

## DIABETES MELLITUS, DEMENTIA, AND COGNITIVE FUNCTION IN OLDER PERSONS

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**Abstract:** Dementia and cognitive decline are among the most common and most feared conditions of old age making the identification of modifiable risk factors for dementia an urgent public health priority. Recently, an increasing body of data suggests that type 2 diabetes mellitus, a common condition in older persons, is associated with the development of dementia and cognitive decline. A systematic review of the medical literature of the past 15 years identified 40 original-report articles in the English language pertaining to the relation of diabetes to dementia and cognitive function in older persons. Most, but not all, of these studies suggest a detrimental effect of diabetes on cognitive function. Current research efforts are aimed at understanding the underlying neurobiologic mechanisms whereby diabetes causes dementia and cognitive impairment in order to develop rational interventions to prevent this recently documented adverse consequence.

**Key words:** Diabetes, risk, dementia, Alzheimer's disease, cognitive function, longitudinal studies.

### Introduction

Life expectancy in developed countries has steadily increased during the last century with the oldest segments of the population growing the fastest (1). Currently, there are about 35 million persons over the age of 65 years in the US, and this number is expected to more than double by the year 2050, to about 87 million persons (1). In the absence of the identification of modifiable risk factors, this demographic change is expected to result in a corresponding increase in the frequency of common chronic diseases of aging. Dementia is a common problem in older persons (2) and is associated with mortality and significant morbidity (3-6). Several genetic and environmental risk factors for dementia and Alzheimer's disease, and cognitive decline, have been identified, including possession of at least one copy of the apolipoprotein E ε4 allele (7-9), infrequent participation in cognitively stimulating activities (10), proneness to psychological distress (11), number of depressive symptoms (12), the presence of stroke (12;13), elevated homocysteine levels (12;14), and the metabolic syndrome (15). Emerging data suggests that diabetes mellitus, also a common medical condition in older persons and associated with mortality and significant morbidity (16), may also be a risk factor for neurological conditions of aging (17), including dementia and cognitive decline. Perhaps the first evidence of a potential link between diabetes and cognitive impairment was reported more than 80 years ago when treatment with exogenous insulin was not yet available. In a case control study, persons with diabetes scored 15-20% lower on tests of memory and attention when compared to persons without diabetes (18). Although this study raised the possibility of an association between diabetes and progressive cognitive impairment, more than 70 years elapsed before the

first longitudinal studies were published providing more solid evidence in favor of a causal relation.

This review focuses predominantly on the relation between type 2 diabetes and cognitive function. Type 2 diabetes represents more than 90% of all cases of diabetes and an even higher percentage of cases of diabetes in older persons. The review is based on a PubMed search limited to the following search terms: 1) "diabetes" in the title and any of three terms in the title or abstract, "dementia", "cognitive function" or "cognition"; 2) a publication date between January 1, 1990 and December 31, 2004; and 3) publication in the English language. A total of 156 publications met these criteria of which 42 were review articles, letters or comments, or case-reports with less than 10 participants, 54 were not about dementia or cognitive function in older persons, and 20 were not about the chronic effects of diabetes on cognitive function. The remaining 40 publications were included in this review, supplemented by additional studies, including studies identified by review of the references cited in the publications.

### Cross-sectional studies

Considerable data on the relation of diabetes to dementia and cognition come from cross-sectional studies which examine the association of these variables at a single point in time.

#### *Diabetes and dementia*

Four cross-sectional studies reported an association between the presence of diabetes and the presence of dementia. Two studies, one conducted in a nursing home (19) and one clinic-based (20) reported an association between diabetes and vascular dementia, but not diabetes with Alzheimer's disease.

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Because many persons with dementia do not come to the attention of the health care system (21), nursing home patients and clinic patients are unlikely to be representative of persons with cognitive impairment in the community. Two large population-based studies confirmed the association between diabetes and the likelihood of dementia (22;23), one of which also looked at the cause of dementia and found the association with vascular dementia but not with Alzheimer's disease (23).

### *Diabetes and cognitive function.*

Ten cross-sectional studies examined the relation of diabetes to level of cognitive function with mixed results. Of five clinic or nursing home-based studies, four found that diabetes was related to lower level of cognitive function (24-27), and one with only 78 participants found no association (28). Of five community or population-based studies, three found that diabetes was associated with lower level of cognitive function (29-31), one found a weak association (32), and two found no association (33;34). Of the two negative community-based studies, one population-based study from France (33) analyzed data from more than 2,500 older persons. However, they relied on a single global measure of cognition, the Mini-Mental State Examination (35), which has well-known ceiling effects and may not have been sufficiently sensitive to detect an association between diabetes and cognition. The other negative study (34) used a more comprehensive battery of eight cognitive tests, but associations were tested separately with each test. Thus, it is possible that small effects of diabetes could have been missed in both studies.

