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Effects of vildagliptin, a DPP-4 inhibitor, in elderly diabetic patients with mild cognitive impairment

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ABSTRACT

Introduction: There is an unclear association between type 2 diabetes and mild cognitive impairment in the elderly. Both diseases are more prevalent in the older adults compared to the younger counterpart. Some anti-diabetic drugs seem to influence positively the evolution of mild cognitive impairment. This retrospective study investigated the effect of vildagliptin, an inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), on the cognitive functioning of elderly diabetic patients with mild cognitive impairment (MCI) documented at mini mental state examination (MMSE).

Methods: We included 60 diabetic elderly people which were divided in 2 groups: Group A, 30 patients with HbA_1c (glycated hemoglobin) $\leq 7.5\%$ and treated with metformin, and Group B, 30 patients with $HbA_1c > 7.5\%$, and treated with metformin plus vildagliptin. We collected data on MMSE, fasting plasma glucose (FPG) and HbA_1c at baseline and after 180 ± 10 days from the beginning of treatment.

Results: The two groups exhibited significantly different values in FPG ($P < 0.05$) and HbA_1c ($P < 0.01$) at baseline, and in MMSE score ($P < 0.001$) after treatment. The intragroup comparison showed a significant ($P < 0.05$) reduction in MMSE score in group A, and in HbA1c ($P = 0.01$) in group B.

Conclusion: Vildagliptin in addition to metformin resulted in the maintenance of MMSE score, showing a protecting role on cognitive functioning compared to the metformin only group.

1. Introduction

Type 2 Diabetes mellitus (T2D) is an increasing global health problem (Tabish, 2007). T2D affects approximately 150 million people worldwide, and its prevalence will double by the year 2025 (Wild, Roglic, Green, Sicree, & King, 2004). T2D is characterized by the combination of relative insulin deficiency and insulin resistance. Symptoms of T2D may be absent or mild for several years (Ndisang, Vannacci, & Rastogi, 2017; Papatheodorou, Papanas, Banach, Papazoglou, & Edmonds, 2016). Mild Cognitive Impairment (MCI) indicates a transition phase between normal cognitive aging and dementia without changes in daily functioning. MCI patients have memory deficit that can be isolated or associated to a slight decline of other cognitive functions (language, visual-spatial abilities, executive functions, reasoning abilities) (Petersen et al., 1999, 2001). There is growing evidence that T2D could be associated to an increased rate of MCI and progression to dementia (Li, Wang, & Xiao, 2016). In fact, chronic hyperglycemia is able to induce high oxidative stress levels, leading to an acceleration in the atherosclerotic process and micro- and macro-angiopathic complications (Chisari et al., 2019; Fiorentino, Prioletta, Zuo, & Folli, 2013). The mechanism underlying vascular dementia is the chronic atheromatous process leading to the luminal

Abbreviations: AD, Alzheimer's disease; AGEs, advanced glycation end products; AIFA, Agenzia Italiana del Farmaco; Aβ, amyloid beta; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; DPP-4i, DPP-4 inhibitors; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, geriatric depression scale; GLP-1, increases glucagon-like peptide-1; HbA1c, glycated haemoglobin; HDL, high density lipoprotein cholesterol; IL, interleukin; KDOQI, kidney disease outcomes quality initiative; LDL, low density lipoprotein cholesterol; MAGE, mean amplitude of glycemic excursions; MCI, mild cognitive impairment; MMSE, mini mental state examination; T2D, type 2 diabetes mellitus TSH thyroid stimulating hormone

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stenosis of vessels (Hardigan, Ward, & Ergul, 2016; Malaguarnera, Vacante, Frazzetto, & Motta, 2012).

