Current Neurology and Neuroscience Reports (2019) 19: 58
https://doi.org/10.1007/s11910-019-0973-4

DEMENTIA (K.S. MARDER, SECTION EDITOR)

Diabetes Therapies for Dementia

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Published online: 12 July 2019

Abstract

Purpose of review Type 2 diabetes (T2D) is a well-established risk factor for the development of dementia. Dementia and T2D share some underlying pathophysiology that has led to interest in the potential to repurpose drugs used in the management of T2D to benefit brain health. This review describes the scientific data available on the use of T2D medications for the risk reduction or management of dementia, in people with and without T2D.

Recent findings Results from basic laboratory research support the potential for commonly-used medications for T2D, including those with direct glucose-lowering properties, to have a beneficial effect on brain health. However, human studies have been mostly observational in nature and report conflicting results. Preliminary data suggest that intranasal insulin, metformin, and GLP-1 agonists show promise for dementia, but confirmatory evidence for their benefit in dementia is still lacking.

Summary Current evidence does not support the repurposing of T2D medications for dementia risk reduction or management. Research in the field of T2D and dementia is active, and further data are required before definitive conclusions can be drawn.

Keywords Type 2 diabetes · Dementia · Drugs

Introduction

Dementia is a clinical syndrome characterized by progressive deterioration of cognitive and functional ability resulting in large health and social care needs. Worldwide, in 2010, an estimated 35.6 million people had dementia [1]. This number is expected to double every 20 years [1]. Currently, there are few pharmacological treatments for dementia, limited to symptomatic management with temporary benefits. Moreover, there are no disease-modifying agents for dementia [2]. The absence of progress in developing successful treatments for dementia is driving biomedical researchers to explore not only novel therapeutics but also the potential of repurposing commonly used drugs indicated for other diseases to reduce the incidence and prevalence of dementia.

Type 2 diabetes mellitus (T2D) is a well-established risk factor for all cause dementia, including Alzheimer's dementia [3–5]. The risk factors and pathophysiological mechanisms for T2D and dementia are complex and likely overlap, most notably via either vascular, neurodegenerative, or both pathways [6–9]. Indeed, risk factors such as obesity, physical inactivity, and increasing age, combined with mechanisms such as insulin signalling changes and insulin resistance, are common to both T2D and dementia [6, 10•]. Such risk factors and mechanisms may be theoretically modified by drugs used to treat T2D. Although there is no evidence supporting glucose-lowering per se as a strategy to prevent or delay dementia [11] the clustering of such risk factors and mechanisms have led to increased interest in drugs used to treat T2D as agents that may prevent or delay dementia [2, 10•, 11, 12, 13•]. The aim of this review is to describe the evidence supporting the use of such T2D treatments in the prevention, delay, or treatment of dementia, irrespective of the presence of T2D itself. Where possible, this review will also include details of currently active trials of interest whose results remain unknown.

We conducted a PubMed search using the following terms "type 2 diabetes and dementia," restricting to articles published

This article is part of the Topical Collection on *Dementia*

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in the previous 5 years. Of the 768 articles identified, we excluded 710 which were not directly relevant to T2D treatments in dementia, 22 that were review articles, 21 papers based on animal models, 1 paper that was not written in English, 1 study protocol, 1 extension of an included study that provided no extra evidence of relevance to this review, 4 studies based on analyses in a single large dataset that were superseded by subsequent analysis within the same dataset, and 1 which included fewer than 99 persons [14]. The remaining seven studies were included in this review and are summarized in Table 1 and within the text. Human clinical trials describing the associations between glucose-lowering agents and dementia risk are described in Table 2. A summary of active clinical trials in the field is provided in Table 3.

Metformin

Metformin, often used as a first-line drug treatment for newly diagnosed T2D [15], is a biguanide which acts by reducing glucagon-cAMP signalling and gluconeogenesis, and activating 5′ AMP-activated protein kinase (AMPK) [16]. Results from rat [17, 18] and mouse [19, 20] models suggest that metformin may reduce apoptosis of neurons, enhance neuronal glucose transport, and reduce brain oxidative stress [17–20]. In contrast, metformin may increase Aβ concentrations in cell cultures [21].

