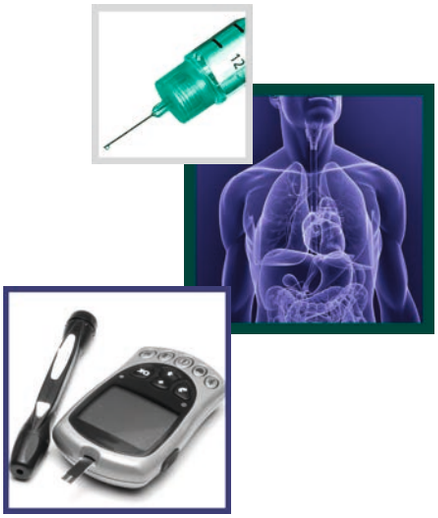
EDITORIAL



Type 2 diabetes and dementia: is there a substantial link?

"The relationship between diabetes and vascular forms of cognitive impairment is not surprising, given that diabetes is a strong cerebrovascular risk factor."

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Type 2 diabetes and dementia are two of the most significant conditions, from a public health standpoint, that are increasing in prevalence globally in epidemic proportions, particularly in the elderly. The rise in the number of people with diabetes is due to an increase in the number of overweight individuals and the incidence of obesity, the main risk factors for diabetes, which are caused by an increase in caloric intake and a decrease in physical activity accompanying modern lifestyles. The rise in prevalence of dementia is due to increasing longevity in societies that have increasing proportions of elderly persons relative to young adults and children. This increasing longevity is accompanied by a higher burden of chronic diseases, such as diabetes and heart disease, which in turn may be risk factors for dementia.

Many epidemiologic studies have demonstrated that diabetes and its related conditions are related to both vascular and neurodegenerative forms of cognitive impairment [1,2], including amnestic and nonamnestic mild cognitive impairment (MCI) [3] and Alzheimer's [4] and vascular dementia [5]. However, the relationship between diabetes and vascular forms of cognitive impairment is stronger and more consistent than the relationship with neurodegenerative forms. The relationship between diabetes and vascular forms of cognitive impairment is not surprising, given that diabetes is a strong cerebrovascular risk factor. It is increasingly proposed that the presence of cerebrovascular disease decreases the threshold of amyloid pathology necessary to manifest Alzheimer's dementia. Thus, an important question that remains to be answered is whether diabetes affects Alzheimer's dementia through cerebrovascular disease or by directly increasing Alzheimer's pathology. Several lines of evidence have attempted to address this question. Insulin resistance in individuals with normal cognition and prediabetes and early diabetes without treatment is associated with reductions in cerebral glucose metabolic rate measured using FDG-PET in frontal, temporoparietal and cingulate regions, similar to those observed when predicting the development of clinical Alzheimer's dementia [6]. Insulin and glucose elevations and

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cerebrovascular disease have differential effects on the hippocampus that manifest as global hippocampal dysfunction, one of the hallmarks of Alzheimer's dementia [7].

Few studies have explored the association of diabetes and brain pathology. The Religious Orders Study reported that diabetes was related to infarcts on autopsy but not Alzheimer's pathology in individuals with dementia [8], this was interpreted as suggesting that the main mechanism linking diabetes to dementia is the presence of infarcts. The Honolulu–Asia Aging Study, reported that diabetes was related to Alzheimer's pathology, particularly in persons with the APOE-ε4 allele [9]. The Adult Changes in Thought study reported that dementia patients without diabetes had a greater amyloid-β peptide load in the cerebral cortex, while those with both diabetes and dementia experienced more microvascular infarcts [10]. A Japanese study that used information on metabolic markers measured one decade before death demonstrated associations between one type of dementia pathology, neuritic plaques and diabetes, as well as with insulin resistance [11]. In summary, pathology studies are conflicting in demonstrating a relationship between diabetes and Alzheimer's pathology. Furthermore, several caveats must be taken into account in autopsy studies. Sample sizes tend to be relatively small and selected from a much larger pool of participants. This lends itself to selection bias and the possibility of chance findings. Second, autopsy studies cannot discern cause and effect. Lastly, there is a growing notion that dementias are more heterogeneous than originally thought. This heterogeneity may explain conflicting findings across studies.