Furthermore, recurrent hypoglycemic episodes could represent a cause of cognitive impairment in the elderly; Whitmer et al., observed that the attributable risk for dementia of 2.39% per year between subjects with and without a history of hypoglycemia (Whitmer, Karter, Yaffe, Quesenberry, & Selby, 2009). Elderly patients with diabetes who experienced hypoglycemia showed a 2-fold increased risk of fall-related events over a 1-year period (Kachroo et al., 2015). A number of studies have demonstrated that some oral antidiabetic drugs (OADs) may improve cognitive functioning in patients with MCI and AD (Alagiakrishnan, Sankaralingam, Ghosh, Mereu, & Senior, 2013). Due to the lack of effective therapies for MCI and AD, the use of OADs for reducing or preventing cognitive decline is emerging as a promising tool.

Vildagliptin, an antidiabetic drug that inhibits the dipeptidyl peptidase-4 (DPP-4), increases glucagon-like peptide-1 (GLP-1) and regulates blood glucose levels, favouring weight loss and lowering cardiovascular risk (Karagiannis, Bekiari, Boura, & Tsapas, 2016).

A retrospective longitudinal study by Rizzo et al. showed that DPP-4 inhibitors (DPP-4i) administration could have protective effects against cognitive decline in diabetic elderly with MCI (Rizzo et al., 2014). Is has been observed that GLP-1 affects brain metabolism, increases neuritic growth, and protects neuronal cells from oxidative stress and death (Biswas, Buteau, & Greene, 2008). It is noteworthy that GLP-1 may cross the blood–brain barrier decreasing AβPP-Aβ burden in AD (Holscher, 2010). The administration of DPP-4i, including vildagliptin, shows some advantages compared to other OADs, in particular they can be given in all stages of renal impairment and present a low risk of hypoglycaemia. Furthermore, their side effect risks are not increased in patients with cognitive impairment (Puttanna & Padinjakara, 2017).

The aim of our study was to evaluate the effect of vildagliptin on the cognitive functioning of elderly diabetic patients with MCI.

2. Materials and methods

2.1. Patient data

We performed a retrospective medical record search of outpatients at the Unit of Diabetology of the Cannizzaro Hospital (Catania, Italy) between June 2016 and June 2017, and selected 146 elderly patients with type 2 diabetes mellitus. The medical records were selected as described in the flow-chart (Fig. 1).

Inclusion criteria were age > 65 years, MMSE score ≥18 and ≤23 (Monroe & Carter, 2012) and diagnosis of diabetes mellitus treated with metformin only, at a dosage of 1 g twice a day. We considered patients with complete data at a follow-up visit after 180 ± 10 days.

Exclusion criteria were incomplete data, significant comorbidities, including heart failure, coronary heart disease, stroke, chronic kidney disease (G3 grade KDOQI) (National Kidney Foundation, 2012), liver cirrhosis, history of pancreatic disease, chronic respiratory failure, depression evaluated by Geriatric Depression Scale (GDS, GDS > 15), diagnosis of dementia based on DSM 5 (Diagnostic and Statistical Manual of Mental Disorders) criteria, anticholinesterase or memantine therapy. Clinical (age, body mass index - BMI, duration of diabetes, number of drugs) and laboratory parameters (hemoglobin, high density lipoprotein - HDL, low density lipoprotein - LDL, triglycerides, folic acid, vitamin B12, thyroid stimulating hormone - TSH) were collected for all patients.

According to the AIFA (Agenzia Italiana del Farmaco, Italian Drug Regulatory Body) patients with inadequately controlled diabetes, defined as HbA1c ≥7.5%, could start dual combination of metformin and DPP-4i. 60 patients showed mild-to-moderate cognitive impairment documented at MMSE (score between 18 and 23). None of the patients with cognitive decline was on anticholinesterase or memantine, or started this therapy until the follow-up visit. 30 patients had HbA1c ≤7.5% and continued therapy with metformin 1 g twice a day, whereas 30 patients had HbA1c > 7.5% and added vildagliptin 50 mg twice a day to metformin 1 g twice a day.

This study was designed and conducted in compliance with the ethical principles of Good Clinical Practice Guidelines and the Declaration of Helsinki (World Medical Association, 2013).

