

# Cognitive Decline in Diabetes: Systematic Overview, Meta-analysis

Diabetes increases the risk for vascular dementia 1.3 fold and Alzheimer's, dementia 4.4 fold.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

**P**eople with diabetes have a greater rate of decline in cognitive function, a greater risk of cognitive decline and a greater risk for the development of dementia compared to people without diabetes.

In the United States, the prevalence of dementia is increasing, according to Tali Cukierman, MD, from McMaster University in Hamilton, Ontario. "According to a 2000 survey, 4.5 million Americans had the most common form of dementia, Alzheimer's disease. This figure is expected to grow to 13.2 million by 2050," said Dr. Cukierman, speaking in San Diego at the American Diabetes Association 65th Annual Meeting and Scientific Sessions.

"People who do not have dementia but suffer cognitive impairment have higher rates of progression to dementia than do cognitively intact individuals. Annually, only 1% of cognitively intact people go on to suffer dementia compared to 12% of those with impairment."

## DIABETES AND COGNITIVE IMPAIRMENT

Diabetes is associated with prevalent cognitive impairment. Large, prospective studies suggest that diabetes is also a risk factor for worsening of cognitive function, Dr. Cukierman said. For example, in the 2,123-patient Framingham Study, patients with diabetes were more likely to achieve scores below the 25th percentile on most tests compared with nondiabetic individuals.

The Adult Health Study followed a cohort of atomic bomb survivors from Hiroshima and Nagasaki. After 34 to 39 years of follow-up, 1,774 participants were screened for dementia, she said. "Compared to nondiabetic individuals, diabetes increased the risk for vascular dementia

The prevalence of dementia – the most common form being Alzheimer's disease – is increasing in the United States.

1.3 fold and 4.4 fold for Alzheimer's dementia."

The significance and size of the impact of diabetes as a risk factor for progressive cognitive impairment is unclear, according to Dr. Cukierman.

## CLINICAL STUDY

"We set out to summarize the available prospective studies measuring cognitive function of people with diabetes over time and to develop an estimate of the magnitude of the risk of incident cognitive impairment in people with diabetes," she said.

Dr. Cukierman's team searched databases with key words and free text, and manually searched the references of relevant articles and reviews. They also consulted with experts in the field to make sure they had not missed any relevant articles.

The studies included reported the use of a structured test or a clinical assessment, listed diabetes status, performed cognitive assessment at the beginning and at the end of follow-up and reported the relationship of diabetes status to cognitive function. The investigators excluded studies that had a loss to follow-up >30%, that restricted their study to a subset of people, that had a follow-up period <1 year and that were not in English.

"We abstracted relevant data and pooled estimates that were obtained using a fixed-effect model," Dr. Cukierman said. "Heterogeneity was assessed using the

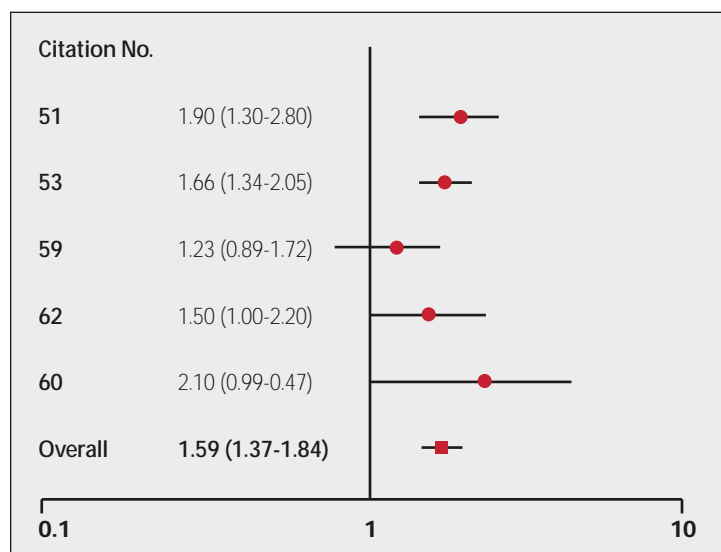


Figure 1. Risk for the development of dementia associated with diabetes status.

Q statistic. Of the 1,165 abstracts and titles that were retrieved, 25 met our criteria. These included information for 8,656 diabetic patients that were followed for 2 to 8 years."

The patients in the meta-analysis ranged in age from 45 to 99 years. There was a great diversity in the types of instruments used to measure cognitive function, with the two most commonly used ones being the Mini Mental State Examination (MMSE) and the Digit Symbol Substitution (DSS).

### MMSE AND DSS

The MMSE is comprised of 30 items with a maximum score of 30. It addresses six different cognitive domains. A score <26 indicates some level of cognitive impairment, a score below <24 suggests further investigation for dementia (Table 1).

