subjects

The records of patients with type 2 DM, who applied to the geriatric outpatient clinic between January 2014 and March 2018, were retrospectively reviewed. DM diagnosis was confirmed with either the fasting plasma glucose value or second hour plasma glucose value of 75-g oral glucose tolerance test (OGTT), or HbA1c criteria of American Diabetes Association (2. Classification & Diagnosis of Diabetes Standards of Medical Care in Diabetes-2019, 2019). Demographic characteristics, comorbidities, medications, comprehensive geriatric assessment parameters and laboratory data were obtained from the records. The patients were divided into three groups according to their antidiabetic treatment: untreated control group (patients achieve individual goal HbA1c without medication), vildagliptin (+) group (patients receiving vildagliptin alone or with combination) and the vildagliptin (-) group which involved patients treated with other agents.

2.2. Ethical approval

All procedures performed in the study involving human participants were in accordance with the ethical standards of the national research committee (Dokuz Eylul University local ethics committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

2.3. Inclusion and exclusion criteria

Patients with type 1 DM, active liver disease, alcohol and substance abuse, severe illnesses that can cause unstable major medical illness (e.g., acute cerebrovascular event, sepsis, gastrointestinal bleeding, acute renal failure, acute respiratory failure), major primary psychiatric disorders (schizophrenia, bipolar disorder or recurrent major depressive disorder), inadequately controlled hypertension, severe peripheral vascular disease, triglyceride levels higher than 600 mg/dL, history of malignancy, and an estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease formula) less than 30 mL/min/1.73m^2 were excluded. Patients treated with GLP-1

analogues or DPP-4 inhibitors except vildagliptin were also excluded from the study.

To be included, patients had to be 60 years and older, and undergone comprehensive geriatric assessment twice within 6 months. Included regimens were metformin, insulin and vildagliptin, alone or combination of two or three. A total of 130 patients with type 2 DM diagnosis who did not have exclusion criteria, were included in the study.

2.4. Patients' characteristics

Patients' demographic characteristics including age, sex, duration of education, accompanying systemic diseases, duration of diabetes mellitus and the number of drugs used were rewieved. Hypertension, coronary artery disease, congestive heart failure, hyperlipidemia, peripheral arterial disease, cerebrovascular disease were obtained from patients' reports. Dementia and depression were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria (American Psychiatric Association, 2013).

2.5. Comprehensive geriatric assessment

To assess global cognitive function, the Mini-Mental State Examination (MMSE) test was selected and each subdomain score was evaluated separately as well as total score. Patients were also administered the Geriatric Depression Scale (GDS) (Durmaz, Soysal, Ellidokuz, & Isik, 2017), the Basic and Instrumental Activities of Daily Living (BADL, IADL), the Mini Nutritional Assessment (MNA) scale, the clock drawing test (CD), and the Clinical Dementia Rating Scale (Unutmaz, Soysal, Tuven, & Isik, 2018). Blood pressure values, weight and standing height measures were recorded at the baseline and follow-up evaluations. Accordingly, BMI values were calculated. Additionally, heart disease or stroke risk of the patients were calculated according to American Heart Association guideline (Goff et al., 2014). The change in points was obtained by subtracting the initial value from the follow-up value, and the delta (Δ) value was specified for each test score. [(Δ) value: 6th months evaluation-Baseline evaluation].

2.6. Laboratory evaluation

Laboratory tests including renal and liver functions, HbA1c, thyroid-stimulating hormone (TSH) level, cholesterol levels, and vitamin D, vitamin B12, and folic acid levels were taken to evaluate the biochemical, metabolic, and nutritional status of the patients. All of these parameters were obtained with the auto-analyzer diagnostic modular system (Roche E170 and P-800). Serum 25-hydroxy D vitamin [25(OH)D] was measured by radioimmunoassay.

2.7. Study size

According to Aschner (Aschner et al., 2014) et al. article in 2014, when the frequency of patients with diabetes in geriatric cases was accepted as 8 %, it was decided to include at least 110 patients to the study, at the level of 3 % acceptable error and 95 % confidence.