2.2. Anthropometric measurements

All measurements were performed after overnight fasting. Height and body weight were measured in all patients in the morning with light dress and without shoes (SECA 220). BMI was calculated as weight in kilograms divided by the square of height in meters.

2.3. Laboratory tests

All subjects received morning blood testing within 2 h after admission. Cubital venipuncture was performed after night fasting. The blood chemistry parameters evaluated at admission were: total cholesterol, HDL, LDL, triglycerides, folate, vitamin B12 and TSH. All subjects underwent blood testing of HbA1c and FPG at admission and after 180 ± 10 days. All blood chemistry parameters were performed on the same analytical platform and the quality evaluation was performed through regular quality control procedures.

2.4. Mini mental state examination

The MMSE evaluates the cognitive status and documents the evolution over time. MMSE is used as a screening test and in advanced stages of disease. Its administration requires from 5 to 15 min. The MMSE is simple and brief and can be used even in the advanced stages of dementia, unlike a battery of neuropsychological tests (such as the MODA or the ADAS-Cog).

The score is given by the sum of the correct answers for each item: from a minimum of 0 (maximum cognitive deficit) to a maximum of 30 (absence of cognitive deficit).

In the calculation of the MMSE score, adjustment coefficients are applied by age, education and cultural level. Based on the MMSE score, three cut-scores were identified: 1) 24–30 absence of cognitive impairment; 2) 18–23 mild to moderate cognitive impairment; 3) 0–17 serious cognitive impairment. MMSE is useful for the assessment of disease progression and treatment response (Folstein, Folstein, & McHugh, 1975; Mitchell, 2009).

2.5. Geriatric depression scale

The GDS has been used broadly in the elderly. The GDS Long Form is a 30-item questions structured to a yes/no format. From the Long Form GDS were selected the 15 items which showed the highest correlation with depressive symptoms and were used for the short version. Corrections are applied to the test according to age, education, and complaints. Scores of 0–4 indicate normal condition; 5–8 mild depression; 9–11 moderate depression and 12–15 severe depression. The Short Form can be used by patients with mild to moderate dementia who have brief duration of attention and/or feel easily fatigued. The test needs about 5–7 min to be completed. The GDS test has been validated in community, acute and long-term care settings (Fountoulakis et al., 1999).

2.6. Statistical analysis

The variables are expressed as mean ± standard deviation or as a range. The comparison between the continuous variables represented was performed with the independent samples Student *t*-test or Pearson's χ^2 test was used when appropriate. A P value < 0.05 was considered statistical significant. Statistical analysis was performed using SPSS