Results from human studies are conflicting regarding the use of metformin for preventing or delaying cognitive decline or dementia and have been only observational in design [22–25]. In the UK General Practice Research Database (GPRD), metformin use was associated with a greater risk of developing Alzheimer's disease (AD) dementia compared with those not on metformin (Odds Ratio (OR) 1.71, 95% CI 1.12–2.60) [22]. However, in this study, neither treatment duration nor the use of other glucose lowering drugs were meaningfully associated with AD risk. In another observational but cross-sectional study, those with self-reported T2D and taking metformin had lower Mini Mental State Examination scores (OR 2.23, 95% CI 1.05–4.75) than those not on metformin [23]. In this study, authors speculate that the explanation for the finding may be because of vitamin B_{12} deficiency related to metformin. However, the small size of the sample of people on metformin and the self-report diagnosis of T2D raise doubts about the validity of the findings and highlight the need for further investigation. Conversely, in a very large Taiwanese health insurance dataset, people with T2D (n = 127,209) using metformin were at reduced risk of incident dementia compared to those not taking metformin (Hazard Ratio (HR) 0.55; 95% CI 0.51–0.60) [24, 26], after 8 years of follow-up. After dividing duration of metformin use into tertiles, the authors also reported that greater duration of metformin use was associated with lower risk of dementia, with the HR for dementia for the first (< 27.0 months), second (27.0–58.1 months), and third (> 58.1 months) tertiles of cumulative duration of metformin therapy = 0.98 (95% CI 0.89–1.07), 0.55 (95% CI 0.51–0.61), and 0.29 (95% CI 0.26–0.32), respectively. Similarly, in the Singapore Longitudinal Ageing Study, people using metformin (n = 204) had a lower risk of cognitive impairment (OR 0.49, 95% CI 0.25–0.60) compared to those not using metformin (n = 161). Further, in the same study, the authors reported that those taking metformin for > 6 years also had a lower risk of cognitive impairment, compared to those taking it for < 6 years [25]. In a recent German study, investigators matched 8276 people with diabetes and dementia to 8276 people with diabetes but without dementia, across 972 general medical practices, by age, sex, index year and physician — and examined the associations of various glucose lowering drugs and dementia risk [27•]. In that study, metformin as a monotherapy (OR 0.71, 95% CI 0.66–0.76) or as dual therapy with a sulfonylurea (OR 0.90, 95% CI 0.66–0.76), was associated with a lower risk of dementia. In a large study of people aged over 65 years from the US Veterans database, 5-year dementia risk in those newly commenced on metformin (n = 17,200) was lower (HR = 0.67, 95% CI 0.61–0.73) than in those newly commenced on a sulfonylurea (n = 11,440), particularly in those aged < 75 years [28].

More recently, investigators from five population-based cohort studies pooled data to further explore the associations of drugs commonly used in T2D with dementia prevalence, incidence, cognitive function, and brain structure [13•]. Of the 3590 people with T2D across the cohorts, there was no association between metformin use (proportions on metformin ranging between 15 and 80% of cohorts) and cognitive function, dementia prevalence, or structural brain measures. Additional adjustment for age, sex, education, physical activity, body mass index, history of smoking, cardiovascular disease, stroke, depression, total cholesterol, Hb_{A1C}, and ApoE4, did not result in an observable association between metformin use and incident dementia. However, additional statistical modelling adjusting for renal function showed metformin to be associated with an increased risk of incident dementia (HR 1.42, 95% CI 1.02–1.98, p = 0.04). Overall, published data available to date raise the possibility of a benefit for brain health from metformin use, but further evidence from clinical trials are needed and such trials are beginning to be conducted (ClinicalTrials.gov Identifier: NCT03733132).

Sulfonylureas

Sulfonylureas block ATP-sensitive potassium channels and stimulate insulin secretion from beta cells in the pancreas [29]. Glimepiride may protect against beta amyloid (Aβ)–induced synaptic damage [30] in neuronal cultures, and glibenclamide may enable Aβ to be cleared through the blood-brain barrier in mice with T2D [31]. However, there

Table 1 Human observational studies describing the associations between T2D medications and dementia risk, published in the last 5 years.