2.8. Statistical analyses

Descriptive statistics are shown as mean ± standard deviation (SD) for variables with normal distribution, median (minimum to maximum) for non-normal distributions, and the number of cases and percentage (%) for nominal variables. Because the distribution of data does not fit normal distribution, the significance of differences between the two groups in terms of averages was investigated by Mann Whitney U test, whereas Kruskal Wallis test was used in more than two groups. Delta scores of cognitive subdomains were adjusted for potential confounders including sex, age, education, duration of diabetes mellitus and HbA1c.

Table 1
Baseline Characteristics of the Patients.

	Control group n:35	Vildagliptin (+) n:43	Vildagliptin (-) n:52	P	P1	P2
DEMOGRAPHIC FEATURES(%)						
Sex (female)	85.7	58.1	61.5	**0.02**	**< 0.01**	0.73
Age	79.7 ± 4.8	74.4 ± 7.9	74.2 ± 7.8	**< 0.01**	**< 0.01**	0.77
Education(> 11 Years)	31.4	23.3	44.2	0.09	0.41	**0.03**
Marital Status (married)	54.3	69	66.7	0.82	0.45	0.83
Weight (kg)	65.0 ± 10.1	74.2 ± 12.4	74.0 ± 10.3	**< 0.01**	**< 0.01**	0.73
BMI (kg/m^2)	28.5 ± 4.2	29.3 ± 5.1	29.1 ± 4.5	0.86	0.74	0.77
Total Number of Drugs	7.1 ± 3.6	8.3 ± 3.9	6.8 ± 2.7	0.10	0.14	**0.03**
Duration of Diabetes Mellitus (years)	11.3 ± 7.6	18.4 ± 9.9	16.4 ± 10.6	**0.02**	**< 0.01**	0.28
COMORBIDITIES (%)						
Hypertension	85.7	79.1	82.7	0.74	0.44	0.65
Ischemic heart disease	17.1	32.6	30.8	0.25	0.12	0.85
Congestive Heart Failure	8.6	4.7	13.5	0.33	0.48	0.14
Peripheral Arterial Disease	5.7	4.7	5.8	0.96	0.83	0.80
Cerebrovascular Disease	5.7	11.6	1.9	0.14	0.36	**0.05**
Dementia	34.3	32.6	17.3	0.12	0.87	0.08
Depression	40.0	37.2	30.8	0.64	0.80	0.50
Charlson Comorbidity Index	1.73 ± 1.07	1.94 ± 1.15	1.78 ± 1.03	0.76	0.51	0.55
LABARATORY FINDINGS						
HBA1C (%)	6.01 ± 0.49	7.63 ± 1.37	7.12 ± 1.57	**< 0.01**	**< 0.01**	**< 0.01**
HDL (mg/dL)	56.58 ± 14.20	48.76 ± 11.00	52.69 ± 14.30	**0.03**	**< 0.01**	0.18
LDL (mg/dL)	117.30 ± 42.84	127.76 ± 37.78	115.75 ± 40.23	0.45	0.29	0.26
TG (mg/dL)	117.28 ± 43.60	165.32 ± 93.83	169.38 ± 89.77	**< 0.01**	**0.02**	0.66
Creatinine (mg/dL)	0.97 ± 0.33	0.93 ± 0.30	0.98 ± 0.39	0.79	0.64	0.50
TSH (uIU/mL)	1.75 ± 1.37	2.92 ± 8.41	1.43 ± 0.89	0.82	0.56	0.92
Vitamin D (ng/mL)	21.47 ± 14.29	21.89 ± 15.34	23.13 ± 19.43	0.99	0.96	0.88
Vitamin B12 (pmol/L)	614.29 ± 366.64	498.36 ± 377.48	426.33 ± 233.35	0.08	0.07	0.96
Folic acid (ng/mL)	10.34 ± 5.77	9.50 ± 5.44	8.74 ± 4.49	0.44	0.42	0.71
GFR (mL/min)	63.31 ± 21.49	71.60 ± 20.07	70.21 ± 20.33	0.19	0.09	0.66

Abbreviations:BMI: Body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein; TG: triglyceride, TSH: thyroid stimulating hormone, GFR: glomerular filtration rate.
p: for comparisons among three groups.
p[1]: for comparisons between vildagliptin and control groups.
p[2]: for comparisons between vildagliptin (+) group and vildagliptin (-) group.