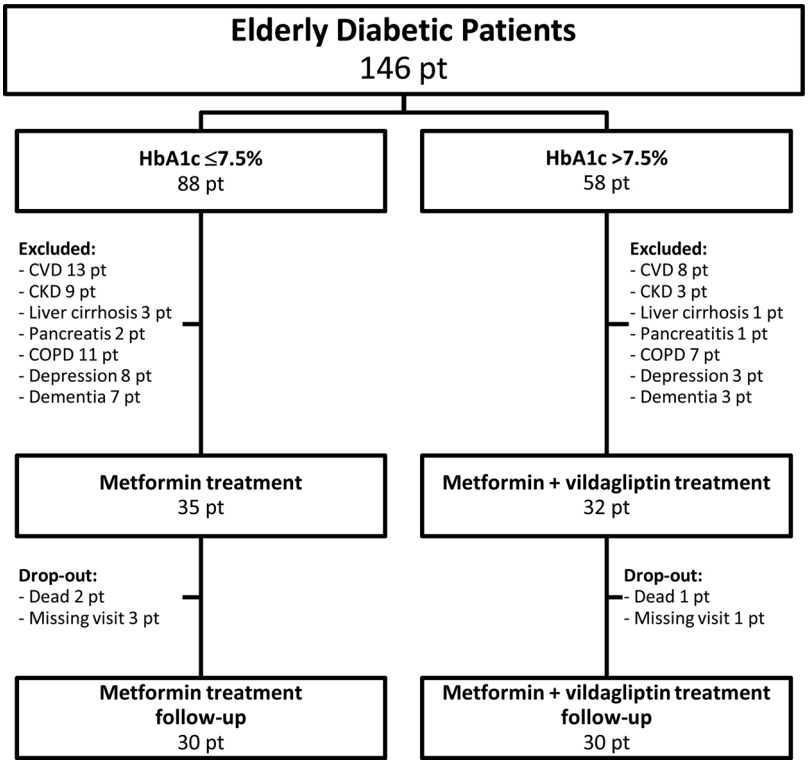

Fig. 1. Flow-chart of patients' selection process.
Pt: patients; CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

15.0 for Windows (Chicago, IL).

3. Results

Demographic and clinical characteristics at baseline were homogeneous (Table 1). No statistically significant differences were observed in laboratory parameters at baseline between the two groups (Table 1).

Most patients in both groups were females (M/F = 27/33) mean age 76.56 ± 7.87 years, overweight (29.01 ± 6.32 kg/m^2) and duration of diabetes was 16.10 ± 6.34 years. The intergroup comparison demonstrated statistically significant differences in FPG ($p = 0.03$) and HbA1c ($p < 0.01$) at baseline, and in MMSE score ($p < 0.001$) after 180 ± 10 days (Fig. 2).

The intragroup comparison showed a statistically significant reduction in MMSE ($p < 0.01$) score in group A, and a statistically significant reduction in HbA1c ($p = 0.01$) in group B (Table 2).

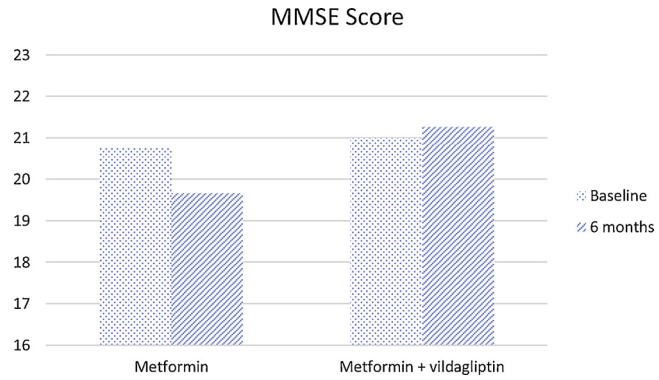

Fig. 2. MMSE score at baseline and at follow-up.
MMSE: Mini Mental State Examination.

Table 1
Groups comparison of patients' characteristics and laboratory parameters at baseline.

	Group A metformin	Group B metformin + vildagliptin	P*
Sex (M/F)	13/17	14/16	0.80
Age (years)	75.46 ± 7.89	77.67 ± 8.23	0.29
BMI (kg/m^2)	28.48 ± 6.69	29.55 ± 5.92	0.51
Diabetes duration (years)	15.49 ± 6.83	16.72 ± 5.81	0.46
Drugs (n)	6.47 ± 2.32	6.33 ± 2.62	0.83
HDL-cholesterol (mg/dl)	50.81 ± 16.26	52.63 ± 14.11	0.65
LDL-cholesterol (mg/dl)	118.33 ± 47.16	125.14 ± 41.95	0.56
Triglycerides (mg/dl)	137.16 ± 69.03	150.86 ± 73.96	0.46
Folate (ng/ml)	9.15 ± 6.65	8.34 ± 5.76	0.62
B12 Vitamin (pg/ml)	616.53 ± 318.58	531.26 ± 396.59	0.36
TSH (μIU/ml)	1.66 ± 1.27	1.84 ± 1.34	0.60

HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol, TSH: thyroid-stimulating hormone, BMI: body mass index [(weight (kg)/height^2 (m^2)]. Data are expressed as Mean ± standard deviation.
* Student's unpaired *t*-test or χ^2 when appropriate.

