



Published in final edited form as:

Endocrinol Metab Clin North Am. 2013 September ; 42(3): 489–501. doi:10.1016/j.ecl.2013.05.009.

Type 2 Diabetes and Cognitive Compromise: Potential Roles of Diabetes-Related Therapies

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Synopsis

Type 2 diabetes, similarly to dementia, disproportionately affects the elderly. Diabetes has consistently been associated with risk of dementia—both Alzheimer’s disease (AD) and more strongly and consistently vascular dementia (VaD)—mild cognitive impairment (MCI), and cognitive decline suggesting that cognitive compromise is a deleterious manifestation of diabetes. This review summarizes observational studies and clinical trials of diabetes medications—insulin, peroxisome proliferator-activated receptor- γ , insulinotropic glucagon-like peptide-1, and metformin—and their respective associations and effects on cognitive outcomes. Despite biological plausibility, results from most human clinical trials have failed to show any efficacy in treating AD symptomatology and pathology. Clinical trials targeting vascular-related outcomes, diabetic patients, or cognitively normal elderly at risk for dementia, may provide greater cognitive benefits.

Diabetes disproportionately affects the elderly. Among U.S. residents aged 65 years and older, 26.9% had diabetes in 2010 and 50% had diabetes or pre-diabetes between 2005 and 2008 (Centers for Disease Control and Prevention 2011). According to the Alzheimer’s association, one in nine people age 65 and older (11%) has AD and about one-third of people age 85 and older (32%) have AD, and the prevalence of all forms of dementia is even higher (Alzheimer’s association 2013). This co-occurrence may reflect simply two simultaneous age-related events, possibly sharing one or more causal pathways, or may reflect a causative relationship between the conditions.

Diabetes is a risk factor for dementia and cognitive decline

Diabetes has consistently been associated with risk of dementia, mild cognitive impairment (MCI) and cognitive decline. A systematic review of effects of diabetes on cognitive dysfunction has suggested that the latter should be considered among the chronic consequences and disabling manifestations of diabetes (Cukierman *et al.* 2005). Furthermore, increased risks of dementia and AD were also associated with borderline diabetes, independent of the future development of diabetes (Xu *et al.* 2007). Diabetes, or impaired fasting glucose, may be present in up to 80% of persons with Alzheimer’s disease (AD) (Janson *et al.* 2004), and the 2010 NIH Consensus Development Conference Statement

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on Preventing Alzheimer's Disease and Cognitive Decline listed diabetes first as a risk factor (Daviglius *et al.* 2010). This co-existence of diabetes (or diabetic markers) with cognitive dysfunctions have lead some investigators to propose that AD constitutes a brain-specific form of diabetes, *i.e.* Type 3 diabetes (de la Monte *et al.* 2006).

Our group has recently shown that diabetic elderly with the earliest signs of cognitive compromise have a faster rate of cognitive decline than non-diabetic elderly (Ravona-Springer *et al.* 2010). Similar associations between diabetes and cognitive compromise have been reported in numerous studies. Among the cognitive domains that have been associated with diabetes are attention, executive functions, perceptual/processing speed, verbal memory, and working memory, as well as global cognitive functioning (measured by the mini-mental state examination [MMSE]) (Arvanitakis *et al.* 2004; Gilmour 2011; Gregg *et al.* 2000; Hassing *et al.* 2004a; Hassing *et al.* 2004b; Knopman *et al.* 2001; Logroscino *et al.* 2004; Nandipati *et al.* 2012). Our recent study has also demonstrated that poor glycemic control is associated with cognitive decline even in non-diabetic individuals (Ravona-Springer *et al.* 2012). Such association, however, was not observed in elderly aged 85 years or older (van den Berg *et al.* 2006), possibly due to a survivors effect. Moreover, within a population of patients who were already demented in the time of the study, diabetics showed slower global cognitive decline than non-diabetics (Sanz *et al.* 2009), although functional status, measured by Activities of Daily Leaving (ADL), continuously declined (Sanz *et al.* 2012). One explanation for this observation may be a floor effect, or that the medical attention that this population receives is helpful in preventing cognitive deterioration.

