Diabetes and dementia: evidence for a connection
Several population studies following large groups of people over several years suggest that individuals with Type 2 diabetes have an increased risk of later developing dementia. These studies have found both an increased risk of Alzheimer’s disease, the most common form of dementia, and vascular dementia, the second most common type.

Population studies can provide preliminary evidence for a connection like the one observed between Type 2 diabetes and dementia, but they cannot prove that it exists. However, the fact that a number of studies point to the link lends considerable weight to the evidence.

There are two chief strategies for confirming the existence of a diabetes and dementia relationship suggested by population studies: (1) discover the biological mechanisms linking the two conditions and (2) test whether treatment approaches based on the relationship are effective. Scientists studying the diabetes/dementia connection are moving forward on both fronts.

Potential mechanisms linking diabetes and dementia: Insulin resistance and high blood sugar
Most individuals who develop Type 2 diabetes first experience insulin resistance, a condition in which cells develop a reduced ability to respond to insulin, a hormone produced in the pancreas. One of insulin’s most important functions is to help cells take in glucose (blood sugar) and convert it to energy. As a result, resistance to insulin threatens cells’ vital energy supply.

The body’s first reaction to this threat is to produce more insulin. For a period of years, the pancreas may be able to produce enough additional insulin to keep adequate sugar moving into cells. In this situation, insulin levels rise abnormally high, but blood glucose levels remain within or slightly above the normal range.

Insulin resistance is the underlying feature of “metabolic syndrome,” a condition that increases risk of heart disease, stroke and Type 2 diabetes. Metabolic syndrome is identified by the presence of three or more of these signs:
- Significant deposits of abdominal fat, resulting in a waist measurement of 35 inches or more for women and 40 inches or more for men
- HDL (“good cholesterol”) levels below 50mg/dL for women or 40mg/dL for men
- Levels of triglycerides, another blood fat, above 150 mg/dL
- Blood pressure at or above 130/85
- Fasting blood glucose levels above 100 or 110 mg/dL

If the pancreas reaches the limit of its ability to produce more insulin, blood sugar climbs. When fasting blood sugar consistently exceeds 126 mg/dL, a person has progressed from insulin resistance to Type 2 diabetes.

The following are some of the lines of evidence linking insulin resistance and high blood sugar to an increased risk of dementia:
- Studies have linked high fasting insulin levels to an increased risk of Alzheimer’s disease. In one study, insulin levels greater than 89.4 pmol/L were associated with as great an increase as having APOE-e4, a gene that significantly raises Alzheimer risk.
- In the brain, insulin resistance may lead to overactivity of the enzyme glycogen synthase kinase 3 (GSK3). GSK3 performs the first chemical step that leads tau protein down the path to twisting into “tangles,” a hallmark Alzheimer abnormality.
- Insulin is released in large quantities after a meal, and then rapidly broken down. The chief enzyme responsible for its breakdown is insulin degrading enzyme (IDE), which also breaks down beta-amyloid. Beta-amyloid is a protein fragment regarded as another prime Alzheimer suspect because it builds up into the plaques considered the other hallmark of the disease.
IDE has a chemical “preference” for insulin, so high levels of the hormone can divert IDE from amyloid breakdown, possibly creating an environment favorable to beta-amyloid buildup.

- High blood sugar levels trigger production of abnormal molecules that cause cellular damage from both inflammation and highly reactive forms of oxygen. Many experts consider both of these types of damage additional Alzheimer hallmarks.
- Insulin resistance, metabolic syndrome and Type 2 diabetes have been well established as risk factors for heart disease and stroke. Even if these conditions turn out not to directly affect specific Alzheimer-related processes, they may increase dementia risk through their effect on the heart and blood vessels, including those in the brain.

**Treatment strategies based on the diabetes and dementia connection**

Scientists are exploring several treatment strategies based on emerging understanding of the dementia/diabetes connection. Prevention strategies involving lifestyle changes are one of the most exciting areas of research. Scientists know that genetics (heredity) plays a role in many cases of insulin resistance and diabetes, because these conditions tend to run in families and to affect certain ethnic groups more than others. High-risk groups include African-Americans, Latinos, Native Americans, Asian Americans and Pacific Islanders.

But even when heredity is a strong predisposing factor, lifestyle changes can help reduce risk. For example, the Diabetes Prevention Program, a nationwide, federally funded clinical trial enrolling 3,234 participants (including 45 percent from high-risk ethnic groups) found that overweight individuals with higher-than-normal blood sugar could reduce their future risk of diabetes by 58 percent (71 percent for those participants over age 60!) through:

- Losing 5 – 7 percent of body weight (10 – 15 pounds in someone who weighs 200 pounds)
- Walking or other moderate exercise for 30 minutes five days each week
- Eating a healthy, low-fat diet

No study so far has demonstrated that treating insulin resistance or diabetes can prevent or slow Alzheimer’s or other dementias. But prevention and treatment of obesity, insulin resistance and Type 2 diabetes are worthwhile goals in their own right because these conditions are strongly linked to heart disease, stroke, nerve damage, kidney failure, limb amputation and other health consequences.

Scientists are also testing whether drugs used to treat Type 2 diabetes may be helpful in treating or preventing Alzheimer’s disease in people who do not have diabetes. Two related drugs under investigation are rosiglitazone and pioglitazone, which help lower blood sugar by making the body’s cells respond better to insulin. Both drugs have been tested in small Phase II trials in people with mild- to moderate Alzheimer’s. In the pioglitazone trial, participants were also taking cholinesterase inhibitors or memantine.

The most serious side effects seen in the studies included fluid retention and heart failure.

Although neither drug showed a dramatic benefit, scientists saw enough positive signs in each trial’s results to feel that both drugs deserve to be tested in larger studies. In the rosiglitazone study, data suggested individuals without the APOE-e4 Alzheimer risk gene might be more likely to benefit than those who have it. A large Phase III study of rosiglitazone was recently launched in the U.S. and Canada. No responsible health authority recommends using diabetes drugs to treat or prevent Alzheimer’s until more is known about their risks and benefits for this purpose.

**For more information**

The Alzheimer’s Association, the world leader in Alzheimer research, care and support, is dedicated to finding prevention methods, treatments and an eventual cure for Alzheimer’s. For information about clinical studies seeking volunteers in your area or answers to other questions, please contact us anytime, day or night.

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