

# Antidiabetic therapies and Alzheimer disease

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Given current lack of therapies for dementia, there is substantial interest in identifying potentially modifiable risk factors. Clarifying the potential of these factors to mitigate risk as well as determining the mechanisms that link these factors to dementia is expected to lead to new approaches for both preventing and treating neurodegenerative diseases such as Alzheimer disease. Modifiable factors include cardiovascular risks as well as related lifestyle-centric factors such as diet and physical activity (reviewed in this issue). Given reports that type 2 diabetes and associated features increase the risk for developing dementia, there has been tremendous interest in exploring whether use of antidiabetic medications may impact the risk of dementia, as well as whether antidiabetic medications could be used to prevent or treat dementia, particularly Alzheimer disease. This review will briefly cover the known links between diabetes and risk for dementia, the state of evidence linking antidiabetic treatments with either protection against dementia or possibly increased risk for cognitive dysfunction, and provide a brief overview of what has been learned from clinical trials testing antidiabetic treatments in Alzheimer disease.

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## Introduction

Type 2 diabetes (T2D) affects 422 million adults worldwide.<sup>1</sup> The number of individuals affected by T2D in the future is expected to rise, as several factors which confer risk for T2D are also increasing, including over- and undernutrition, declining physical activity, increased stress, and presence of adverse socioeconomic and environmental factors.<sup>2,3</sup> This health crisis is occurring simultaneously to another looming health epidemic, namely an increase in the incidence of dementia, especially the Alzheimer clinical syndrome.

Considerable evidence indicates that type 2 diabetes (T2D) and related features such as insulin resistance are associated with increased risk for dementia. Consequently, there has also been a great deal of interest in deter-

mining to what extent antidiabetic treatments may either protect against dementia or be used as treatments for cognitive dysfunction. This review will provide a brief overview of studies that link T2D with dementia, and in particular the Alzheimer clinical syndrome, describe the state of the evidence linking antidiabetic treatments with Alzheimer disease (AD) prevention or possibly increased risk for cognitive dysfunction, and finally, consider the evidence offered by clinical trials testing antidiabetic treatments in Alzheimer disease.

## Type 2 diabetes and dementia

In addition to the well-known risk factors for AD, including age, apolipoprotein (*APOE*)  $\epsilon$ 4 genotype, and parental history of AD, there has been a long-standing interest in determining the risk conferred by vascular risk factors, and

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especially T2D. Population-based studies largely support an association between T2D and elevated dementia risk. The Rotterdam study was among the first to show an elevated risk of dementia with T2D,<sup>4,5</sup> including vascular dementia and AD. Both the Hisayama study in Japan<sup>6</sup> and the Vantaa 85+ study in Finland<sup>7</sup> found a doubling of dementia risk with T2D. Among participants in the Religious Orders Study, T2D was associated with a 65% increase in the risk of developing AD compared with those without T2D.<sup>8</sup> The Kungsholmen Project, a longitudinal population-based study based in Stockholm, found that T2D as well as pre-diabetes accelerated the progression from mild cognitive impairment (MCI) to dementia by 3.18 years.<sup>9</sup> The Cache county study also found an increased risk of dementia among individuals with T2D, although the effect was restricted to women.<sup>10</sup> Similarly, the Framingham study found that the risk for dementia conferred by T2D may be restricted to subgroups, including younger participants (<75 years of age), and individuals who do not carry the AD risk gene *APOE*  $\epsilon$ 4 genotype.<sup>11</sup> The increased association between T2D and dementia appears to be stronger when T2D is present in midlife rather than older age,<sup>12,13</sup> with some suggestion that diabetes-related abnormalities occurring as early as young adulthood may impact later cognitive function.<sup>14</sup>