### **Longitudinal studies**

In addition to the aforementioned psychometric issues, the inconsistent results of the cross-sectional studies could also reflect other important limitations of cross-sectional studies in general, and of cross-sectional studies of cognitive function in particular. Cross-sectional studies assess the putative risk factor and outcome at the same time. By contrast, longitudinal studies can more accurately document the temporal relation between a risk factor and an outcome allowing a more secure conclusion regarding the causal pathway. In addition, persons with more malignant disease are under-represented in cross-sectional studies which could bias the results. Finally, to the extent that education and related lifestyle factors can greatly influence the results of cognitive function tests administered at a given point in time, measuring change in cognitive function over time is likely to represent a less biased outcome because education-related effects are probably constant across assessment points. Thus, the results of cross-sectional studies of cognition in old age can be difficult to interpret, and more secure findings can often be obtained using repeated measures of cognition in a longitudinal study design. It should be noted that longitudinal studies are more costly, more time consuming, and often more difficult to conduct. In addition, they have their own sources of bias, especially loss of participants during follow-up to death,

which is unavoidable in studies of the elderly, or to refusal or other potentially avoidable reasons for loss of contact.

### *Diabetes and incident dementia*

Nine community-based longitudinal studies have examined the relation of diabetes to the risk of developing dementia (36-44). In general, these studies found that the presence of diabetes increased the risk of incident dementia by approximately two-to-threefold. Research results have been mixed, however, with regard to the relation of diabetes to specific causes of dementia which were examined in some but not all of these studies. Alzheimer's disease is the leading cause of dementia in the US and Europe. Diabetes was related to an increased risk of clinically diagnosed Alzheimer's disease in four prospective studies (37;40;43;44). The largest of these studies included more than 6,000 participants, 11% of whom had diabetes, who were followed for about two years, with a high follow-up rate of more than 80%: persons with diabetes had a two-fold increase in risk for Alzheimer's disease and no association with vascular dementia was found (40). However, four other studies did not observe an association between diabetes and Alzheimer's disease (36;38;39;42). Vascular disease is generally considered the second leading cause of dementia in the US and Europe. Of six studies which examined the relation of diabetes to risk of clinically diagnosed vascular dementia, five reported an increased risk (36;38;39;42;44), and one reported a null finding (40). Among the studies that found a relation between diabetes and vascular dementia, only one had data from more than two time points: this study followed more than 1, 200 participants annually for an average of four years and found that diabetes was associated with a threefold increase in risk for vascular dementia but no association with Alzheimer's disease was noted (38). Finally, of the six studies that examined the relation of diabetes to both Alzheimer's disease and vascular dementia, only one found a relation in both dementia subtypes (44).

These somewhat mixed results with the causes of dementia likely reflect the limitations of clinical criteria for identifying the cause of dementia syndromes, especially vascular dementia. In particular, clinical ascertainment of cerebral infarction is suboptimal as is the determination of the temporal relation of infarction to cognition in community-based studies. Further, in the absence of a diagnostic marker of Alzheimer's disease, comorbidities in persons with cerebral infarctions cannot be excluded making the clinical differentiation of Alzheimer's disease from vascular dementia and mixed vascular cognitive impairment plus Alzheimer's disease extremely difficult (45). Longitudinal clinical-radiologic and clinical-pathologic studies are needed to further elucidate the relation of diabetes to the brain pathology causing cognitive impairment.

### *Diabetes and subsequent cognitive impairment*

Three community-based studies reported the relation of diabetes to subsequent level of cognitive function (46-48). Although these studies have the advantage of assessing diabetes

prior to collection of data regarding cognitive function, they have the disadvantage of relying on a single assessment of cognitive function with the limitations described above. As a result, the strong effects of education and related factors on level of cognition could make it difficult to discern an association between diabetes and cognitive impairment. Two of the longitudinal studies showed a weak association between diabetes and subsequent lower cognitive performance. The largest of these studies was the Framingham Study, with data from more than 1,800 persons who had been followed for up to 30 years prior to cognitive function assessment (46). This study showed a weak association between diabetes and subsequent lower cognitive performance, with lower scores on one of eight cognitive tests. In a second study, diabetes was associated with a lower score in two of ten tests (48). The third study found no association between diabetes and level of cognition (47).

#### ***Diabetes and change in cognitive function***

Eight longitudinal community-based studies have examined the relation of diabetes to change in cognitive function over time, and seven of these found that diabetes was associated with more rapid decline in cognition (43;49-54). For example, one population-based sample of more than 900 persons (6% with diabetes) underwent baseline cognitive testing and repeat testing four years later (54). Persons with diabetes had more decline than those without diabetes on two measures of perceptual speed, one of verbal learning, and one of visuospatial ability, but not on the Mini-Mental State Examination or on four other tests. The only negative study (55) had only two years of observation which may be insufficient to reliably capture individual differences in rates of cognitive change given the insidious nature of cognitive decline in old age (56).