Analysis of the data was carried out in SPSS for Windows 22 package program (SPSS Inc., Chicago, IL, USA). Results of $p < 0.05$ were considered statistically significant.

3. Results

Three groups were designed in the retrospective follow-up study according to antidiabetic treatment: 35 untreated control patients, 43 vildagliptin users and 52 patients not receiving vildagliptin. The average age of the study group was 75.72 ± 7.46 years. There were totally 35 demented patients. The control group was older, of a lighter weight and had a higher female gender ratio ($p \leq 0.01$). The control group had lower duration of diabetes mellitus, HbA1c and TG levels, but higher HDL levels. The Vildagliptin (-) group had a higher rate of educated participants and lower number of drugs. Except from age, basal weight, sex, education and number of total drugs there was no significant difference in demographic characteristics or the number of participants with major cognitive impairment between the groups ($p > 0.05$). The characteristics of the groups are shown in Table 1.

In the baseline evaluation orientation, record, attention, copying and total points of MMSE were worse in the vildagliptin (+) group. BADL scores were lower in the vildagliptin (+) group, as well ($p < 0.05$). When the differences between 6 months and baseline values were observed, among three groups the delta changes in language and copying scores were significant ($p < 0.05$). Language points increased in control group. Copying points improved in vildagliptin group more than the other two groups. Delta changes of MMSE subgroup scores were adjusted for sex, age, education, duration of diabetes mellitus, HbA1c and dementia, only the Δcopying score between vildagliptin and the other two groups remained significant. Table 2 summarizes basal comprehensive geriatric assessment parameters and delta changes

according to the follow-up evaluation.

In addition, HbA1c and weight control were found to be significant only in patients treated with vildagliptin at the end of sixth month. Even if HbA1c values were the lowest, HbA1c values increased significantly in the control group. Cholesterol levels did not change in each group at the 6th month follow-up. Table 3 shows baseline and follow-up metabolic features of each group separately.

4. Discussion

In this retrospective follow-up study, it was shown that vildagliptin therapy may help to improve some domains of cognitive function even after adjustments for age, sex, education level and HbA1c values. Additionally, vildagliptin therapy was found beneficial in the setting of weight and metabolic control in patients with diabetes.

The link between AD and DM is so complex that its pathophysiologic pathways cannot be clearly elucidated, but it is considered that several mechanisms, sine qua non conditions for DM, including insulin resistance, impaired glucose metabolism, the production of advanced glycosylation end-products, impairment in amyloid β degradation, increased oxidative stress, and inflammation play an important role in the development of AD (Li et al., 2015) (Alagiakrishnan & Sclater, 2012). Moreover, DM increases ischemic changes in the brain, either by ischemic stroke or cardiovascular diseases, which lead to irreversible brain damage and also cause the vascular cognitive impairment in patients with DM (Biessels, Deary, & Ryan, 2008; Shukla, Shakya, Perez-Pinzon, & Dave, 2017). Brain-Derived Neurotrophic Factor (BDNF), which has a regulatory role in neuronal differentiation and synaptic plasticity, is reduced with hyperglycemia (Krabbe et al., 2007). Moreover, recent evidence highlights the effect of insulin and its receptor action on cognitive functions. It was reported that intranasal insulin

Table 2
Baseline Evaluations and Delta (Δ) Changes of the Patients.