4. Discussion

In our study, the patients treated with metformin plus vildagliptin did not show a reduction in cognitive performances at the end of the study period, contrarily to the patients treated with metformin only. At the beginning of the study, plasmatic levels of FPG and HbA1c were higher in vildagliptin plus metformin group; nevertheless, after 180 ± 10 days, values of FPG and HbA1c in vildagliptin plus metformin group did not show significant differences compared to the metformin only group. T2D is a risk factor for progression of MCI into dementia (Li et al., 2016). DPP-4i reduce the central and peripheral insulin resistance, and indirectly improve cognitive function through the reduction of inflammation and oxidative stress (Tsai et al., 2015; Zheng et al., 2016).

Dementia is an acquired disorder on an organic basis with a decay of

Table 2
Intra- and inter-group comparison at baseline and at follow-up.

	Group A metformin		p	Group B metformin + vildagliptin		p	Inter-group comparison	
	basal	Follow-up		basal	Follow-up		basal	Follow-up
FPG	136.45 ± 48.70	136.13 ± 46.38	*0.98*	164.79 ± 47.93	143.18 ± 42.12	*0.07*	0.03	0.54
HbA1c	7.09 ± 1.21	7.01 ± 1.28	*0.80*	8.02 ± 1.27	7.13 ± 1.32	*0.01*	< 0.01	0.72
MMSE	20.77 ± 1.22	19.67 ± 1.47	*< 0.01*	21.00 ± 1.41	21.27 ± 1.44	*0.47*	0.502	< 0.001

FPG: fasting plasma glucose, HbA1c: glycated hemoglobin, MMSE: mini mental state examination score.

intellectual functions. Diagnosis of dementia requires the detection of a decay of the mnesic function associated with at least one other deficit concerning cognitive functions and executive functions. These functions include memory, language skills, visual perception, problem solving, self-management, and the ability to focus and pay attention. Alterations of intellectual functions must occur in the absence of alterations in the state of consciousness and such alterations must compromise the patient's relationship life on a personal, occupational and social level (Sachdev, Mohan, Taylor, & Jeste, 2015). MCI refers to an intermediate stage from normal cognition to dementia, which may involve single or multiple cognitive domains. Any form of MCI, both amnestic and non-amnestic, could anticipate vascular dementia (Roberts & Knopman, 2013). Patients with T2D show higher incidence of MCI, compared to those without diabetes. The mechanism underlying the link between MCI and T2D remains unknown; there is evidence that glycemic alterations, advanced glycation end products (AGEs) and diabetic complications could represent major risk factors (Yuan & Wang, 2017).

A recent systematic review highlighted that GLP-1 and DPP-4i showed beneficial effects against neurotoxic substances, neurovascular damage due to free radicals and AGEs in diabetes, and pathological modifications in neurodegenerative and neurovascular disorders. Potential neuroprotective mechanisms could involve the increase of neurotrophic factors neuronal functioning, reduction of apoptosis and pro-inflammatory factors (Erbil et al., 2019).

Both DPP-4i saxagliptin and vildagliptin have been tested in preclinical studies of streptozotocin induced AD (Femminella et al., 2017). Patients treated with saxagliptin and vildagliptin showed a reduction of Aβ deposition, tau phosphorylation, and markers of inflammation, and an increase in hippocampal GLP-1 levels and memory functioning (Kosaraju, Gali et al., 2013; Kosaraju, Murthy et al., 2013). Zhang et al. studied the molecular effect of vildagliptin on cognitive impairment in a streptozocin-induced T2D rat model. In their study vildagliptin was found to decrease the apoptosis of hippocampal neurons and to reduce the hyperexpression of caspase-3, Bcl-2 and Bcl-2 associated X protein through the Akt/GSK3β signalling pathway (Zhang et al., 2018).