MCI is characterized by memory complaints without loss of function in daily activities (Petersen *et al.* 1999). Diabetes has been related to a 40% higher risk of MCI, both amnesic and nonamnesic (Luchsinger *et al.* 2007). Two other studies reported a trend towards increased risk of MCI in a diabetic elderly population (Solfrizzi *et al.* 2004), and in a sample of postmenopausal women (Yaffe *et al.* 2004), but these changes, however, were statistically non-significant. A more recent study may shed some light on these inconsistencies: the frequency of diabetes was similar in elderly subjects with and without MCI, but MCI was associated with diabetes onset before the age of 65, diabetes duration of 10 years or longer, treatment with insulin, and the presence of diabetes complications (Roberts *et al.* 2008).

According to the DSM-IV (Text Revision), dementia is characterized by the development of multiple cognitive deficits that must include memory impairment and other cognitive disturbances (American Psychiatric Association 2000). Our prior research showed that subjects with diabetes in midlife had a 3-fold increased risk of dementia three decades later (Schnaider Beerl *et al.* 2004). Increased risk of dementia in diabetic patients was reported in other studies as well (Leibson *et al.* 1997; Ott *et al.* 1999; Peila *et al.* 2002; Whitmer *et al.* 2005; Xu *et al.* 2004), but not all (Yaffe *et al.* 2004). Furthermore, diabetes seems to increase the risk of certain subtypes of dementia in different extents. The most common subtypes of dementia are Alzheimer's disease (AD) and vascular dementia (VaD). According to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), in order to fulfill research criteria for probable AD, a patient must present a significant episodic memory impairment and at least one supportive biomarker (such as medial temporal lobe atrophy) (Dubois *et al.* 2007). Even VaD itself is not a single disease, but a group of syndromes based on varying vascular mechanisms. These include dementias related to multiple infarcts, small vessel ischaemic disease, Alzheimer's disease with cerebrovascular disease (sometimes known as 'mixed dementia'), and others (O'Brien 2006). Diabetes was reported to increase the risk of AD by 45–90% (Arvanitakis *et al.* 2004; Leibson *et al.* 1997; Ott *et al.* 1999; Wang *et al.* 2012), but the risk for VaD was consistently and substantially higher, with increases ranging from 100% to 160% (Hassing *et al.* 2002; MacKnight *et al.*

2002; Xu *et al.* 2004), suggesting that diabetes is more closely associated with VaD than with AD.

Taken together, these findings suggest an association between diabetes and cognitive decline. Some of the studies evaluated diabetes in midlife, decades before dementia ascertainment, supporting the notion that cognitive impairment is a consequence of diabetes.

The effects of diabetes treatments on memory and cognition

The research of different pharmacological and non-pharmacological treatments of diabetes, and the known biological mechanisms of those treatments, may help us in understanding this association. Insulin and oral hypoglycemics are the most common treatments for diabetes. Diabetes medications have been associated with improved cognitive functioning, and have been demonstrated to affect AD markers, such as neuritic plaques (Beeri *et al.* 2008), as well as vascular integrity (Kalaria 2009). The SALSA study had reported that diabetic patients on antidiabetic monotherapy (insulin or oral), and more so on any combination therapy, had less cognitive decline, especially among those with a longer duration of the disease (Wu *et al.* 2003). Our previous postmortem study examined the association between AD neuropathology and diabetes medications in several brain regions that support cognitive functioning: hippocampus, entorhinal cortex, amygdala, and several neocortical regions. In each region, the study demonstrated substantially lower neuritic plaque density for the diabetic group taking both insulin and other antidiabetic medication, compared to diabetic patients on monotherapy or on no therapy (Beeri *et al.* 2008). Here we will briefly review the association of some of the most common antidiabetic treatments with cognitive functioning.