The DSS is a paper and pencil exercise in which the participant reviews a key and then he or she is required to copy the matching symbols into the squares. Scoring is according to the number of correct items the participant achieves in 2 minutes.

### RESULTS

"Five studies that we looked at had a follow-up ranging from 2 to 6 years and reported the effect of diabetes status on change in MMSE score over time," Dr. Cukierman said. "Three studies, with a follow up of 4 to 6 years, reported the same for the DSS. In most cases, the overall score of people declined over time."

Consistently, people with diabetes had a greater cog-

nitive decline than people without diabetes. In two studies where an improvement in score was noted, people with diabetes improved less than did people without diabetes, Dr. Cukierman and colleagues found.

Some studies included in the analysis followed people without dementia at baseline. Scores were categorized according to those who had experienced cognitive decline and those who did not. The results are presented as the odds of experiencing cognitive decline over time in people with diabetes versus those without diabetes, she said.

"Looking at the result for the MMSE, most studies reported increased odds for cognitive decline associated with diabetes status and the test for heterogeneity was negative."

Overall, people with diabetes were 1.2 fold more likely to experience cognitive decline than were people without diabetes, and this result was statistically significant.

The results for the DSS studies were similar. People with diabetes were 1.7 fold more likely to experience cognitive decline than were people without diabetes, and this result was also statistically significant, Dr. Cukierman reported. In addition to categorization according to score, some of the studies included a clinical diagnosis of dementia as their outcome.

Some studies followed a group of people without dementia at baseline and were evaluated at follow-up for clinically diagnosed dementia. "In all cases, diabetes status increased the risk for the development of future dementia. People with diabetes were 1.6 fold more likely to develop dementia over time, a statistically significant finding," Dr. Cukierman said (Figure 1).

Four of the studies Dr. Cukierman's team looked at included information about the distribution of dementia cases between the two main causes of dementia, Alzheimer's and vascular. Diabetes status increased the risk for both, but more so for vascular dementia, they found.

### CONCLUSIONS

In studies that are adjusted for a variety of confounders, diabetes status was associated with an increased risk of cognitive decline and dementia. This association was seen in studies of different populations and follow-up durations and was noted using different instruments and analysis techniques (Figure 1).

"Our study did have a limitation, in that cognitive decline was defined and assessed in different ways, a fact that made pooling difficult," Dr. Cukierman said.

TABLE 1. THE MINI MENTAL STATE EXAMINATION

## Areas Tested by the Mini Mental State Examination MMSE

*Orientation:*

• 10 points can be scored for answering questions about date and location. Examples:

“What is the day of the week?”

“What year was last year?”

“What building are we in?”

*Memory:*

• This tests recall. Immediate memory scores 3 points (one point for each of 3 objects). People are asked to remember three words (eg, pen, ball, ring). The three object names will be asked for later in the test.

*Attention and Calculation:*

• One test, scoring a maximum of 5 points, requires the person to subtract 7 from 100 and continue. The answers are 93,86,79,72, 65. Some clinicians ask for 5 to be serially subtracted from 100.

• The person may also be asked to spell a 5-letter word backwards. The best of the two scores is included in the final score.

*Language, Writing and Drawing:*

• The final 9 points tests spoken and written language, the ability to write, copy and remember named objects.

• This includes naming objects (eg, a brush and a pen). This scores 1 point for each correct answer.

• Carry out a 3-step process- 3 points.

• Repeat a sentence- 1 point.

• Copy a figure or shape- 1 point.

• Write a sentence on a piece of paper- 1 point.

The scores are then added up to give a result.

“However, this highlights the robustness of the results. Across instruments and definitions, diabetes status consistently and in a similar manner increased the odds of cognitive decline.”

**WHY THE INCREASED RISK?**

Diabetes is a known risk factor for cardiovascular and cerebrovascular diseases. Depression is known to be associated with diabetes, and depression is hard to differentiate from dementia and cognitive impairment, she said.

“Chronic recurrent episodes of hypoglycemia may contribute to the cause of cognitive decline,” Dr. Cukierman said. “However, we know from the Diabetes Control and Complications Trial, that at least in type 1 diabetes, participants with tighter glucose control experience more episodes of hypoglycemia yet do not experience more cognitive impairment.”

Chronic hyperglycemia may be another explanation for dementia, as it may have direct toxic effects on the brain. The relative or absolute lack of insulin may

also be a possible explanation. There is evidence that insulin and insulin receptors have a role in the cognitive function of the brain, she added.

Diabetes is a risk factor for progression of cognitive impairment and future dementia. These should be considered chronic consequences of diabetes. Future trials involving people with diabetes should evaluate cognitive function and should assess the effect of different therapies on change in cognitive status.

“This overview was restricted to diabetes, however at least two of the studies in this review did show that impaired glucose tolerance and impaired fasting tolerance were risk factors for decline in cognitive function,” Dr. Cukierman concluded. “More studies looking at these factors are warranted.” ■

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