Poor glycemic control and mean amplitude of glycemic excursions (MAGE) may worse cognitive performances through an augmentation in oxidative stress, and the consequent production of neurotoxic substances, such as peroxynitrite and nitrotyrosine (Rizzo et al., 2010). A study by Rizzo et al. assessed the effects of sitagliptin and vildagliptin, which showed different efficacy on MAGE, on oxidative stress, and on systemic inflammatory markers in patients with T2D. The Authors observed a significant reduction in nitrotyrosine ($P < 0.01$), and in proinflammatory cytokines involved in the atherosclerotic process such as ($P < 0.05$), and IL-18 ($P < 0.05$), in patients treated with vildagliptin compared to those receiving sitagliptin (Rizzo, Barbieri, Marfella, & Paolisso, 2012). Furthermore, it has been observed that the administration of DPP-4i may reduce daily glucose fluctuation and symptomatic or asymptomatic hypoglycemic events (Dumbrill & Moulton, 2018; Paolisso, Monami, Marfella, Rizzo, & Mannucci, 2012). Thus, the action of DPP-4i on hypoglycaemia, could play a significative protective role on cognitive function, as observed in our patients treated with vildagliptin.

Our study has some limitations: first of all, it is a retrospective study that includes a small number of cases, and besides the short duration of follow-up. If pro-cognitive effects were confirmed in larger prospective studies and in the long term, vildagliptin could open new horizons in terms of secondary prevention of cognitive decline. Further studies are needed to investigate the direct or indirect effects (through an increase in GLP-1 levels) of vildagliptin on cognitive status of elderly with T2D.

Author contributions statement

Borzì AM, Vacante M, Condorelli G: Conception and Design; Condorelli G, Buscemi C: Acquisition of Data; Borzì AM, Vacante M, Buscemi C, Luca S, Basile F, Biondi A, Vicari ESD: Analysis and Interpretation of Data; Borzì AM, Vacante M: Drafting the Article; All authors: Final Approval of the Completed Article.

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Declarations of interest

None.

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References

Alagiakrishnan, K., Sankaralingam, S., Ghosh, M., Mereu, L., & Senior, P. (2013). Antidiabetic drugs and their potential role in treating mild cognitive impairment and Alzheimer's disease. *Discovery Medicine, 16*(90), 277–286.

Biswas, S. C., Buteau, J., & Greene, L. A. (2008). Glucagon-like peptide-1 (GLP-1) diminishes neuronal degeneration and death caused by NGF deprivation by suppressing Bim induction. *Neurochemical Research, 33*(9), 1845–1851. https://doi.org/10.1007/s11064-008-9646-4.

Chisari, G., Chisari, L. M., Borzì, A. M., Luca, S., Grasso, A., & Chisari, C. G. (2018). Microbiological etiology of chronic skin lesions in type 2 diabetic subjects. *Infectious Disorders Drug Targets, 19*(2), 207–212. https://doi.org/10.2174/1871526518666180411095823.

Dumbrill, J. L., & Moulton, C. D. (2018). Effects of incretin-based therapies on neurocognitive function in humans: A systematic review of the literature. *Primary Care Diabetes, 12*(1), 51–58. https://doi.org/10.1016/j.pcd.2017.06.009.

Erbil, D., Eren, C. Y., Demirel, C., Küçüker, M. U., Solaroğlu, I., & Eser, H. Y. (2019). GLP-1's role in neuroprotection: a systematic review. *Brain Injury,* 1–86. https://doi.org/10.1080/02699052.2019.1587000.

Femminella, G. D., Bencivenga, L., Petraglia, L., Visaggi, L., Gioia, L., Grieco, F. V., ... Ferrara, N. (2017). Antidiabetic drugs in Alzheimer's disease: Mechanisms of action and future perspectives. *Journal of Diabetes Research, 2017*, 7420796. https://doi.org/10.1155/2017/7420796.

Fiorentino, T. V., Prioletta, A., Zuo, P., & Folli, F. (2013). Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases. *Current Pharmaceutical Design, 19*(32), 5695–5703.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189–198.

