

July 17, 2006

## Link Between Diabetes and Alzheimer's Deepens

By **DENISE GRADY**

Several new studies suggest that [diabetes](#) increases the risk of Alzheimer's disease, adding to a store of evidence that links the disorders. The studies involve only Type 2 diabetes, the most common kind, which is usually related to [obesity](#).

The connection raises an ominous prospect: that increases in diabetes, a major concern in the United States and worldwide, may worsen the rising toll from Alzheimer's. The findings also add dementia to the cloud of threats that already hang over people with diabetes, including [heart disease](#), strokes, kidney failure, blindness and amputations.

But some of the studies also hint that measures to prevent or control diabetes may lower the dementia risk, and that certain diabetes drugs should be tested to find whether they can help Alzheimer's patients, even those without diabetes. Current treatments for Alzheimer's can provide only a modest improvement in symptoms and cannot stop the progression of the disease.

The new findings were presented yesterday by the Alzheimer's Association at a six-day conference in Madrid attended by 5,000 researchers from around the world.

Alzheimer's affects 1 in 10 people over age 65, and nearly half of people over 85. About 4.5 million Americans have it, and taking care of them costs \$100 billion a year, according to the association. The number of patients is expected to grow, possibly reaching 11.3 million to 16 million by 2050, the association said.

But those projections do not include a possible increase from diabetes.

"Alzheimer's is going to swamp the health care system," said Dr. John C. Morris, a neurology professor at [Washington University](#) in St. Louis and an adviser to the Alzheimer's Association.

Not everyone with diabetes gets Alzheimer's, and not all Alzheimer's patients are diabetic. But in the past decade, several large studies have found that compared with healthy people of the same age and sex, those with Type 2 diabetes are twice as likely to develop Alzheimer's. The reason is not known, but researchers initially suspected that cardiovascular problems caused by diabetes might contribute to dementia by blocking blood flow to the brain or causing strokes.



More recently, though, scientists have begun to think that the diseases are connected in other ways as well. In both, destructive deposits of amyloid, a type of protein, build up: in the brain in Alzheimer's, in the pancreas in Type 2 diabetes.

People with Type 2 often have a condition called insulin resistance, in which their cells cannot properly use insulin, the hormone needed to help glucose leave the blood and enter cells that need it. To compensate, the pancreas makes extra insulin, which can reach high levels in the blood. Too much insulin may lead to inflammation, which can contribute to damage in the brain.

In addition, abnormalities in glucose metabolism and insulin levels in the brain itself may be harmful. Some research has found that too much insulin in the brain can contribute to amyloid buildup. Researchers have even suggested that Alzheimer's disease may actually be "Type 3 diabetes," a form of the disease affecting the nervous system.

About 20 million people in the United States have Type 2 diabetes. The number has doubled in the past two decades. An additional 41 million are "prediabetic," with blood sugar rising toward the diabetic level. Diabetes rates are expected to increase because rates of obesity are rising, and epidemiologists predict that one in three American children born in 2000 will eventually develop Type 2 diabetes.

Worldwide, diabetes is also on the rise, increasing to 230 million cases from 30 million in the past 20 years.

One of the new studies found that even people who had borderline diabetes were 70 percent more likely than those with normal blood sugar to develop Alzheimer's. The study, by researchers from the Karolinska Institute in Sweden and the Stockholm Gerontology Research Center, included 1,173 people 75 and older.

The incidence of dementia was highest in borderline diabetics who also had high [blood pressure](#). But the higher risk occurred only in those who did not carry the gene apo E4, which is associated with some cases of Alzheimer's.

The director of the study, Dr. Weili Xu, said that since increased exercise and changes in [diet](#) can reverse borderline diabetes, they may also help ward off dementia.

Another study found that in people with diabetes, the higher their blood sugar, the greater the risk of dementia. Higher levels of blood sugar mean the diabetes is severe or is being poorly treated, or both.

The study, led by Rachel A. Whitmer of the Division of Research at Kaiser Permanente

in Oakland, Calif., was based on the records of 22,852 patients with Type 2 diabetes who were followed for eight years.

Initially, none had dementia. The researchers looked at glycosylated hemoglobin, a blood test that reflects blood sugar levels for the previous two months. Normal is 7 or lower. Here, the risk of dementia rose when the level reached 10. Those with readings from 10 to 11.9 had 13 percent more risk than people with levels below 10. From 12 to 14.9, the risk was 24 percent higher. Over 15, it jumped to 83 percent higher.



In an interview, Dr. Whitmer said one implication of the study was that tight control of blood sugar was important in elderly patients, even though some doctors tended to relax the rules for them.

“Tight control is important for the whole life span,” Dr. Whitmer said. “The older you are, the more likely you are to get dementia.”

She added: “With the whole diabetes [epidemic](#) we’re seeing much more Type 2, so are we going to see even more Alzheimer’s than we thought we would see? If we continue in this direction, it’s a little bit frightening.”

Another study suggested that a certain class of diabetes drug, commonly called a glitazone, might lower the risk of Alzheimer’s in people with diabetes. Pilot studies in small groups of patients have hinted that the drugs may be of some help, and the National Institute on Aging is sponsoring research in this area.

In the study, researchers used the records of 142,328 patients in the Veterans Affairs system who did not have dementia but were just starting to take a glitazone or insulin. They tracked the patients for six years. Compared with those using insulin, among the patients who took pioglitazone (Actos) or rosiglitazone (Avandia), there were nearly 20 percent fewer cases of Alzheimer’s. The glitazones had a similar advantage over another diabetes drug, metformin.

Glitazones lower blood sugar by helping the body to use insulin more efficiently, so that less insulin is needed. The drugs may also lower inflammation.

Though the results sound like good news for patients, the director of the study, Donald R. Miller, an epidemiologist at [Boston University](#) and at the [Department of Veterans Affairs](#), cautioned that the findings were not conclusive and that they did not mean that people should start taking the drugs to ward off Alzheimer’s.

“This is preliminary, the first study of its kind,” Dr. Miller said, emphasizing that more

studies were needed to verify his results.

GlaxoSmithKline, the maker of rosiglitazone, sponsored the study but did not control the way it was done or interpreted, Dr. Miller said.

Another study, a small one with only 25 patients, tested pioglitazone for 18 months in nondiabetic people with Alzheimer's to see if it was safe and showed signs of slowing the disease.

The drug did seem safe, causing only some foot and ankle swelling. But compared with people taking placebos, patients taking the drug showed no statistically significant differences in memory, thinking, daily function or abnormal behavior.

But there were hints that some measures worsened less in the patients on the drug, and the researchers, led by Dr. David S. Geldmacher of the [University of Virginia](#), said it deserved further study in Alzheimer's. The study was sponsored by the drug's maker, Takeda.

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