	Control group n:35	Vildagliptin (+) n:43	Vildagliptin (-) n:52	P	P1	P2
MMSE subdomains						
MMSE Total score	24.94 ± 4.31	21.81 ± 6.16	26.04 ± 5.04	**< 0.01**	**0.02**	**< 0.01**
Orientation $_{temporal}$	3.91 ± 1.54	3.19 ± 1.93	4.23 ± 1.39	**< 0.01**	0.08	**< 0.01**
Orientation $_{spatial}$	4.26 ± 0.91	3.91 ± 1.42	4.48 ± 1.05	**0.03**	0.51	**0.01**
Orientation $_{total}$	8.17 ± 2.29	7.09 ± 3.18	8.71 ± 2.37	**0.01**	0.16	**< 0.01**
Record	2.97 ± 0.16	2.79 ± 0.60	2.98 ± 0.13	**0.03**	0.08	**0.02**
Attention	3.97 ± 1.38	2.70 ± 1.89	3.90 ± 1.70	**< 0.01**	**< 0.01**	**< 0.01**
Recall	1.49 ± 1.14	1.23 ± 1.15	1.75 ± 1.13	0.09	0.34	0.07
Language	7.71 ± 0.66	7.74 ± 0.72	7.88 ± 0.42	0.37	0.71	0.31
Copying	0.63 ± 0.49	0.42 ± 0.49	0.79 ± 0.41	**< 0.01**	0.06	**< 0.01**
MMSE TotalΔ score	− 0.28 ± 2.87	− 0.27 ± 2.57	− 0.01 ± 2.95	0.07	0.50	0.44
Orientation $_{temporalΔ}$	− 0.20 ± 0.93	− 0.27 ± 1.07	0.00 ± 0.90	0.24	0.57	0.11
Orientation $_{spatialΔ}$	0.08 ± 0.61	− 0.09 ± 0.68	0.03 ± 0.59	0.22	0.12	0.26
Orientation $_{totalΔ}$	− 0.11 ± 1.36	− 0.37 ± 1.25	0.03 ± 1.15	0.14	0.10	0.08
RecordΔ	− 0.02 ± 0.38	0.00 ± 0.37	− 0.01 ± 0.13	0.92	0.97	0.74
AttentionΔ	− 0.14 ± 1.33	0.00 ± 1.15	0.09 ± 1.14	0.63	0.66	0.30
Recall Δ	0.00 ± 0.68	0.13 ± 0.96	0.09 ± 0.97	0.63	0.32	0.66
Language Δ	0.20 ± 0.58	− 0.20 ± 0.80	**-0.09 ± 0.63**	**0.03**	**0.01**	0.62
Copying Δ	− 0.20 ± 0.47	0.13 ± 0.46	− 0.07 ± 0.47	**< 0.01***	**< 0.01***	**0.02***
Comprehensive Geriatric Assessment						
GDS	2.89 ± 3.57	3.11 ± 3.06	3.24 ± 3.54	0.62	0.31	0.71
BADL	86.49 ± 18.08	84.26 ± 22.10	94.00 ± 11.21	**< 0.01**	0.56	**< 0.01**
IADL	15.43 ± 6.55	14.48 ± 6.84	17.85 ± 5.67	**0.02**	0.49	**0.01**
MNA	10.97 ± 2.82	12.07 ± 2.15	12.24 ± 1.93	0.09	0.09	0.65
GDSΔ	− 0.28 ± 2.64	− 1.03 ± 2.72	− 0.77 ± 2.74	0.31	0.15	0.76
BADLΔ	− 1.68 ± 8.84	− 3.72 ± 15.26	− 3.34 ± 9.53	0.18	0.76	0.14
IADLΔ	− 2.03 ± 4.38	− 0.75 ± 4.11	− 0.83 ± 4.28	0.34	0.28	0.62
MNAΔ	0.51 ± 2.13	− 0.25 ± 2.84	0.33 ± 2.02	0.64	0.36	0.52
Framingham Heart Disease Risk Score						
Risk Score	42.80 ± 13.91	40.13 ± 16.33	37.45 ± 18.24	0.62	0.55	0.65
Risk ScoreΔ	− 0.19 ± 9.46	− 0.73 ± 12.64	− 0.55 ± 9.41	0.98	0.69	0.84