## Type 2 diabetes and the pathology of Alzheimer disease

There are several potential mechanisms by which T2D may impact risk for dementia. Vascular mechanisms are likely, given the well-known adverse effects of T2D on vascular health; T2D is associated with cardiovascular disease,<sup>15</sup> lower cerebral perfusion,<sup>16</sup> small-vessel disease,<sup>17,18</sup> and stroke.<sup>19</sup> T2D-associated abnormalities in insulin are also plausible contributors to dementia risk. Peripheral insulin resistance has been associated with several brain differences, including lower cerebral glucose uptake,<sup>20</sup> reduced cerebral perfusion,<sup>21</sup> and atrophy.<sup>22</sup> In addition to the peripheral insulin abnormalities that are present in T2D, central insulin resistance—characterized by downregulation of insulin receptors, lowered binding

of insulin, and abnormal insulin signaling—is also a feature of the AD brain.<sup>23-26</sup>

As covered elsewhere in this issue, AD is defined by the presence of  $\beta$ -amyloid plaques, neurofibrillary tangles, and ultimately, neurodegeneration.<sup>27</sup> However, the extent to which T2D can be directly related to the cardinal features of AD is unclear, particularly in human studies. Animal studies are supportive of a link, demonstrating that T2D can exacerbate AD pathology, including development of amyloid plaques, tau pathology, and neurodegeneration.<sup>28-30</sup> Some human evidence also points toward a link between T2D and AD pathology; Matsuzaki et al examined lab and autopsy information for 135 individuals and found that antemortem plasma glucose, fasting insulin, and the homeostatic model assessment of insulin resistance (HOMA-IR) were associated with increased risk for amyloid plaques post mortem, especially among individuals with *APOE*  $\epsilon$ 4 genotype.<sup>31</sup>

More often, however, human studies examining the link between T2D and AD pathology have been negative, particularly with regard to amyloid. Heitner et al compared 49 diabetics to 52 age-matched controls and did not find elevated AD pathology.<sup>32</sup> In a larger study of 1037 subjects examined at autopsy, T2D (n=279) was not associated with plaque and tangle burden, although *APOE*  $\epsilon$ 4 moderated the association such that carriers had higher odds of accumulating tangles. Alafuzoff et al examined 701 brains, where 134 were from individuals who were diabetic, and did not find an association between T2D and AD pathology.<sup>33</sup> Similarly, in vivo studies using positron emission tomography (PET) or CSF analysis suggest that T2D is not associated with greater amyloid accumulation,<sup>34-36</sup> although Moran et al found a relationship between T2D and higher tau pathology as measured in CSF.<sup>35</sup>

One possibility that has been advanced is that antidiabetic treatment among individuals with T2D could mitigate AD pathology. Beeri et al examined brain autopsy data derived from 248 subjects, half with T2D and half non-T2D

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patients matched on age, sex, and postmortem interval.<sup>37</sup> Examining medication usage specifically, individuals with a history of combined use of insulin and oral antidiabetic medication (n=18) had significantly fewer amyloid plaques in all brain regions assessed, suggesting a possible beneficial effect of therapy on AD pathology.

Thambisetty et al are among the few who—like Beeri et al—also examined medication usage in relation to AD pathology as assessed with PET or post mortem assessment of AD pathology. They found that T2D was not associated with AD pathology, and that among the subset taking antidiabetic medications, there was no difference in level of AD pathology. Unlike the study by Beeri et al, however, combination therapy was not examined and the number of individuals who were taking insulin was small.<sup>38</sup> A couple of studies have also found that individuals with T2D have lower AD pathology compared to controls. Ahtiluoto et al found that the proportion of individuals with  $\beta$ -amyloid plaques measured on autopsy was significantly lower among diabetic compared to nondiabetic individuals.<sup>7</sup> Likewise, Nelson et al observed significantly lower neurofibrillary counts in the subiculum and lower amyloid plaque count in temporal lobe among diabetics compared with non diabetics.<sup>18</sup> However, these latter two studies did not examine the impact of medication specifically, and in light of the largely mixed literature on the relationship between T2D and AD pathology, it is almost impossible to draw conclusions on the impact of medications from observational studies alone.