The association between diabetes and LOAD has not been determined to be causal. The ideal way to demonstrate that the association between diabetes and dementia is at least partially causal and to gain further insight into underlying mechanisms is through conducting clinical trials. Several clinical trials have or are currently exploring this question. There are now two studies investigating lifestyle interventions that include measures of cognitive impairment. These are the Finnish Diabetes Prevention Study (FDPS) and the Diabetes Prevention Program (DPP) Outcomes Study (DPPOS). The FDPS was a trial comparing lifestyle intervention versus no intervention in 522 overweight or obese middle-aged individuals with glucose intolerance [12]. The risk of diabetes was decreased by approximately 58% in the intervention group after approximately 3 years' follow-up. The DPP was a trial comparing lifestyle interventions versus metformin versus placebo in over 3000 participants with glucose intolerance. The lifestyle intervention, which consisted of a program to achieve weight loss and increase physical activity, was the most effective, with a 58% reduction in the incidence of diabetes compared with placebo after 3 years, a reduction similar to that achieved in the FDPS. After 3 years, the DPP became an observational study called the DPPOS; however, participants remained in their randomized groups and those in the placebo group undertook a lifestyle intervention. The DPPOS reported that benefits in the prevention of diabetes continued after 10 years of follow-up [13]. The FDPS and DPPOS may report results of their cognitive assessments in 2012; if the intervention arms of the FDPS and the DPPOS show decreased cognitive impairment compared with the control arm, it would provide solid support to the notion that the relationship of diabetes with cognitive impairment is causal. If no association is found, multiple explanations should be considered, including the timing of the intervention in relation to the measurement of cognitive impairment. In this scenario of negative findings in both studies, consideration should be given to the possibility that the association between diabetes and cognitive impairment is not causal.

A pilot 6-month trial of rosiglitazone, an insulin sensitizer used in diabetes treatment, in 30 subjects with mild Alzheimer's dementia or MCI showed that persons in the treatment arm experienced better outcomes [14]. A subsequent Phase II randomized placebo-controlled trial of rosiglitazone lasting 24 weeks in 511 persons with mild-to-moderate Alzheimer's dementia found no effect on their cognitive outcomes in the primary analysis [15]; however, there was a significant interaction between APOE-ε4 and cognition and persons on rosiglitazone without any APOE-ε4 allele showed an improvement in cognition. However, a Phase III trial of rosiglitazone (NCT00428090) in mild-to-moderate Alzheimer's dementia patients failed to show a significant benefit [16]. This result does not support the hypothesis that diabetes and Alzheimer's dementia are related. However, it is important to consider that in persons with established dementia it may be too late to see a response. In addition, rosiglitazone may have

adverse cardiovascular effects that could eclipse other beneficial effects. It is possible that the use of thiazolidinediones at earlier stages, such as in persons with MCI, could reduce the risk of dementia. The RECALL (NCT00242593) study is examining the effects of rosiglitazone on cognition in individuals with MCI. In addition, the POEM trial (NCT00736996) is exploring the effects of pioglitazone compared with exercise or placebo in persons with MCI.

Metformin is a medication belonging to the biguanide class of drugs that has been shown to be effective in the prevention of diabetes in the DPPOS. 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 individuals with MCI. The results of this trial will be reported in 2012. A study in cellular models demonstrated that metformin increases the production of amyloid-β through upregulation of β-secretase [17], thus raising the concern that metformin could increase the risk of Alzheimer's disease. However, the relevance of these findings to humans is not clear and the study needs to be replicated in other models.

The causal relationship of diabetes with cognitive impairment could also be demonstarted by examining the effect of diabetes control on cognitive impairment. Recently, the ACCORD-MIND trial (NCT00182910) reported that the tight glycemic control arm (aiming at HbA1c <6%) was not related to better cognitive outcomes, although the intensive control arm was related to a slower loss of brain volume [18]. However, data from the IDEATel study, a randomized trial of telemedicine versus usual care in 2169 elderly persons with diabetes, demonstrated that those in the intervention group had reduced global cognitive decline during a maximum of 6 years' follow-up [19]. The intervention group showed better diabetes control parameters compared with usual care. Importantly, the glycemic control goals of IDEATel followed glycemic guidelines (HbA1c <7%) that were less stringent than the goals in the ACCORD trial, which showed increased mortality in its tight glycemic control arm.

In summary, despite strong evidence from epidemiologic studies that Type 2 diabetes and dementia are related, a causal link has not been definitively established. However, the results of clinical trials for interventions for Type 2 diabetes and its prevention should be reported in the near future. These studies will provide important evidence alluding to whether there is a substantial link between diabetes and dementia.

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