Author, Year of publication	Study design	Sample	Sample characteristics	Results
Chin-Hsiao, 2019 (26)	Retrospective cohort study using Taiwan National Health Insurance reimbursement database T2D - inception 1999-2005 and followed until December 31, 2011	People with T2D Unmatched cohort: 147,729 ever used metformin and 15,676 never used metformin. Propensity score matched-pair cohort of 15,676 ever used metformin and 15,676 never used metformin	Mean age: 63 years (SD=10) Female=43% No dementia at baseline Education not reported	Unmatched cohort • Metformin use associated with reduced dementia hazard. HR= 0.55; 95% CI 0.508-0.596). • Longer duration of metformin use associated with lower dementia hazard. HR for first (<27.0 months), second (27.0-58.1 months) and third (>58.1 months) tertile of cumulative duration of metformin therapy = 0.975 (95% CI 0.893-1.066), 0.554 (95% CI 0.506-0.607) and 0.286 (95% CI 0.259-0.315). Matched cohort • Metformin use associated with reduced dementia risk. HR= 0.707 (95% CI 0.632-0.791) • HR for the respective tertiles were 1.279 (95% CI 1.100-1.488), 0.704 (95% CI 0.598-0.829) and 0.387 (95% CI 0.320-0.468).
Bohlken, 2018 (27•)	Matched case-control study in 972 German General Practices from 2013 to 2017	8,276 people with diabetes and dementia. 8,276 people with diabetes without dementia	Mean age: 80 years (SD=6.9) Female=56% Education not reported	• Metformin monotherapy (OR = 0.71) or combined with sulfonylureas (OR = 0.90), associated with decreased dementia risk. • Thiazolidinediones use associated with decreased dementia risk (OR = 0.80). • Insulin associated with increased dementia risk (OR = 1.34)
Kim, 2018 (45)	Propensity matched Korean National Health Insurance Service Senior cohort DPP-4 Vs sulfonylureas followed for ~1362 days	People with T2D New users of DPP4 agents (n=7552) and 7552 users of sulfonylureas	Mean age: 75 years (SD~5) Female=56% No dementia at baseline Education not reported	• Risk of all-cause dementia lower in DPP4 (HR= 0.66; 95%CI 0.56-0.78; $p < 0.001$). • Risk of Alzheimer's dementia lower in DPP4 group (HR 0.64; 95% CI 0.52-0.79; $p < 0.001$). • Statistically non-significant lower risk of vascular dementia in DPP4 group (HR 0.66; 95% CI 0.38-1.14; $p = 0.139$).
Lu, 2018 (33)	Retrospective cohort study using Taiwan National Health Insurance reimbursement database Followed from 2000-2013	People with T2D Analysis of 51,415 individuals aged ≥65 years without dementia in first year of second-line glucose-lowering treatment	Mean age: 72 years (SD=5.8) Female=51% No dementia at baseline Education not reported	• Metformin and pioglitazone use associated with lower dementia risk than those taking metformin and sulfonylurea (HR 0.56; 95% CI 0.34-0.93).
Tseng, 2018 (32)	Retrospective cohort study from the Taiwan National Health Insurance reimbursement database T2D developed 1999-2008 and followed until December 31, 2011	People with T2D 11,011 users of pioglitazone propensity score-matched to 11,011 never-users of pioglitazone	Mean age: 59 years (SD=10) Female=44% No dementia at baseline Education not reported	• Pioglitazone use associated with lower dementia risk (HR 0.716 95% CI 0.545–0.940). • Longer duration of use associated with greater decrease in dementia risk when duration divided into tertiles (first tertile (<11.0 months) HR=0.806 (0.544–1.193); second tertile (11.0–19.6 months HR=0.654 (0.430–0.994); third tertile (>19.6 months) HR: 0.694 (0.469–1.026). • Benefit of pioglitazone seen most in those not previously exposed to metformin - ever used metformin HR 0.802 (0.580–1.109); never used metformin HR 0.494 (0.284–0.857)
Orkaby, 2017 (28)	Retrospective cohort study of US veterans without dementia over 65 years of age with T2D. New users of metformin compared to new users of a sulfonylurea followed over 5 years.	People with T2D Metformin: n=17,200 Sulfonylureas: n=11,440	Mean age: 74 years (SD=5.9) Female=1% No dementia at baseline Education not reported	• Metformin associated with lower dementia risk (HR=0.67, 95%CI 0.61–0.73). • This beneficial effect stronger in those <75 years of age (HR =0.89; 95% CI 0.79–0.99) compared with those>75 years HR=0.96; 95% CI 0.87–1.05.
Isik, 2017 (46)	Prospective cohort study following people with and without AD over 6 months	People with T2D, with and without AD Sitagliptin (n=104) Metformin and/or insulin (n=101)	Mean age: ~ 75 years (SD~8.4) Female~60% 52 people with AD Education not reported	• In non-AD group, those taking sitagliptin (n=43) or insulin (n=22) had an improvement in Mini Mental State Examination (MMSE) score (increase 0.95, p=0.034 and MMSE increase 0.94, p=0.039 respectively). Those taking metformin (n=69) showed no improvement. • In the AD group, those taking sitagliptin (n=11) had an improvement in MMSE (increase ~1, p=0.047). • No effect observed for those taking metformin in either group.