Abbreviations: Δ: delta (6th month evaluation-Baseline evaluation), GDS: Geriatric depression scale, BADL: Basic activities of daily living, IADL: Instrumental activities of daily living, MNA. Mini nutritional assessment, Δ:
p: for comparisons both three groups.
p^1: for comparisons between vildagliptin and control groups.
p^2: for comparisons between vildagliptin (+) group and vildagliptin (-) group.
 * Only Δcopying score remained significant after adjustment ($p < 0.05$).

administration improves cognitive performance of early AD and amnestic Mild Cognitive Impairment (MCI) patients (Craft et al., 2012; Reger et al., 2008). Therefore, treatment of Type 2 DM may have a potential effect to prevent or delay cognitive impairment.

Among these strategies, the incretin-based therapies, termed dream team, include GLP-1 agonists and DPP-4 inhibitors. The latter provides an antihyperglycemic effect as well as the cardioprotection in patients with diabetes (Groeneveld, Kappelle, & Biessels, 2016; Sebastião et al., 2014). Our study demonstrated that the patients treated with vildagliptin showed significant improvements in weight, BMI and HbA1c levels although they were the poorest glycemic control. Whereas, there was no change in cardiovascular risk prediction score in patients with

or without vildagliptin therapy, which was incompatible with the aforementioned study.

In addition to their effectiveness on glycemic control, DPP-4 inhibitors may improve several pathophysiological mechanisms underlying AD including neuronal insulin resistance, mitochondrial dysfunction, oxidative stress, Aβ42 burden, tau phosphorylation, neuroprotection/neurogenesis and neuroinflammation in experimental studies, suggesting that what is good for DM may also be good for AD (Duffy & Holscher, 2013; Gault, Lennox, & Flatt, 2015; Holscher, 2014; Kosaraju et al., 2013; Pellegrini et al., 2011; Pintana, Apaijai, Chattipakorn, & Chattipakorn, 2013; Pipatpiboon, Pintana, Pratchayasakul, Chattipakorn, & Chattipakorn, 2013; Pratchayasakul

Table 3
Baseline and Follow-up Metabolic Features of Patients.

	Control group Baseline	Control group 6th month	p	Vildagliptin (+) Baseline	Vildagliptin (+) 6th month	P	Vildagliptin (-) Baseline	Vildagliptin (-) 6th month	P
Weight(kg)	64.9 ± 10.1	69.1 ± 11.1	0.38	74.1 ± 12.4	70.6 ± 12.0	**0.02**	74.0 ± 10.2	73.7 ± 11.2	0.22
BMI(kg/m^2)	28.5 ± 4.1	29.5 ± 4.4	0.10	29.3 ± 5.0	28.4 ± 5.0	**0.03**	29.0 ± 4.5	29.3 ± 4.7	0.84
HBA1C (%)	6.0 ± 0.4	6.3 ± 0.3	**< 0.01**	7.6 ± 1.3	7.1 ± 1.1	**0.04**	7.1 ± 1.5	6.8 ± 1.0	0.54
HDL(mg/dL)	56.5 ± 14.2	55.2 ± 11.0	0.82	48.7 ± 11.0	50.9 ± 11.2	0.27	52.6 ± 14.3	53.3 ± 11.9	0.93
LDL(mg/dL)	117.3 ± 42.8	126.6 ± 34.2	0.58	127.7 ± 37.7	119.2 ± 41.2	0.20	115.7 ± 40.2	116.3 ± 31.3	0.64
TG(mg/dL)	117.2 ± 43.6	146.6 ± 78.7	0.10	165.3 ± 93.8	157.6 ± 62.3	0.33	169.3 ± 89.7	143.5 ± 63.9	0.11
Creatinine(mg/dL)	0.9 ± 0.3	0.9 ± 0.2	0.07	0.9 ± 0.3	0.9 ± 0.3	0.69	0.9 ± 0.3	1.2 ± 1.5	0.47
TSH(uIU/mL)	1.7 ± 1.3	2.0 ± 1.6	0.41	2.9 ± 8.4	2.7 ± 7.7	0.67	1.4 ± 0.8	1.5 ± 1.1	0.11
GFR(mL/min)	63.3 ± 21.4	65.8 ± 18.8	0.35	71.6 ± 20.0	73.3 ± 19.1	0.65	70.2 ± 20.3	71.1 ± 21.0	0.25