#### Medications for type 2 diabetes and risk for dementia

Determining whether antidiabetic medications mitigate risk for dementia is complicated. Among individuals with T2D, observational studies are confounded by the fact that the effect of antidiabetic medication is not easily separated from the presence of T2D. Furthermore, there are multiple approaches to treating T2D. In addition to recommendations pertaining to diet, physical activity, and other lifestyle factors, treatment of T2D may involve several drug classes, including metformin, sulfonylureas, thiazolidinediones (TZDs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, alpha-glucosidase inhibitors, glucagon-like peptide 1 (GLP1)-based therapies (GLP-1 agonists and dipeptidyl peptidase-4 inhibitors), and insulin. Only a subset of these have been examined in relation to dementia in observational studies (as either monothera-

pies, or as part of combination therapies), and even fewer have been tested in human clinical trials for AD.

Metformin is typically the first medication prescribed for T2D, reducing the production of glucose in the liver, increasing uptake of glucose by the periphery, and improving insulin sensitivity. In a study of records from individuals 50 years of age or older in Taiwan's National Health Insurance database, where n=25 393 had a diagnosis of T2D and n=101 816 did not have a diagnosis of T2D, Hsu et al found that dementia was increased 2.6-fold among individuals with T2D.<sup>39</sup> Encouragingly, use of metformin reduced the risk of dementia by 24% compared with no use of antidiabetic medication. Sulfonylureas—which trigger release of endogenous insulin by binding to and closing ATP-sensitive K<sup>+</sup> channels on the cell membrane of pancreatic  $\beta$ -cells—reduced dementia risk by 15%. When used in a combined regimen, these two oral antidiabetic agents decreased the risk of dementia in patients with T2D by 35% over 8 years. Adjusting for cerebrovascular disease did not change the association, suggesting that the reduced risk may occur independently from vascular mechanisms.

Heneka et al examined the association between pioglitazone and incidence of dementia utilizing data from a mandatory German public health insurance company.<sup>40</sup> Data included longitudinal observations from 145 928 subjects who were 60 years of age or older and free of dementia and insulin-dependent diabetes at baseline. Subjects were either nondiabetics, diabetics who did not use pioglitazone, diabetics treated with pioglitazone for shorter periods (less than 8 calendar quarters of use), or diabetics treated for longer periods (eight or more quarters of pioglitazone use). Controlling for age, sex, use of rosiglitazone or metformin, and cardiovascular comorbidities, a diagnosis of diabetes without pioglitazone treatment was associated with a 23% increased risk for dementia. In turn, long-term use of pioglitazone was associated with a lower dementia incidence, while shorter-term pioglitazone use was associated with a dementia risk comparable to that of nondiabetics.

Utilizing data from the Sacramento Area Latino Study on Aging (SALSA Study), Wu et al examined the longitudinal association between antidiabetic medications and physical and cognitive functioning among older

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community-dwelling Mexican Americans.<sup>41</sup> Antidiabetic drugs included insulin in addition to oral glucose-lowering agents comprising metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and meglitinides. Among 1789 study participants, 585 (32.7%) were identified as having T2D at baseline. There was a positive effect of antidiabetic medication on both physical and cognitive function, with combination therapy of two or more antidiabetic agents resulting in a lower risk than monotherapy.

However, associations between antidiabetic medication and dementia are not uniformly in the direction of increased protection. A case-control study of 14 172 participants aged 65 years and older found that metformin was associated with an increased risk of AD dementia.<sup>42</sup> In the Rotterdam Study, risk of incident dementia was highest among patients treated with insulin.<sup>4</sup> Likewise, a Taiwanese study found that combination therapy with insulin was associated with greater risk of AD.<sup>43</sup> It is possible in these studies that T2D or the severity of T2D—not medication—conferred the increased risk, although controlling for time since diagnosis (which was done in Huang et al<sup>43</sup>) may approximate disease severity.