Key: AD: Alzheimer's disease; T2D: Type 2 diabetes; DPP-4: Dipeptidyl peptidase IV inhibitors; HR: hazard ratio; CI: confidence interval; OR: odds ratio

Table 2 Human clinical trials describing the associations between T2D medications and dementia risk.

Author, Year of publication	Study design	Sample	Sample characteristics	Intervention arms	Results
Craft, 2012 (50) NCT00438568	Randomized, double-blind, placebo-controlled trial	People without T2D with amnestic mild cognitive impairment (n=64) or mild to moderate AD (n=40)	Mean age: ~73 years (Standard error=1.5) Female~43% Education ~15 years (SD~0.5)	Daily: Intervention arm 1 (n=36) 20 IU of intranasal insulin Intervention arm 2 (n=38) 40 IU of intranasal insulin Control (n=30) placebo For 4 months	• Treatment with 20 IU of insulin improved delayed memory($P<0.05$) • Both doses of insulin preserved caregiver-rated functional ability ($P<0.01$). • Both insulin doses preserved ADAS-cog scores for younger participants and ADCS-ADL scale scores
Sato, 2011 (34) NCT not available	Randomized, open-label controlled trial	People with mild AD and T2D	Mean age: 77 years (SD~6) Female=52% Education ~12 years (SD=2.5)	Intervention (n=21) 15–30 mg pioglitazone daily Control (n=21) No drug	• Pioglitazone group had improved parietal lobe blood flow and cognition. • No improvement in control group. • Increased plasma Aβ40/Aβ42 ratio in the control group, but no significant change in pioglitazone group.
Stein, 2011 (61) ACTRN 12606000324516	Randomized double blinded placebo-controlled trial	Community-dwelling people with AD (n=63); mild-moderate (n=32) taking 1000units Vitamin D daily	Median age: 78 years (IQR=69-80) Female=53% Education not reported	Intervention arm 1 Placebo Vitamin D added & placebo intranasal insulin Intervention arm 2 Placebo Vitamin D added & intra nasal insulin (60 IU qid) Intervention arm 3 6000 IU Vitamin D added & placebo intranasal insulin Intervention arm 4 6000 IU Vitamin D added & intranasal insulin (60 IU qid)	• No significant change in cognition nor disability after high-dose Vitamin D. • Nasal insulin after placebo high-dose Vitamin D associated with improved ADAS-cog by a median (IR) of 9 (1–11, $p = 0.02$)
Ryan, 2006 (35) NCT not available	Randomized double-blind controlled trial	People with T2D receiving metformin monotherapy at 18 centers in the U.S	Mean age: 60 years (SD=1) Female~40% No dementia at baseline Education not reported	Add on therapy of: Arm 1: rosiglitazone (n=69) Arm 2: glyburide (n=72) For 24 weeks	• Rosiglitazone improved working memory with both ($p <0.001$) • Glyburide improved working memory ($p =0.017$). • Improvement (25–31% reduction in errors) most apparent on the Paired Associates Learning Test

Key: AD: Alzheimer's Disease; T2D: Type 2 diabetes; ADAS-cog: Alzheimer Disease's Assessment Scale–cognitive subscale; ADCSADL:Alzheimer's Disease Cooperative Study–activities of daily living; HR: hazard ratio; CI: confidence interval; OR: odds ratio; NCT: ClinicalTrials.gov identifier; ACTRN: Australian New Zealand Clinical Trials Registry Number

Table 3 Summary of active clinical trials of T2D medications for dementia risk reduction or management