The association of circulating/CSF insulin levels and insulin administration with cognition

Produced nearly exclusively by the pancreas, insulin is readily transported into the CNS across the blood-brain barrier (BBB) using a saturable, receptor-mediated process. Insulin receptors are highly concentrated in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, and cerebellum (reviewed by (Banks *et al.* 2012)). Localization of insulin receptors in hippocampus and medial temporal cortex is consistent with evidence that insulin influences memory (Cholerton *et al.* 2011). Conditions such as insulin resistance—in which insulin is chronically elevated—may eliminate the salutary effects of insulin on cognition and other brain function (Craft 2006). Elevating insulin levels, through excess production (endogenously or provoked exogenously), excess administration of insulin or reduced clearance, will typically result in a down-regulation of insulin signaling pathways (reviewed by (White 2003)). One consequence of insulin resistance and chronic excess insulin (hyperinsulinemia) is reduced insulin transport into brain, which ultimately produces brain-insulin deficiency (Baura *et al.* 1996), and may attenuate the many beneficial influences of insulin. Support for this notion may be seen in recently published results from the PIVUS study: insulin resistance was negatively correlated with verbal cognitive performance, brain size, and temporal lobe gray matter volume, and these correlations were not affected by diabetic status or cognitive status (Benedict *et al.* 2012). Those findings are similar to an earlier report on pre-diabetic and diabetic patients, in which greater insulin resistance was associated with reduced glucose metabolic rate in frontal, parietotemporal, and cingulate regions, compatible with an AD pattern (Baker *et al.* 2011). Those individuals also showed a more diffuse and extensive activation patterns, and recalled fewer items on a delayed memory test (Baker *et al.* 2011). Since type 2 diabetic patients and approximately half of all adults over the age of 60, regardless of diabetic status, are insulin resistant (Craft 2006), studying the effects of insulin on cognition is of great importance.

Craft has pioneered the study of the role of insulin regulation in AD and cognitive decline. In normal physiological conditions, insulin administered at optimal (*i.e.* low) doses facilitates memory, as was demonstrated by direct administration of insulin to the brain in rodents (Park *et al.* 2000), and intravenous insulin administration in humans (Craft *et al.* 2003). The latter study also showed that higher levels of insulin were needed for achieving effective memory facilitation in ApoE 4-negative AD patients, supporting the notion of insulin resistance in this subgroup (Craft *et al.* 2003). The authors suggested that for these patients, factors relating to insulin resistance may be important drivers of AD pathogenesis.

For memory-impaired adults, insulin was found to improve memory functions also when administered intranasally at acute dosage (Reger *et al.* 2008a) and chronic treatment for 3 weeks (Reger *et al.* 2008b) or 4 months (Craft *et al.* 2012). A recently published analysis of results from this trial further suggest sex and ApoE genotype differences in the response to the treatment: whereas women showed improved memory only when administered the lower dose, men showed cognitive improvement also for the higher dose, and this sex difference was most apparent for ApoE 4-negative individuals (Claxton *et al.* 2013). Importantly, sex differences were also observed in the association between cognitive functioning and circulating insulin: men with non-amnesic or amnesic MCI had higher fasting plasma insulin than cognitively normal men, while women with amnesic MCI had lower fasting plasma insulin than cognitively normal women (Cholerton *et al.* 2012).

Insulin may exert its effects on cognition and AD risk through modulation of the β -amyloid peptide (A β). A β , a metabolite of the amyloid precursor protein (APP), aggregates in extracellular depositions, neuritic plaques, which constitute one of the hallmarks of AD pathology (Braak and Braak 1997). The close bidirectional relationship between insulin and A β is described in detail in a recently published review article (Craft *et al.* 2013). Subchronic elevations of CNS insulin concentrations by intranasal administration have been associated with reduced circulating concentrations of A β (Reger *et al.* 2008b). Very similar to the attenuation of the positive effects of insulin on memory facilitation, excessive insulin elevations through intravenous infusion increased levels of the A β in cerebrospinal fluid (CSF), most notably in older subjects (Watson *et al.* 2003). Importantly, greater increases in CSF A β levels attenuated the insulin-mediated memory facilitation (Watson *et al.* 2003). Moreover, insulin administration was found to reduce plasma APP concentrations, particularly in ApoE 4-negative individuals, both in cognitively intact subjects (Boyt *et al.* 2000) and AD patients (Craft *et al.* 2000). The effective insulin dose in reducing plasma APP was higher for ApoE 4-negative AD patients than for normal adults and ApoE 4-positive AD patients (Craft *et al.* 2003). Finally, insulin administration was associated with inflammation, a key factor in the pathogenesis of AD (Rogers and Shen 2000). Anti-inflammatory effects were observed with low doses of insulin (Dandona 2002), but excessive hyperinsulinemia exacerbates inflammation (Krogh-Madsen *et al.* 2004). Craft's research group has demonstrated that intravenous infusion of insulin to levels associated with insulin resistance increased CSF inflammatory markers (Fishel *et al.* 2005).