As cognition is not a unitary process but is composed of several dissociable cognitive systems, such as episodic memory and perceptual speed, risk factors may be related to decline in some cognitive abilities more than others (9). One study examined the relation of diabetes to change in five different cognitive systems (43). Because level of cognition and rate of cognitive decline vary widely in old age, composite cognitive measures based on multiple individual tests of varying difficulty can help reduce floor and ceiling artifacts and other sources of measurement error commonly encountered in studies of cognitive aging. The study found that over several years of follow-up, persons with diabetes had a 40% increased rate of decline in perceptual speed but not in other cognitive systems such as episodic memory or semantic memory when compared to persons without diabetes (43). This study suggests that diabetes may affect perceptual speed more than other cognitive domains. The relation of diabetes to decline in perceptual speed is of interest because cerebral infarction also has been shown to have a relatively selective association with perceptual speed in this cohort (57). This finding is consistent with the

results of four other longitudinal studies that found a relation of diabetes with tests of perceptual speed (49;50;53;54), with one study reporting a null result (51).

#### **Neurobiologic mechanism linking diabetes to cognitive decline**

With emerging data supporting a relation between diabetes and risk of dementia and loss of cognitive function, it will be important to understand the neurobiologic mechanisms underlying the association. Several studies have examined plausible biologic mechanisms, but many questions remain unanswered.

One possibility is that diabetes is related to cognitive impairment through a direct effect on Alzheimer's disease pathology. In vivo studies suggest that diabetes is associated with brain atrophy, and a recent neuroimaging study reported that diabetes, regardless of vascular disease, was associated with atrophy of the medial temporal lobe, a region prominently affected by Alzheimer's disease (58). We are aware of only two clinical-pathologic studies that directly examined the relation of diabetes to Alzheimer's disease pathology, both of which were based on plaques and tangles identified with silver stains (44;59). Neither study found an association, suggesting that Alzheimer's disease pathology may not account for the relation of diabetes to cognitive impairment. However, it is possible that more specific measures of Alzheimer's disease, such as antibodies to amyloid- $\beta$  or paired helical filaments, may be needed to identify a relation.

Another possibility is that the relation of diabetes to cognitive impairment is the result of an association with cerebrovascular disease. Indeed, one of the studies that failed to show a relation between diabetes and Alzheimer's disease pathology showed an association of diabetes with large (>1 cm) cerebral infarction (44). Diabetes is a well-documented risk factor for stroke (60;61), and stroke (13;62) and cerebral infarction (57;63-66) increase the likelihood that dementia, even dementia due to Alzheimer's disease, will be expressed clinically. The relation of diabetes to cerebral infarction needs further examination.

Several other potential mechanisms could account for the association of diabetes to cognitive impairment. Insulin has been reported to play a role in learning and memory (67), enhance memory function in persons with Alzheimer's disease (68), affect plasma levels of amyloid- $\beta$  (69), and regulate tau phosphorylation in neurons (70). In addition, a locus on chromosome 10 near the insulin-degrading enzyme gene has been linked to late-onset Alzheimer's disease (71). Finally, insulin receptors have been found to be upregulated in postmortem Alzheimer's disease cortex, possibly as a compensatory mechanism for impaired insulin receptor transduction (72). Other possible mechanisms linking diabetes to impaired cognitive function include increased levels of oxidative stress and advanced glycation end products (73),

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altered hippocampal synaptic plasticity (74) and inflammatory pathways (15). Further research will be needed to determine whether these or other mechanisms contribute to the observed association of diabetes with cognitive impairment in old age.

### Conclusions

Dementia is an important and growing public health problem. Identifying risk factors for dementia and cognitive decline, the principal manifestation of dementia, is critical. In particular, the identification of potentially modifiable risk factors for dementia may have a substantial public health impact. Emerging evidence supports that diabetes mellitus, a common and treatable condition in older persons, increases the risk of dementia, and may increase the risk of clinically diagnosed Alzheimer's disease. Further, persons with diabetes have a faster rate of cognitive decline than persons without it. Some data suggest that diabetes may affect specific cognitive systems, such as perceptual speed, more than others. Several plausible neurobiologic mechanisms underlying the relation of diabetes to cognitive impairment are being examined, including the involvement of cerebrovascular processes and other mechanisms. Future research, particularly large longitudinal clinical-radiologic and clinical-pathologic studies, may help to elucidate the biologic mechanisms linking diabetes to dementia. Together, these data raise the possibility that prevention, early diagnosis, and optimal treatment of diabetes may offer a practical means of decreasing risk of dementia and cognitive decline in older persons.

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