Study identifier	Study name	Study design	Active intervention	Comparator	Study sample	Duration and primary outcomes
NCT03733132 Recruiting	Metformin Effect on Brain Function in Insulin Resistant Elderly People	Double-blind, placebo-controlled, randomized	Metformin, up to 2500 mg daily	Placebo	• > 65 years • Abdominal girth > 102 cm in men and > 88 cm in women • Fasting glucose >/= 100–140 mg/dL	• 10 months • Change from baseline in brain ATP production as measured by phosphorus magnetic spectroscopy
NCT03707171 Not yet recruiting	Effects of Liraglutide on the Cognitive Function in Patients with Type 2 Diabetes Mellitus	Open label, non-randomized	Liraglutide adjusting dose, up to 1.8 mg per day	Placebo	• 18 to 80 years • Type 2 diabetes	• 12 weeks • Changes in cognitive function at 4, 8 & 12 weeks
NCT02847403 Unknown recruitment status	Long-acting Exenatide: a Tool to Stop Cognitive Decline in Dysglycemic Patients With Mild Cognitive Impairment?	Open label, randomized	Long-acting exenatide 2 mg subcutaneous once weekly	No drug	• 51 to 79 years • Dysglycemia/rediabetes • Diagnosis of mild cognitive impairment	• Improvement of ADAS-cog Alzheimer's Disease Assessment Scale defined by ADAS-cog score at 16 and 32 weeks (V3) compared to baseline
NCT01843075 Unknown recruitment status	Evaluating the Effects of the Novel GLP-1 Analogue, Liraglutide, in Patients With Mild Alzheimer's Disease (ELAD Study)	Quadruple blind, randomized	Daily administration of 1.8 mg liraglutide subcutaneous injection	Daily administration of matched placebo by subcutaneous injection	• 50 years and older • Diagnosis of probable Alzheimer's disease	• 12 Months • Change in cerebral glucose metabolic rate from baseline to follow up in the treatment group compared with placebo group
NCT03819127 Recruitment completed	Effects of Vildagliptin, a DPP-4 Inhibitor, in Elderly Diabetic Patients with Mild Cognitive Impairment	Single blind, randomized	Metformin 1 g plus vildagliptin 50 mg twice a day	Metformin 1 g twice a day	• 65 years and older • Mini Mental State Examination score ≥ 18 and ≤ 23 • Diagnosis of diabetes mellitus	• 24 weeks • Evaluation of cognitive decline using Mini Mental State Examination
NCT01243424 Recruitment completed	A Multicentre, International, Randomized, Parallel Group, Double Blind Study to Evaluate Cardiovascular Safety of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes Mellitus at High Cardiovascular Risk	Double blind, randomized	Linagliptin 5 mg 4 times per day	Glimepiride 1–4 mg 4 times per day	• 40 to 85 years • Type 2 diabetes	• 432 weeks • Cognition sub-study: Occurrence of accelerated cognitive decline at end of follow-up
NCT02462161 Recruiting	Study of Nasal Insulin to Fight Forgetfulness — Short-Acting Insulin Aspart	Quadruple blind, randomized	Administration of 20 IU insulin aspart two times per day with an intranasal delivery device	Administration of placebo two times per day with an intranasal delivery device	• 50 to 89 years • Previous or subsequent diagnosis of Alzheimer's disease or mild cognitive impairment	• 12 weeks • Change in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)/mild cognitive impairment (MCI) scores and memory composite scores
NCT02415556 Recruiting	Memory Advancement by Intranasal Insulin in Type 2 Diabetes	Quadruple blind, randomized	Inhaled 40 IU of regular human insulin once daily	Inhaled intranasal sterile saline once daily	• 50 to 85 years • People with and without Type 2 Diabetes (four arms)	• 48 weeks • Change in Paired Associates Learning total errors and Visuospatial learning and memory
NCT02503501 Active, not recruiting	A Phase II, Single Center, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and the Therapeutic Effectiveness of Intranasal Glulisine in Amnestic Mild Cognitive Impairment and Probable Mild Alzheimer's Disease	Quadruple blind, randomized	Intranasal insulin Glulisine 20 IU 2 times per day	Intransal saline 20 IU two times per day	• 50 to 90 years • Clinical and research diagnosis of amnestic — Mild Cognitive Impairment OR probable mild Alzheimer's Disease	• 6 months • Change in cognition as measured by the Alzheimer's Disease Assessment Scale — Cognitive 13 (ADAS-Cog 13)

ATP adenosine triphosphate

have been very few studies examining the benefit of these drugs for dementia prevention and treatment in humans.

Sulfonylurea use was not associated with AD risk in the GPRD database, except when used in combination with metformin [22]. Conversely, in the large Taiwanese dataset, those taking a sulfonylurea were at a lower risk of incident dementia at 8 years, compared with those with no medication use (HR 0.85, 95% CI 0.71–1.01) [24]. Furthermore, the combination with metformin was associated with an even more favourable (larger) dementia risk reduction (HR 0.65, 95% CI 0.56–0.74).