Peroxisome proliferator-activated receptor- γ and AD

These observations led to the investigation of how therapeutic strategies, originally aimed at treating diabetes, may also benefit elderly with a wide range of cognitive impairments, including AD. Agonists to the peroxisome proliferator-activated receptor- γ (PPAR- γ) are known to improve insulin sensitivity, decrease circulating insulin, and increase insulin-mediated glucose uptake with minimal risk of hypoglycemia (Olefsky 2000). In addition, PPAR- γ agonists were found to inhibit inflammation, and specifically the A β -stimulated secretion of pro-inflammatory products and the A β -stimulated expression of the cytokine genes (Combs *et al.* 2000), making them good candidates for therapeutic agents in treating AD. The beneficial effects of PPAR- γ agonists have been demonstrated in a line of studies

on transgenic AD mice, typically displaying widespread microglial activation, age-related amyloid deposits, and dystrophic neurites. Tg2576 mice that were treated with chronic oral administration of ibuprofen, an efficient activator of PPAR- (Lehmann *et al.* 1997), have shown marked reduction in A β deposits (Lim *et al.* 2000). Positive effects of PPAR- agonists on AD mice were also shown for two compounds, rosiglitazone and pioglitazone, which are commonly prescribed for diabetics. Rosiglitazone treated Tg2576 mice showed age-dependent reversal of cognitive deficits (Rodriguez-Rivera *et al.* 2011), but with no evidence of reduction in A β deposits (Pedersen *et al.* 2006). In APP^{swe}/PS1^{dE9} mice the drug improved spatial memory, decreased insoluble A β_{1-42} , and decreased plaque number in the hippocampus (O'Reilly and Lynch 2012). Transgenic mice carrying the Swedish (K670N/M671L) and Indian (V717F) AD mutations of human APP showed rescue of memory impairments, removal of amyloid plaques in the hippocampus and entorhinal cortex, and decreased phosphorylated tau protein following rosiglitazone treatment (Escribano *et al.* 2010). Pioglitazone administered to the latter transgenic mice fully restored cerebrovascular reactivity, albeit it failed to improve spatial memory or to reduce A β plaque load (Nicolakakis *et al.* 2008). In triple transgenic AD mice, however, long-term pioglitazone treatment improved cognition and decreased hippocampal A β and tau deposits (Searcy *et al.* 2012).

Despite the findings from animal studies in favor of PPAR- agonists for the treatment of AD symptomatology and pathology, results from human clinical trials have been rather disappointing. In a placebo-controlled, double-blind, parallel-group pilot study, rosiglitazone treated amnesic MCI and early AD patients showed preservation of some cognitive functions, whereas placebo-assigned subjects showed the expected memory decline (Watson *et al.* 2005). This cognitive maintenance was not consistent throughout the trial period, and was not observed in all functions. Also important to note is that the study group did not include patients with moderate or severe AD. A larger trial did not observe overall cognitive benefit of rosiglitazone in mild-to-moderate AD patients, although improvement was noted in ApoE ϵ ₄-negative subjects on a task of general cognitive function at the highest dose (Risner *et al.* 2006). Subsequent Phase III trials found no evidence of statistically or clinically significant efficacy of rosiglitazone in cognition or global function, regardless of genotype, when used as monotherapy (Gold *et al.* 2010) or as adjunctive therapy to AChE inhibitors (Harrington *et al.* 2011). Pioglitazone produced similar results. Trials of mild-AD patients with diabetes reported improved general cognition, improved verbal memory, and improved cerebral blood flow in the parietal lobe, following six months of treatment (Hanyu *et al.* 2009; Sato *et al.* 2011). Nevertheless, a trial of non-diabetic patients meeting research criteria for probable AD, showed no improvements on cognitive and functional measures (Geldmacher *et al.* 2011).