### Antidiabetic medication as an intervention for dementia

Despite the mixed findings of observational studies, a large body of literature and several compelling hypotheses still suggest that antidiabetic therapies hold potential as treatments for dementia. Of particular interest, are observations that T2D and AD appear to share mechanisms in common, including abnormalities in insulin signaling, mitochondrial dysfunction, abnormal energy homeostasis, and neuroinflammation.<sup>44</sup> Hundreds of studies have examined the extent to which antidiabetic medications may impact brain pathology—particularly features of AD—with the majority of animal studies pointing toward potential benefits on amyloid pathology,<sup>45,46</sup> tau pathology,<sup>47,48</sup> synapses,<sup>49,50</sup> oxidative stress,<sup>51</sup> neurogenesis,<sup>52</sup> neuroinflammation,<sup>53</sup> and cognitive function.<sup>25,54,55</sup>

However, human clinical trials—such as observational studies—show mixed findings. Promising effects of antidiabetic medications have been observed in relatively smaller trials. In a promising small trial, Luchsinger et al tested the effects of metformin among 80 participants

with amnesic MCI and no diagnosis of T2D and found a beneficial effect of metformin on verbal memory.<sup>56</sup> A small placebo-controlled crossover study randomized twenty nondiabetic participants with MCI or mild AD dementia to metformin followed by placebo or vice versa for 8 weeks and found a significant positive effect of metformin on executive function, specifically Trials B.<sup>57</sup> In addition to metformin, small trials of TZDs have also shown beneficial effects. A small pilot study which randomized patients with AD/amnesic MCI to oral rosiglitazone or placebo for 6 months found better delayed recall at both 4 and 6 months, as well as better selective attention at 6 months.<sup>58</sup> Pioglitazone was tested among 42 individuals with mild AD and an accompanying diagnosis of T2D<sup>59</sup> and found a benefit of pioglitazone compared with control on MMSE and the Japanese version of ADAS-Cog scores. However, a caveat was the open-label study design.

Larger trials have been routinely negative. An efficacy and tolerability study of rosiglitazone randomized 518 patients with mild-to-moderate AD to various doses of rosiglitazone (2, 4, or 8 mg) or placebo.<sup>60</sup> No effects were observed at 24 weeks on the primary end points including change from baseline in ADAS-Cog or the Clinician's Interview-Based Impression of Change Plus Caregiver Input. In a follow-up phase 3 study with the same outcomes, 693 participants were stratified by *APOE* genotype. Again, no significant effects of rosiglitazone were observed in either the overall sample or within *APOE4* subgroups at week 24.<sup>61</sup>

In the largest trial of its kind to date, a global, phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial evaluated the efficacy of low-dose pioglitazone as a treatment to delay onset of MCI in cognitively unimpaired individuals who were identified as high risk by a genetic risk algorithm.<sup>62</sup> In addition to examining cognitive outcomes, an additional aim of the study was to qualify the genetic biomarker risk algorithm for assigning 5-year risk for developing MCI due to AD. The study—which involved 50 clinical sites and screening of 25 000 people—enrolled 3494 cognitively unimpaired participants who were screened on *APOE* and *TOMM40* genotype. The trial ended early following an interim futility analysis, which showed an inadequate treatment effect of 0.8 mg of sustained release pioglitazone in delaying the onset of MCI due to AD.<sup>63,64</sup>