In analysis of pooled data from five large population-based studies, there was no association between sulfonylurea use (20–49% of cohorts) and incident dementia [13•]. However, in subgroup analysis restricted to only those people taking glucose lowering medications, sulfonylurea was associated with reduced dementia risk (HR 0.64, 95% CI 0.46–0.88), when compared to non-use of sulfonylurea. The implications of this result remain unclear as the authors also reported associations between sulfonylurea use and a greater decline in global cognitive performance and lower total brain volume, when compared to those using either lifestyle changes or other glucose lowering medications. These associations were also no longer present when people with prevalent dementia were excluded, suggesting that a causal effect may be unlikely. Taken together, the results of published studies to date suggest that sulfonylureas are unlikely to have beneficial effects in modifying dementia risk, but definitive studies are lacking.

Thiazolidinediones

Thiazolidinediones activate the proliferator-activated receptor-γ (PPAR-γ), influence glucose metabolism by its effects on gene transcription, and reduce insulin resistance in tissues [29]. The potential brain health benefits of pioglitazone are supported by observational research of the large Taiwanese health insurance dataset [32, 33], in which pioglitazone use was associated with reduced risk of dementia (HR 0.72 95% CI 0.55–0.94) particularly in those with the longest duration of use [32]. In further research of the same sample dataset, the authors reported that the use of pioglitazone in addition to metformin in people with T2D was associated with a lower risk of dementia (HR 0.56 95% CI 0.34–0.93), compared to a combination of metformin and sulfonylurea [33]. There was also a trend for a beneficial effect of pioglitazone over other second-line treatments coupled with metformin in reducing dementia risk, but these differences were not statistically significant. Pioglitazone was also associated with improvements in cerebral perfusion and cognition, specifically working memory, in a small-sized randomized controlled trial ($n = 42$) [34]. However, the results of a randomized trial of either rosiglitazone or glyburide in people with T2D but no dementia for 24 weeks reported similar improvements in working memory in both groups [35]. As both interventions resulted in improvements in glycemic control as well as in insulin levels, it is difficult to uncouple whether the effects are due to changes in insulin sensitivity, glucose levels, or both. Although pioglitazone is the most commonly used thiazolidinedione, potentially beneficial effects may not be limited to only this agent. In the German case-control studies described above, thiazolidinedione use in general was reported to be associated with a reduction in risk of dementia (OR = 0.80, 95% CI 0.68–0.95) [27•]. In sum, while thiazolidinediones may have potentially beneficial effects on brain health, the clinical applicability of these results is offset by adverse risks, notably cardiovascular events and bladder cancer [36]. The development of agents with similar benefits without these harmful side effects may provide further opportunities.

Glucagon-Like Peptide-1 (GLP-1) Agonists

GLP-1 receptor agonists act via insulin secretion enhancement and glucagon secretion inhibition, and undergo degradation by dipeptidyl peptidase (DPP-4) [37]. These agonists may have beneficial effects on synaptic plasticity and protect against oxidative stress, effects which are potentially acting through receptors expressed in the brain [38, 39]. GLP-1 receptor agonists have been shown to have beneficial effects including protecting against impairments in cognitive tasks and hippocampal plasticity, as well as lowering of Aβ plaque burden and its associated inflammatory response, albeit in small studies of animal models of AD [40]. The limited data to date suggest that while GLP-1 agonists may show promise in the treatment of dementia, their efficacy remains to be demonstrated in humans, including in clinical trials which are already underway [41, 42] (NCT03707171, NCT02847403, NCT01843075).

Dipeptidyl Peptidase IV (DPP-4) Inhibitors

Inhibitors of dipeptidyl peptidase IV (DPP-4) or "gliptins" increase β cell insulin response to glucose and reduces glucagon secretion by minimizing GLP-1 degradation [43]. There have been few studies to examine their effect on cognition in people with T2D. The use of DPP-4 inhibitors, independent of glucose control, in people with T2D and mild cognitive impairment (MCI) was associated with better cognitive function in a retrospective observational study [44]. A large study leveraging the Korean National Health Insurance Senior cohort used propensity score matching, to compare people newly initiated to DPP-4 inhibitors and people newly initiated to sulfonylurea [45]. In this study, new DPP-4 users had a lower all-type dementia risk (HR 0.66; 95% CI 0.56–0.78; $p < 0.001$) and Alzheimer's disease type dementia risk (HR 0.64; 95% CI 0.52–0.79; $p < 0.001$) over 4 years. Few