Abbreviations: BMI: Body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein; TG: triglyceride, TSH: thyroid stimulating hormone, GFR: glomerular filtration rate.

et al., 2011). On the other hand, the clinical studies have reported that plasma DPP-4 activities are related to impaired cognitive functions in the elderly population without diabetes, partly attributed to the increase of oxidative stress induced by DPP-4 (Chen et al., 2017). In a retrospective longitudinal study conducted with MCI patients, the addition of DPP-4 inhibitors to treatment regimen improved all cognitive parameters within 2 years (Rizzo et al., 2014) Moreover, sitagliptin, a DPP4 inhibitor, was demonstrated to provide dual benefits by improving glycemic control and cognitive function in elderly patients with diabetes and AD during the 6-month follow-up in our previous study (Isik et al., 2017). In the present study, vildagliptin improved the copying ability of the patients compared to others with higher education, but this effect was not seen in the performance of the cognitive functions in global or other subdomains. Perhaps these effects could have occurred if the duration of treatment was longer than 6 months. Since vildagliptin does not cause hypoglycemia and weight gain, and its effect on cognitive functions has not been so far elaborated in detail, it is one of the safest anti-diabetic agents in older adults. A recent study with mild cognitive impairment patients showed that adding vildagliptin to metformin therapy prevented MMSE score reduction and maintained better HbA1c control compared to only metformin therapy at the end of sixth months, in accordance with present study results (Borzi et al., 2019). Considering the increasing prevalence of Alzheimer's Disease and diabetes in older adults, the cognitive decline in diabetic patients called diabetes-related cognitive decrements and lack of a definitive treatment for AD (Biessels & Despa, 2018; Isik et al., 2017), it is crucial to note that the addition of vildagliptin to conventional anti-DM treatment has positive effects on copying, a subdomain of cognitive functions, as well as on glycemic control. This is very important for the practice of geriatrics because patients benefit more with less medicine. However, it would be better if the sample size for each group was large enough to be able to analyze subgroup performance according to the presence of cognitive impairment. The possible positive effects of vildagliptin on cognitive function, just like sitagliptin, may be attributable to increased plasma GLP-1 levels. Also, inhibition of DPP-4 may be associated with improved insulin sensitivity, enhanced hippocampal neurogenesis and reduced oxidative stress (Gault et al., 2015; Isik et al., 2017).

To the best of our knowledge, this is the first longitudinal clinical study with a sufficient sample size to investigate the cognitive effects of vildagliptin in older patients with DM. However, it has some limitations. First, the number of patients with cognitive impairment was not sufficient to allow subgroup analysis according to cognitive status. Second, the cognitive assessment was performed with MMSE, a simple test that can evaluate global cognitive functions, but cannot do so in all cognitive subdomains in detail. Third, even though adjustments were made, basal demographic characteristics (education, gender), metabolic status and basal cognitive performance were different between the groups. Fourth, the short follow-up duration and retrospective nature of the study were the other limitations.

4.1. Conclusion

The addition of vildagliptin, a DPP4 inhibitor, to conventional anti-DM treatment improved the copying subdomain of cognitive functions, and glycemic control in older patients with diabetes within 6 months. Further randomized controlled trials are needed to clarify the effects of vildagliptin or other DDP-4 inhibitors on cognitive functions in older adults.

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Statement of authorship

Author EAB performed manuscript writing and data collection and analysis; Author ZYSA contributed to data acquisition and interpretation, Authors OD, SEK involved in data collection and drafting the manuscript; Authors PS and LS reviewed the manuscript and provided critical revisions, Author ATI designed the study, carried out conceptualism and revised for the approval. All authors have approved the final article.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

None.

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