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Diabetes, related conditions, and dementia

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ABSTRACT

This manuscript provides a brief review of the epidemiologic evidence linking type 2 diabetes (T2D) and its precursor conditions, elevated adiposity and hyperinsulinemia, to dementia. Elevated adiposity in middle age is related to a higher risk of dementia but the data on this association in old age is conflicting. Hyperinsulinemia, a consequence of higher adiposity and insulin resistance is also related to a higher risk of dementia, including late onset Alzheimer's disease (LOAD). Studies have consistently shown a relation of T2D with higher dementia risk, but the associations are stronger for vascular dementia compared to LOAD. One implication of these associations is that strategies used to prevent T2D can be used to prevent dementia. Several studies in the prevention and treatment of T2D are currently measuring cognitive outcomes and will provide information on whether T2D treatment and prevention can prevent cognitive decline and dementia.

1. Introduction

Type 2 diabetes (T2D) and dementia are 2 of the most common conditions in the elderly. This manuscript is a brief review of the epidemiological evidence supporting an association between T2D and dementia, and covers representative publications in the field.

T2D disproportionately affects the elderly. Almost 25% of the population 60 years and older had T2D in 2007 [1]. If pre-diabetes is considered, the prevalence is over 50% in persons 60 years and older. A rise in adiposity (also referred to as fatness, or obesity) is the cause of the increase in T2D. Two-thirds of American adults are overweight or obese. The common link of these conditions (obesity, prediabetes, and T2D) is insulin resistance, which causes hyperinsulinemia [2]. Given the high prevalence of T2D and its related conditions, their associations with dementia may have enormous public impact.

Late onset Alzheimer's disease (LOAD) is the most common form of dementia, accounting for between 70% and over 90% of all cases, and its prevalence is expected to quadruple by the year 2047 in the United States [3]. As much as 50% of the population aged 85 years and older, the fastest growing segment of the population, may have LOAD [4]. Vascular dementia (VD) is the second most common form of dementia, although it varies widely depending on the criteria used [5]. Mixed dementia is a term that has been coined to describe the mix of clinical features of LOAD and VD. The reference to dementia in this review is a reference to LOAD, VD, or mixed dementia.

2. Potential mechanisms and type 2 diabetes with dementia

T2D is preceded or accompanied by elevated adiposity that causes insulin resistance. Insulin resistance causes hyperinsulinemia to maintain normal glucose levels. When the pancreas cannot sustain hyperinsulinemia to overcome insulin resistance, pre-diabetes or T2D ensues [6]. This natural history is part of the metabolic syndrome, that includes hypertension, dyslipidemia, and elevated systemic inflammation [2]. All components of the metabolic syndrome are risk factors for brain infarcts, clinically termed strokes [7]. Pathology studies have demonstrated that the presence of amyloid plaques is lower in brains of persons with dementia who also have infarcts [8,9], suggesting that the presence of infarcts is an insult that lowers the threshold of amyloid in the brain that is necessary to cause dementia. A study of religious orders across the United States based at Rush University in Chicago found that T2D was related to infarcts on autopsy but not AD pathology in persons with dementia [10]. However, the Honolulu-Asia Aging Study [11], a study of Japanese-Americans, found that T2D was related to AD pathology, particularly in persons with the APOE-ε4 allele. The Adult Changes in Thought Study, based at the University of Washington, reported that persons without DM and with dementia had a greater amyloid-β peptide load and in the cerebral cortex, while those with both T2D and dementia patients had more microvascular infarcts. The number of microvascular infarcts was greater in persons with dementia and treated T2D, whereas amyloid plaque load tended to be greater for persons with dementia with untreated T2D [12]. The

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interaction between infarcts and amyloid pathology in persons with dementia and T2D seems complicated and more studies are needed.

One of the tantalizing issues in the relation between T2D and dementia is the plausibility of non-cerebrovascular mechanisms. Craft has reviewed how peripheral hyperinsulinemia affects amyloid beta clearance in the brain [13]. Another potential non-cerebrovascular mechanism is advanced products of glycosylation (AGE), elevated in T2D, which results in up-regulation of its receptor (RAGE). The role of RAGE in LOAD has been reviewed by Yan et al. [14]. LRP is a family of lipoprotein receptors that affect lipid metabolism and are affected by T2D. The role of LRP in LOAD has been reviewed by Zlokovic [15].