Fountoulakis, K. N., Tsolaki, M., Iacovides, A., Yesavage, J., O'Hara, R., Kazis, A., ... Ierodiakonou, C. (1999). The validation of the short form of the Geriatric Depression

Scale (GDS) in Greece. *Aging (Milan, Italy), 11*(6), 367–372.
Hardigan, T., Ward, R., & Ergul, A. (2016). Cerebrovascular complications of diabetes: Focus on cognitive dysfunction. *Clinical Science (London, England: 1979), 130*(20), 1807–1822. https://doi.org/10.1042/CS20160397.
Holscher, C. (2010). Incretin analogues that have been developed to treat type 2 diabetes hold promise as a novel treatment strategy for Alzheimer's disease. *Recent Patents on CNS Drug Discovery, 5*(2), 109–117.
Kachroo, S., Kawabata, H., Colilla, S., Shi, L., Zhao, Y., Mukherjee, J., ... Fonseca, V. (2015). Association between hypoglycemia and fall-related events in type 2 diabetes mellitus: Analysis of a U.S. commercial database. *Journal of Managed Care & Specialty Pharmacy, 21*(3), 243–253. https://doi.org/10.18553/jmcp.2015.21.3.243.
Karagiannis, T., Bekiari, E., Boura, P., & Tsapas, A. (2016). Cardiovascular risk with DPP-4 inhibitors: Latest evidence and clinical implications. *Therapeutic Advances in Drug Safety, 7*(2), 36–38. https://doi.org/10.1177/2042098615623915.
Kosaraju, J., Gali, C. C., Khatwal, R. B., Dubala, A., Chinni, S., Holsinger, R. M. D., ... Basavan, D. (2013). Saxagliptin: A dipeptidyl peptidase-4 inhibitor ameliorates streptozotocin induced Alzheimer's disease. *Neuropharmacology, 72*, 291–300. https://doi.org/10.1016/j.neuropharm.2013.04.008.
Kosaraju, J., Murthy, V., Khatwal, R. B., Dubala, A., Chinni, S., Nataraj, S. K. M., & Basavan, D. (2013). Vildagliptin: An anti-diabetes agent ameliorates cognitive deficits and pathology observed in streptozotocin-induced Alzheimer's disease. *The Journal of Pharmacy and Pharmacology, 65*(12), 1773–1784. https://doi.org/10.1111/jphp.12148.
Li, W., Wang, T., & Xiao, S. (2016). Type 2 diabetes mellitus might be a risk factor for mild cognitive impairment progressing to Alzheimer's disease. *Neuropsychiatric Disease and Treatment, 12*, 2489–2495. https://doi.org/10.2147/NDT.S111298.
Malaguarnera, M., Vacante, M., Frazzetto, P. M., & Motta, M. (2012). The role of diabetes and aging in the determinism of hypertension and the related cerebrovascular complications. *Archives of Gerontology and Geriatrics, 55*(2), 221–225. https://doi.org/10.1016/j.archger.2011.08.008.
Mitchell, A. J. (2009). A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *Journal of Psychiatric Research, 43*(4), 411–431. https://doi.org/10.1016/j.jpsychires.2008.04.014.
Monroe, T., & Carter, M. (2012). Using the Folstein Mini Mental State Exam (MMSE) to explore methodological issues in cognitive aging research. *European Journal of Ageing, 9*(3), 265–274. https://doi.org/10.1007/s10433-012-0234-8.
National Kidney Foundation (2012). KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *American Journal of Kidney Diseases, 60*(5), 850–886. https://doi.org/10.1053/j.ajkd.2012.07.005.
Ndisang, J. F., Vannacci, A., & Rastogi, S. (2017). Insulin resistance, type 1 and type 2 diabetes, and related complications 2017. *Journal of Diabetes Research, 2017*, 1478294. https://doi.org/10.1155/2017/1478294.
Paolisso, G., Monami, M., Marfella, R., Rizzo, M. R., & Mannucci, E. (2012). Dipeptidyl peptidase-4 inhibitors in the elderly: More benefits or risks? *Advances in Therapy, 29*(3), 218–233. https://doi.org/10.1007/s12325-012-0008-x.