prospective data are available. In a small prospective observational study, people with and without AD (205 people) were followed over 6 months, some of whom had been commenced on sitagliptin [46]. The authors reported that sitagliptin use was associated with an increase in Mini Mental State Examination score at 6 months of approximately one unit in those with ($n = 11$) and without dementia ($n = 43$). Although these data show promise, the efficacy of DPP-4 inhibitors in dementia remain unknown, and the publication of results from two large completed clinical trials of the drug linagliptin is soon anticipated (NCT03819127) [47, 48].

Insulin

Insulin promotes serum glucose uptake in the periphery as well as the central nervous system [12]. Insulin dysregulation occurs early in T2D, and can also occur in dementia, and represents a potential therapeutic target to modify the risk of cognitive impairment [6, 12]. Some observational studies have shown insulin use in people with T2D to be associated with greater dementia risk [27•]. However, caution should be exercised in the interpretation of these data as the use of insulin in T2D is usually associated with longer duration of disease, poor glucose control or more complications, and hence may be a marker of diabetes severity rather than a true risk factor for dementia. One study randomized people with dysglycemia ($n = 3392$, mean age 63 years) to either long-acting insulin, omega-3 fatty acid or standard care, to achieve a fasting blood glucose of ≤ 5.3 mmol/L. The investigators of this Outcome Reduction with Initial Glargine Intervention (ORIGIN) study reported that after 6 years of follow-up, cognition was similar in the insulin and omega-3 fatty acid arms [49].

Intranasal inhaled insulin is of interest as a therapy for dementia even in people without T2D, given the high concentration of insulin receptors in several areas of the brain relevant to dementia [50, 51]. The presence of these receptors supports insulin-mediated neuronal glucose uptake [6, 52, 53] and may reduce brain insulin resistance which is recently thought to be one of the plausible underlying mechanisms of AD pathology [6, 54, 55]. Insulin may also reduce the formation of, and synaptic toxicity of Aβ oligomers [51, 56, 57]. Although intravenous insulin infusion and normalization of glucose may improve memory scores in people with AD without T2D, [58] it carries a risk of peripheral hypoglycemia. In contrast, the use of intranasal insulin can increase intracerebral insulin levels without such a peripheral effect. In a small-scale trial ($n = 104$), intranasal insulin, when compared to placebo, was shown to be beneficial for cognition and function in people with MCI or mild to moderate AD [50]. Intranasal long-acting insulin also showed promise in improving memory in two small trials of a similar sample [54] of people with AD or MCI [59, 60]. In contrast to these data, the combination of 8 weeks of high-dose vitamin D (for insulin receptor upregulation) with a 2-day dose of intranasal insulin administration in another small trial ($n = 32$) did not show benefit for cognition [61]. It is possible that a longer duration of intranasal treatment intervention may have resulted in a more positive result. Overall, the potential benefits of intranasal insulin for preventing or delaying cognitive decline in people with and without T2D warrant further investigation and such studies are still ongoing (NCT02462161, NCT02415556, NCT02503501) [62].

Conclusion

In summary, there appears to be equipoise from human observational studies whether or not T2D medications have beneficial effects on dementia risk and symptomatology, including in persons with and without T2D. Drugs that increase insulin sensitivity or improve glucose uptake in the brain, such as intranasal insulin, show some promise. RCT evidence is expected to become available in the near future. Oral agents such as metformin and GLP-1 receptor agonists, either individually or in combination, are also attractive agents for further investigation, with some observational evidence supporting their potential benefit, and because they may act via mechanistic pathways plausibly involved in dementia. More research and stronger evidence are required before clinicians would be able to recommend any of the currently available diabetes therapies for dementia and brain health.

Compliance with Ethical Standards

Conflict of Interest Chris Moran, Michele L. Callisaya, and Velandai Srikanth each declares no potential conflicts of interest. Zoe Arvanitakis reports grants from National Institutes of Health (R01 NS084965 and RF1 AG059621), during the conduct of the study; other from Amylyx, outside the submitted work.

Human and Animal Rights and Informed Consent This article is a review of the published scientific literature, and no human or animal subjects were studied by any of the authors.

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