3. Summary of prospective epidemiological studies linking type 2 diabetes and related conditions to dementia

Numerous studies have examined the relation between T2D and dementia. Table 1 shows the results of some representative prospective studies in different countries and age groups. In general, the association between T2D and dementia seems to be stronger for vascular dementia compared to LOAD, but these observations are inconsistent. Some studies have also reported an interaction between T2D and the APOE-ε4 allele, while others have not found this interaction.

Elevated adiposity in middle age may be associated with higher dementia risk [16–18]. However, the reports relating adiposity in older age to dementia are conflicting [19–23]. The Cardiovascular Health Study recently reported that elevated self-reported BMI at age 50 years was associated with a higher risk of dementia, while BMI at age 65 or older *in the same individuals* did not [24]. Causes for this paradox may include survival bias related to high adiposity, but also weight loss that may precede the clinical recognition of dementia by decades [25]. This study underscores the importance of the period in life at which adiposity is ascertained in relation to dementia.

Several cross-sectional studies show an association between hyperinsulinemia and an increased risk of LOAD [26–28]. Two longitudinal studies, one in elderly Japanese Americans in Hawaii [29], and another in elderly Black, Caribbean Hispanic, and Non-Hispanic Whites in New York City [30] found that the risk of incident LOAD was higher in persons with hyperinsulinemia independent of a history of stroke. These studies also found that the risk of LOAD related to hyperinsulinemia was higher among persons with the APOE-ε4.

There is limited evidence on the association between the metabolic syndrome and dementia in the elderly. A cross-sectional study in Europeans found that LOAD prevalence was higher in persons with the metabolic syndrome [31]. In Northern New York City the metabolic syndrome was not related to LOAD risk, while its individual components T2D and hyperinsulinemia were [32]. The discrepancy between these studies could be due to the fact that the study in New York City was conducted in an older population, ethnically diverse, and with a high prevalence of vascular risk factors [33]. In Japanese Americans the metabolic syndrome in middle age was associated with VD, but not LOAD [34].

4. Implications of the relation between T2D and dementia

T2D can be prevented and treated, and strategies used to prevent and treat T2D could be used to prevent or treat dementia. Two studies that have demonstrated the efficacy of T2D prevention with lifestyle interventions, the Finnish Diabetes Prevention Study (FDPS) [35], and the Diabetes Prevention Program Outcomes Study (DPPOS) [36] include comprehensive neurocognitive batteries that started in 2009 which will permit the exploration of whether T2D prevention through lifestyle interventions prevents dementia. Thiazolidinediones are PPAR-gamma agonists and potent insulin sensitizers [37]. Based on their powerful insulin sensitizing actions they have been studied as a potential treatment of AD based on the hypothesis that treating

Table 1
Summary of representative studies relating type 2 diabetes to risk of dementia.