The lack of efficacy in these trials may be due to several reasons, including the complicated effects that inflammation exerts in AD pathogenesis, treatment at the wrong stage of the disease, or inappropriate dosing. Importantly, there is a debate on whether rosiglitazone effectively crosses the BBB in rodents: intraperitoneal administration to gerbils (Sheu *et al.* 2011) or oral delivery to mice (Strum *et al.* 2007) resulted in effective and rapid penetration to the brain, while intravenous administration to rats resulted in low brain uptake (Festuccia *et al.* 2008); the ability of pioglitazone to cross the BBB is less controversial (Grommes *et al.* 2013; Maeshiba *et al.* 1997). In addition, human trials raised some safety concerns regarding the effects of rosiglitazone on cardiovascular functioning and heart failure in diabetic patients (Mannucci *et al.* 2010). Combined, these findings suggest that there is continuous and consistent evidence of the beneficial effects of insulin and insulin sensitizing therapies on cognition, however, the emphasis on insulin in treating AD should be shifted towards a different approach.

Is glucagon-like peptide-1 a promising novel approach in treatment of AD?

One such pharmacologic approach to insulin resistance involves the use of insulinotropic glucagon-like peptide-1 (GLP-1), a hormone that facilitates insulin release under high blood sugar conditions, and does not affect blood sugar levels in non-diabetic people, enhances insulin signaling, and protects neurons from toxic effects (Holscher 2010). GLP-1 agonists bind GLP-1 receptor that is coupled to a second messenger pathway via G proteins (Green *et al.* 2004), and improve dyslipidemia, blood pressure, and other diabetes-associated vascular conditions (Sivertsen *et al.* 2012). GLP-1 is proposed to play a role in a regulatory mechanism involved in the actions of GLUT1 glucose transporters and glucose metabolism, by ensuring less fluctuation of brain glucose levels in response to alterations in plasma glucose (Gejl *et al.* 2012). The neuroprotective actions of GLP-1 have been demonstrated in *in vivo* and *in vitro* studies. GLP-1 has been documented to induce neurite outgrowth, reduce apoptosis, protect neurons from oxidative stress, protect synaptic plasticity and memory formation from the detrimental effects of A β , and reduce plaque formation and the inflammation response in the brains of mouse models of AD (reviewed by (Holscher 2010)). Intraperitoneal injection of GLP-1 receptor agonist to AD transgenic mice reduced hippocampal amyloid burden, while improving spatial memory (Bomfim *et al.* 2012).

The association between AD and the non-insulin antidiabetic therapy metformin

Metformin is a biguanide (Bailey and Turner 1996) that lowers blood glucose levels by increasing hepatic and muscle cell insulin sensitivity, by decreasing intestinal glucose absorption (Tian *et al.* 2004), and crosses the BBB readily (Labuzek *et al.* 2010). Metformin improved insulin sensitivity and decreased insulin levels in persons without diabetes (Kitabchi *et al.* 2005) and was therefore proposed as a new target for research in the context of cognitive compromise. *In vitro*, metformin significantly decreased phosphorylated tau and ameliorated A β ₁₋₄₂ levels in neuronal insulin resistance and AD-associated cell cultures (Gupta *et al.* 2011). Counter-intuitively, in primary cortical culture models, metformin significantly increases the generation of both intracellular and extracellular A β species, but in combined use with insulin, metformin enhances insulin's effect in reducing A β levels (Chen *et al.* 2009). Finally, in murine primary neurons from wild-type and human tau transgenic mice, metformin reduced tau phosphorylation (Kickstein *et al.* 2010). *In vivo*, the association between metformin and AD-like neuropathology was examined in obese, leptin-resistant mice. Metformin attenuated the increase of phosphorylated tau and the reduction of the synaptic protein synaptophysin, but did no better than saline in decreasing A β levels, and did not attenuate the impairments of spatial learning and memory (Li *et al.* 2012). Metformin successfully attenuated cognitive deficits of diabetic rats (Bhutada *et al.* 2011), and high-fat diet fed rats (Pintana *et al.* 2012).