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Given observed abnormalities in insulin receptor density and insulin signaling in AD, a novel approach to therapy tested in several small and larger trials involves intranasal delivery of insulin. Intranasal delivery tempers the risks that would be involved if insulin were delivered peripherally, including insulin resistance and hypoglycemia. Early results from intranasal insulin trials were promising. For example, an early pilot trial tested a 3-week intervention comparing intranasal insulin with placebo in 24 individuals with amnesic MCI or mild AD and found positive impacts on verbal memory and attention.<sup>65</sup> In a separate trial that examined differing doses of intranasal insulin among 33 people with amnesic MCI/early AD and 59 cognitively unimpaired adults, beneficial effects were observed on verbal memory specifically among memory-impaired *APOE*  $\epsilon$ 4 non-carriers. In contrast, memory-impaired *APOE*  $\epsilon$ 4 carriers showed a decline in verbal memory in response to intranasal insulin.<sup>66</sup> In 2013, the multi-site Study of Nasal Insulin in the Fight against Forgetfulness (SNIFF) trial was launched. Participants with amnesic MCI or AD (n=289) were enrolled at 26 sites. Recently presented results of the primary analysis of data from 240 individuals who utilized a newly available nasal delivery device indicated no impact of intranasal insulin on the primary cognitive outcome.<sup>67</sup> The results of additional analyses (for eg, analyses by *APOE*  $\epsilon$ 4 genotype) are still pending, and it is important to note that a mid-study change in delivery device, which occurred due to malfunction of the original device, may have also impacted the outcome.

Tight control of T2D is not associated with cognitive benefit. The ACCORD study did not support a beneficial effect of intensive glycemic treatment (HbA1c <6%) on cognitive function, either at the time the intensive treatment arm was stopped due to mortality risks,<sup>68</sup> or 47 months later.<sup>69</sup> Furthermore, tight glycemic control could increase the occurrence of hypoglycemia, which in turn may contribute to cognitive impairment.<sup>70</sup>

Only a small number of trials have examined the impact of antidiabetic medications on potential markers of AD pathology. The effect of metformin on CSF biomarkers of AD was evaluated in a small trial (n=20), but results did not show any effect.<sup>57</sup> In a small trial carried out by the Craft group testing the impact of rosiglitazone on cognitive function, plasma A $\beta$ 42 levels did not change in the group receiving rosiglitazone (n=20), but showed a decline

among individuals in the placebo group.<sup>58</sup> In a small study from Sato et al which tested pioglitazone, plasma A $\beta$ 40/A $\beta$ 42 remained stable in the treated group but increased in the control group. The import of these findings is unclear given the small Ns and limited validation of plasma amyloid assays as markers of CNS amyloid. Markers of amyloid and tau pathology have also been evaluated in cerebrospinal fluid as part of single center and larger multi-site trials of intranasal insulin. Insulin has been found to lower ptau/A $\beta$ 42 in at least one study,<sup>71</sup> although another single site study from this same group<sup>72</sup> did not show an effect, and early results from SNIFF did not suggest an effect on CSF biomarkers.

### Considerations for the future

Given the evidence that links T2D with dementia risk, pathophysiological similarities between T2D and AD, as well as promising small trials, why are medications targeting these mechanisms ineffective in larger trials?

An issue that has plagued prior trials concerns the timing of interventions in relation to disease course: are treatments initiated when a disease process is already substantially underway and thus less effective? Among individuals with AD, and even MCI, by definition there is usually substantial plaque and tangle burden apparent, as well as neurodegeneration. With regard to testing medications which act on insulin, the issue of timing may also extend beyond cognitive severity or degree of amyloid and tau pathology. For example, activity of the enzymes phosphodiesterase, glycogen synthase kinase 3 $\beta$ , and insulin degrading enzyme, are altered in T2D as well as AD, linking the two diseases, but abnormalities may occur upstream of the development of AD pathology, such that interventions may need to be initiated earlier to be effective. Furthermore, consider the example of hormone therapy as tested in the Women's Health Initiative study. After risks of hormone therapy such as coronary heart disease, breast cancer, and cognitive decline were discovered, the suggestion was offered that initiating hormone therapy several years post-menopause onset was a poor strategy.<sup>73</sup> Therapies targeting the hormone insulin may need to be equally sensitive to timing issues, as age and disease associated changes to insulin receptors evolve and may differ among individuals.

