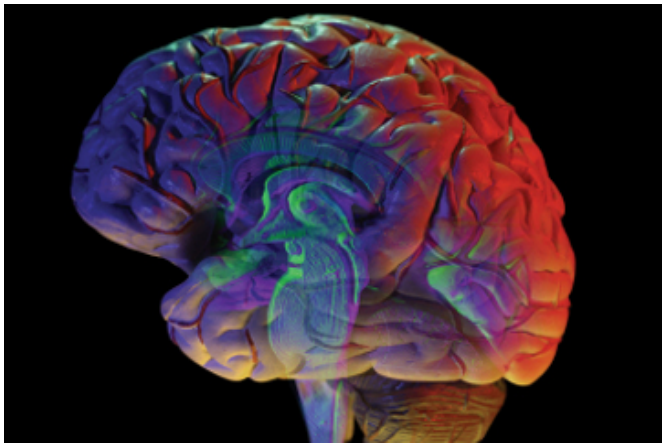
# Diabetes and depression: The impact of this widespread disease on the brain is often overlooked

10 September 2013



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(Medical Xpress)—The complications of uncontrolled diabetes are well recognized: nerve damage, kidney disease, blindness, and circulation problems that affect the extremities. The disease's impact on the brain, however, is often overlooked. This oversight could spell trouble for millions of Americans who face the daily challenge of controlling their blood sugar.

An estimated 26 million Americans have diabetes, according to the American Diabetes Association. Another 79 million have prediabetes, a condition in which blood sugar levels are higher than normal but not high enough for a diabetes diagnosis.

A growing body of evidence suggests that the cognitive health of millions with the disease is as much at risk as are other body systems from the effects of out-of-control blood sugar.

"Unlike for certain other diseases, scientists originally didn't know where to look in the brain for the effects of diabetes," said Gail Musen, an HMS assistant professor of psychiatry and assistant investigator in the Section on Clinical, Behavioral, and Outcomes Research at Joslin Diabetes Center.

"We knew, theoretically, that because it affects so much else in the body, it also could affect the brain," she said.

Since Musen's first study of diabetes and brain function nearly a decade ago, the scientific community has gained a greater understanding of how diabetes—primarily type 1 diabetes—affects brain function.

**Shrinking brain**

Musen's 2006 study, reported in the journal *Diabetes*, was the first comprehensive study of density changes in the brain's gray matter as a result of type 1 diabetes.

Its findings suggested that persistent hyperglycemia, or high blood sugar, and acute severe hypoglycemia, or low blood sugar, have an effect on brain structure. The gray matter reductions were small and did not necessarily show any clinically significant cognitive impairment, but the brain regions involved included the memory, attention and language processing centers.

More recently, Musen and her colleagues discovered reduced white matter integrity and cortical thickness in patients with long-standing type 1 diabetes.

"It's not clear," she said, "whether such changes to the brain will have a more profound effect as a patient ages."

Currently, Musen is using functional MRI, which

measures the brain in action, to determine whether regions of the brain with gray matter density loss show impaired function.

Even though people with diabetes may show normal performance in terms of accuracy or processing speed on cognitive tasks, their brain activity may differ from that of patients without diabetes. Such changes, she said, may precede clinically relevant cognitive issues, such as memory loss an mild cognitive impairment, a precursor to Alzheimer's disease.

Another study, led by neurophysiologist Vera Novak, an HMS associate professor of medicine and a neurophysiologist at Beth Israel Deaconess Medical Center, identified a key mechanism that can lead to memory loss, depression, and other types of cognitive impairment in older adults with type 2 diabetes.

In a study published in 2011 in *Diabetes Care*, Novak reported that two molecules, sVCAM and sICAM, cause inflammation in the brain. Novak found that gray matter in the brain's frontal and temporal regions—areas responsible for such critical cognitive functions as decision making, verbal memory and complex task performance—were most affected.

The long-term stress and strain of diabetes management can lead to a decreased quality of life and an increased likelihood of depression. Working with colleagues at Joslin Diabetes Center, Nicolas Bolo, an HMS lecturer on psychiatry and the director of neuroimaging in psychiatry at Beth Israel Deaconess, is studying whether impaired glucose metabolism can explain the increased prevalence of depression in people with type 1 diabetes.

"It appears that chronic hyperglycemia and insulin resistance—the hallmarks of diabetes— trigger the release of these adhesion molecules and set off a cascade of events leading to the development of chronic inflammation," says Novak. "Once chronic inflammation sets in, blood vessels constrict, blood flow is reduced, and brain tissue is damaged."

Some scientists have begun calling Alzheimer's disease "type 3 diabetes" because of its characteristic complications of profound memory loss and severe cognitive decline.

Musen is cautious about this label.

"It's a good hypothesis and has generated a lot of science," she said, "but we need better studies" before drawing firm conclusions.

**A chicken-or-egg question**

For some time, clinicians have known that diabetes and depression often go hand in hand, but now the mechanism behind this relationship is becoming more evident. A 2010 Harvard School of Public Health study in the Archives of Internal Medicine found a biological link between the two: depression increases the risk for diabetes and diabetes increases the risk for depression.

"We've thought for a long time that the burden of type 1 diabetes is enough to increase depression," said Bolo. The long-term stress and strain of diabetes management— multiple finger sticks to check blood sugar levels, daily injections of insulin, and the worry of complications—can lead to a decreased quality of life and an increased likelihood of depression.

Working with colleagues at Joslin Diabetes Center, Bolo is studying whether impaired glucose metabolism can explain the increased prevalence of depression in people with type 1 diabetes. The team is using high-tech magnetic resonance spectroscopy to noninvasively measure metabolites in the brain.

One of these metabolites is glutamate, the principal excitatory neurotransmitter. Early results showed that brain glucose levels, as expected, are higher in people with type 1 diabetes. Glutamate is higher as well in the brains of these patients, especially in emotion centers such as the anterior cingulate cortex.

"High glucose levels in the brain increase glutamate in regions involved in emotional control, which means increased depression among people with type 1 diabetes," said Bolo.

Bolo's research may lead to specific treatments that target the glutamate pathway in the brain and, thus, offer relief for diabetes patients suffering depression. Studies show that one such drug, ketamine, holds promise as an antidepressant that would act by blocking the action of a key protein involved in glutamate signaling in the brain. Researchers say this drug could be potentially life-saving for people with depression; unlike antidepressants such as Prozac and mood stabilizers, ketamine becomes effective in hours instead of weeks.

Although the findings of Musen, Novak and Bolo shed light on how diabetes can affect the brain, the standard advice for warding off complications, including cognitive decline, remains the same: control your blood sugar, maintain a healthful diet, and take care of yourself.

"We know that following this advice can improve peripheral systems, like vision," said Musen, "but it can help cognition as well."

Provided by Harvard Medical School