To date, we do not have adequate clinical data on the efficacy of metformin in preventing or treating AD and other dementia related disorders in humans. Nevertheless, a study of elderly diabetic individuals showed that metformin attenuated the decline in global cognitive function but not in verbal memory, an effect that was similar to that of a diet regime, and inferior to that of a combined treatment with rosiglitazone (Abbatecola *et al.* 2010). In addition, the association between metformin and risk of dementia was examined in two large cohort-based studies, and yielded contradictory results. A study of individuals aged 65 or older found no evidence that use of metformin is associated with lower risk of developing AD (Imfeld *et al.* 2012). Furthermore, the findings even suggested that long-term use of metformin may be associated with a slightly higher risk of developing AD, compared to nonuse of this drug, and such a finding was not seen for use of other antidiabetic drugs (Imfeld *et al.* 2012). In contrast, a study of Taiwanese aged 50 years or older, found that the use of metformin in the treatment of diabetes significantly decreased the risk of dementia,

compared with no medication (Hsu *et al.* 2011). More research, particularly clinical placebo-controlled trials, is needed to clarify the potential benefits of metformin to cognitive health.

Summary

Based on current evidence, there is little doubt that diabetes and cognitive compromise are closely related. This relationship is manifested in a wide range of cognitive impairments, starting from cognitive decline, through mild cognitive impairment, and frank clinical dementia. The underlying mechanisms of these relationships are, however, still elusive. It seems that diabetes is more strongly and more consistently associated with vascular forms of cognitive impairment, rather than with AD-like neurodegenerative forms. Moreover, the different therapeutic strategies show some cognitive benefits, particularly intranasal insulin, which do not seem to be specific to AD: treatments seem less effective in attenuation of AD neuropathology in animal models and in alleviating cognitive dysfunctions in elderly who already succumbed to AD. Clinical trials have primarily targeted AD-related outcomes (e.g. A β accumulation, memory deficits, conversion rate to AD), while evidence suggests that vascular-related outcomes might be more promising. In addition, based on current basic science evidence, it is sensible to assume that mechanisms underlying diabetes complications might underlie dementia in non-diabetics as well. Nevertheless, some of the findings presented suggest that diabetes medications may be more beneficial to diabetic patients rather than to non-diabetics. Finally, both AD and vascular neuropathology are thought to begin to develop and accumulate decades before manifestation of clinical symptoms. Thus, prevention clinical trials utilizing diabetes medication aimed against the development of cognitive compromise, may be more effective for individuals at risk but initially cognitively normal, both diabetics and non-diabetics.

Acknowledgments

Acknowledgement and funding: This study was supported by NIA grants R01 AG034087 (Beeri), P50 AG05138 (Sano), the Ira T. Hirsch Award (Beeri), and by an award from the Helen Bader Foundation (Beeri).

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KEY POINTS

- Diabetes and cognitive compromise are closely related. This relationship is manifested in a wide range of cognitive impairments, starting from cognitive decline, through mild cognitive impairment, and frank clinical dementia.
- Diabetes is more strongly and more consistently associated with vascular forms of cognitive impairment, rather than with AD-like neurodegenerative forms.
- Both AD and vascular neuropathology are thought to begin to develop and accumulate decades before manifestation of clinical symptoms. Thus, prevention clinical trials utilizing diabetes medication aimed against the development of cognitive compromise, may be more effective for individuals at risk but initially cognitively normal, both diabetics and non-diabetics.