First author, year of publication	Setting	Results
Leibson, 1997 [49]	Rates of dementia in 1455 persons 45 years and older with T2D in Rochester, Minnesota were compared to population rates.	Relative risk (RR) relating T2D and all cause dementia was 1.66 (95% confidence interval (CI): 1.34–2.05), RR relating T2D with AD was 2.27 for men (95% CI: 1.55–3.31) and 1.37 for women, (95% CI: 0.94–2.01).
Brayne, 1998 [50]	2609 persons 75 years and older in Cambridge, England	Odds ratios (OR) relating T2D with all cause dementia was 2.62 (0.89–7.75), and 1.44 (1.05–17.00) for AD.
Ott, 1999 [51]	6370 persons 55 years and older in Rotterdam, The Netherlands	T2D related to both all cause dementia (RR = 1.9 [95% CI = 1.3 to 2.8]) and AD (RR 1.9 [1.2–3.1]). Risk of dementia highest in persons treated with insulin (RR 4.3 [95% CI: 1.7–10.5]).
Curb, 1999 [52]	3774 Japanese American men in Hawaii, United States, aged 45 to 68 years at the time of T2D ascertainment and between 71 and 93 years at the time of dementia ascertainment.	RR relating T2D with VD was 1.48 (95% CI: 0.79, 2.78), and 0.98 (95% CI: 0.48, 1.99) for AD
Peila, 2002 [11]	2574 Japanese-American men aged 77 years on average enrolled in the Honolulu-Asia Aging Study, Hawaii, United States. T2D was ascertained in older age	RR for total dementia was 1.5 (95% CI: 1.01–2.2), 1.8 for AD (95% CI: 1.1–2.9), 2.3 for vascular dementia (95% CI: 1.1–5.0). Individuals with both T2D and the APOE-ε4 allele had an RR of 5.5 (CI 2.2–13.7) for AD compared with those with neither risk factor.
Arvanitakis, 2004 [53]	824 persons older than 55 years from the Religious Orders Study in the United States	Hazard ratio (HR) relating T2D with AD was 1.65 (95% CI: 1.10–2.47).
Luchsinger, 2004 [33]	1138 persons aged 65 years and older from Northern Manhattan, United States	Hazard ratio relating T2D and AD was 2.4 (95% CI: 1.8–3.2).
Schnaider Beeri, 2004 [54]	1892 male civil servants aged 40 to 65 at time of T2D ascertainment in Israel	OR relating T2D at midlife with dementia 30 years later was 2.83 (95% CI = 1.40 to 5.71).
Xu, 2004 [55]	1301 persons aged 75 years and older in Stockholm, Sweden	HR for T2D were 1.5 (95% CI 1.0 to 2.1) for dementia, 2.6 (95% CI 1.2 to 6.1) for VaD, and 1.3 (95% CI 0.9 to 2.1) for AD.
Whitmer, 2005 [56]	8845 participants of a health maintenance organization in California, United States, who were between the ages of 40 and 44 at the time of T2D ascertainment	HR relating T2D with dementia was 1.46, (95% CI: 1.19 to 1.79)
Xu, 2007 [57]	1173 persons without known T2D aged 75 years and older in Stockholm, Sweden	Borderline T2D diagnosed with plasma glucose was associated with adjusted hazard ratios (95% CIs) of 1.67 (1.04–2.67) for dementia and 1.77 (1.06–2.97) for AD.
Irie, 2008 [58]	2547 persons 65 years and from the Cardiovascular Health Study in the United States.	RR for AD 1.42 (95% CI: 1.02–1.97) but was 4.53 (95% CI: 2.47–8.30) when the APOE-ε4 allele was also present. There was no association with vascular dementia.

hyperinsulinemia lowers amyloid beta deposition and AD progression. However a recent phase III trial of rosiglitazone (NCT00428090) in mild to moderate LOAD failed to show a benefit [38]. It is possible however that the use of thiazolidinediones in mild cognitive impairment could improve the risk of dementia. The Rosiglitazone Effects on Cognition for Adults in Later Life (RECALL; NCT00242593) study is examining the effects of rosiglitazone on cognition in persons with MCI and is estimated to finish in 2010. The Pioglitazone or Exercise to Treat Mild Cognitive Impairment (POEM; NCT00736996) is exploring the effects of pioglitazone compared to exercise or placebo in persons with MCI and is scheduled to end in 2011. The major limitation of thiazolidinediones in the prevention of dementia is the class side effects of edema and congestive heart failure, and the concerns with increased cardiovascular morbidity with rosiglitazone compared to pioglitazone, which are still a matter of debate.

Metformin is a medication belonging to the biguanide class [39,40]. Metformin clearly reduces insulin levels [41], inflammation and thrombosis [42], and the risk of the metabolic syndrome [43] and T2D [44]. One recent study in cellular models showed that Metformin increases the production of amyloid beta through up-regulation of beta-secretase [45] and the authors raised the concern that Metformin could increase the risk of LOAD. However, this study needs to be replicated, and the relevance of its findings to humans demonstrated. The effect of Metformin on cognition will be assessed in the Metformin arm of the DPPOS. Additionally, there is an ongoing phase II trial of Metformin (NCT00620191) testing whether Metformin can decrease cognitive decline and dementia in persons with MCI.

It is possible that tighter T2D control could improve the risk of dementia in T2D. The recently finalized "Action to Control Cardiovascular Risk in Diabetes—Memory in Diabetes" (ACCORD-MIND; NCT00182910) study will be able to answer whether tighter T2D control reduces the risk of cognitive decline and dementia in persons with T2D [46]. An unpublished analysis of data from the Informatics in Diabetes Education and Telemedicine Study (IDEATel) [47], a randomized trial of telemedicine vs. usual care in 2169 elderly persons with T2D, showed that persons in the intervention group, which showed better control parameters compared to usual care, had less global cognitive decline during a maximum of 6 years of follow-up. Importantly, the glycemic control goals of IDEATel followed glycemic guidelines which were less stringent than the goals in ACCORD, which showed increased mortality in its tight glycemic control arm [48].

Conflict of interest

Dr. Luchsinger has no conflict of interest to report.

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