Are trials enrolling participants who are most likely to benefit? For example, in the case of treatments tested as

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interventions for AD, do the participants harbor AD pathology, or is it a heterogeneous group with various pathologies? Given the unique targets of T2D medications, it may be further necessary to refine the selection of participants to those with metabolic abnormalities. For example, while a phase 3 trial of azeliragon—which inhibits the receptor for advanced glycation end products—was terminated after it was found that patients with mild AD taking azeliragon did not improve on cognition or functional outcomes compared with placebo,<sup>74</sup> a subgroup of AD patients with diabetes and high HbA1c did appear to benefit.<sup>75</sup> Likewise, insulin sensitizers may need to be selectively tested among individuals who have confirmed central (or possibly peripheral) insulin resistance. Genotype will also play a role, as has become clear with multiple studies of T2D, insulin resistance, and trials of antidiabetic medications; in particular, there is substantial accumulating data pointing toward *APOE4* as a critical variable in studies relating to energy metabolism and metabolic dysregulation. Unfortunately, despite the many studies suggesting its importance, how it should be handled in clinical trials is not precisely clear. In at least one study, it appears that carriers benefit from treatment,<sup>76</sup> while in other cases, the evidence suggests noncarriers benefit.<sup>60,77,78</sup> Similar inconsistencies are apparent with regard to T2D and how it associates with dementia or AD neuropathology; in some cases T2D or related features are associated with pathology or dementia to a greater degree among *APOE4* carriers,<sup>79,80</sup> and in other studies the opposite appears to be true.<sup>81,82</sup> Severity of the clinical syndrome, and by extension level of disease pathology may also be an important factor. In the case of peripheral insulin levels for example, there is some evidence that elevated insulin levels impart increased risk early in the disease process, but by later stages, the relationship flips such that depressed levels may contribute to greater dysfunction.<sup>83</sup>

It may also be the case that T2D therapies, while having beneficial effects on certain aspects of disease, may exacerbate other disease features if unopposed. Human, rodent, and cell model studies cumulatively suggest that combination therapy could be preferable to monotherapy.<sup>37,41,84,85</sup>

Other factors that are difficult to parse are whether the

impact of T2D directly impacts the brain through an insulin-mediated mechanism, or whether risks for dementia are due to accompanying factors such as obesity, dyslipidemia, hypertension, or the impact of advanced glycation end-products, all of which may have independent or synergistic impacts on the brain. A beneficial approach may be to consider treatment of T2D as part of a broader strategy to control vascular risk factors to attenuate cognitive decline.<sup>86</sup>

### Conclusion

Despite several epidemiologic studies, animal studies, and small trials, there are no gold-standard studies that have unequivocally sealed the case between T2D and AD, or the impact of T2D medications. A number of issues confound the interpretation of observational studies, including the co-occurrence of T2D, treatment for T2D, and comorbidities. A major gap at present for testing antidiabetic therapies in AD is that the mechanisms which tie T2D to the Alzheimer clinical syndrome are not entirely known and may not be via AD-specific pathology, or they may be upstream phenomena, preceding pathology. Mitigating instigators of pathology may require treating individuals early, prior to development of extensive amyloid and tau tangle burden for maximum effectiveness.

Strategies for optimizing treatment trials are still needed, including improved patient selection, determining the correct timing of treatment in relation to disease course, and identification of suitable biomarkers for evaluating therapies that currently have multifactorial or perhaps even unknown mechanisms of action. Indeed, a major advancement in the field of AD clinical trials has been the improved precision by which individuals with disease pathology can be identified, especially prior to developing cognitive dysfunction. As the field moves toward ever better biomarkers of disease processes, testing and developing drugs related to the specific processes that connect T2D with AD remain a viable area of inquiry and development. ■

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