Papatheodorou, K., Papanas, N., Banach, M., Papazoglou, D., & Edmonds, M. (2016). Complications of diabetes 2016. *Journal of Diabetes Research, 2016*, 6989453. https://doi.org/10.1155/2016/6989453.
Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56*(3), 303–308.
Petersen, R. C., Stevens, J. C., Ganguli, M., Tangalos, E. G., Cummings, J. L., & DeKosky, S. T. (2001). Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 56*(9), 1133–1142.
Puttanna, A., & Padinjakara, N. K. (2017). Management of diabetes and dementia. *British Journal of Diabetes, 17*(3), 93–99. https://doi.org/10.15277/bjd.2017.139.
Rizzo, M. R., Barbieri, M., Boccardi, V., Angellotti, E., Marfella, R., & Paolisso, G. (2014). Dipeptidyl peptidase-4 inhibitors have protective effect on cognitive impairment in aged diabetic patients with mild cognitive impairment. *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences, 69*(9), 1122–1131. https://doi.org/10.1093/gerona/glu032.
Rizzo, M. R., Barbieri, M., Marfella, R., & Paolisso, G. (2012). Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes. *Diabetes Care, 35*(10), 2076–2082. https://doi.org/10.2337/dc12-0199.
Rizzo, M. R., Marfella, R., Barbieri, M., Boccardi, V., Vestini, F., Lettieri, B., ... Paolisso, G. (2010). Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. *Diabetes Care, 33*(10), 2169–2174. https://doi.org/10.2337/dc10-0389.
Roberts, R., & Knopman, D. S. (2013). Classification and epidemiology of MCI. *Clinics in Geriatric Medicine, 29*(4), https://doi.org/10.1016/j.cger.2013.07.003.
Sachdev, P. S., Mohan, A., Taylor, L., & Jeste, D. V. (2015). DSM-5 and mental disorders in older individuals: An overview. *Harvard Review of Psychiatry, 23*(5), 320–328. https://doi.org/10.1097/HRP.0000000000000090.
Tabish, S. A. (2007). Is diabetes becoming the biggest epidemic of the twenty-first century? *International Journal of Health Sciences, 1*(2), V–VIII.
Tsai, T.-H., Sun, C.-K., Su, C.-H., Sung, P.-H., Chua, S., Zhen, Y.-Y., ... Yip, H.-K. (2015). Sitagliptin attenuated brain damage and cognitive impairment in mice with chronic cerebral hypo-perfusion through suppressing oxidative stress and inflammatory reaction. *Journal of Hypertension, 33*(5), 1001–1013. https://doi.org/10.1097/HJH.0000000000000529.
Whitmer, R. A., Karter, A. J., Yaffe, K., Quesenberry, C. P., & Selby, J. V. (2009). Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA, 301*(15), 1565–1572. https://doi.org/10.1001/jama.2009.460.
Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care, 27*(5), 1047–1053.
World Medical Association (2013). World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA, 310*(20), 2191–2194. https://doi.org/10.1001/jama.2013.281053.
Yuan, X.-Y., & Wang, X.-G. (2017). Mild cognitive impairment in type 2 diabetes mellitus and related risk factors: A review. *Reviews in the Neurosciences, 28*(7), 715–723. https://doi.org/10.1515/revneuro-2017-0016.
Zhang, D.-D., Shi, N., Fang, H., Ma, L., Wu, W.-P., Zhang, Y.-Z., ... Chen, S. (2018). Vildagliptin, a DPP4 inhibitor, alleviates diabetes-associated cognitive deficits by decreasing the levels of apoptosis-related proteins in the rat hippocampus. *Experimental and Therapeutic Medicine, 15*(6), 5100–5106. https://doi.org/10.3892/etm.2018.6016.
Zheng, T., Qin, L., Chen, B., Hu, X., Zhang, X., Liu, Y., ... Li, Q. (2016). Association of plasma DPP4 activity with mild cognitive impairment in elderly patients with type 2 diabetes: Results from the GDMD study in China. *Diabetes Care, 39*(9), 1594–1601. https://doi.org/10.2337/dc16-0316.