Diabetes and the brain

Does diabetes accelerate dementia? U investigators are leading the search for the answer to this important question

People who have diabetes are living longer, healthier lives today thanks to improved understanding and management of the disease. That’s good news. But along with this increase in longevity has come another reality: the list of potential complications associated with long-term diabetes—including eye, kidney, cardiovascular, and nerve problems—now also includes dementia and other brain disorders typically associated with advanced age.

Does diabetes accelerate the progression of dementia?

University of Minnesota professor of medicine and endocrinologist Elizabeth Seaquist, M.D., is at the forefront of the effort to answer this important question. As a practicing physician and clinical scientist, she has devoted her decades-long career to improving the lives of people who have diabetes and is deeply motivated by her patients’ health concerns.

“All of us will change as we age,” says Seaquist, who’s investigating the effect of diabetes on brain metabolism, structure, and function. “We’re interested in seeing if the rate of change is greater in people with diabetes.”

With diabetes reaching epidemic proportions globally and people with diabetes living longer, it is a looming public health issue.

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A team effort

Seaquist’s team includes fellow endocrinologist Amir Moheet, M.D., and researchers at the University of Minnesota Center for Magnetic Resonance Research (CMRR), primarily imaging experts Gülin Öz, Ph.D., and Silvia Mangia, Ph.D., and Kamil Ugurbil, Ph.D., the center’s director.

Their collaboration and the imaging resources available at CMRR (see below) are among the factors that distinguish Seaquist’s diabetes research from the work of others in the field.

“Our spectroscopic methods and imaging capabilities are much better than anybody else’s. There are very few groups who can do the kind of manipulation of blood glucose levels in an experimental situation in the magnet that we do,” Seaquist says. “It’s very challenging. But it’s because we have the talents of such a multidisciplinary team that we’re able to do what we do.”

Life-threatening problem

Brain disorders associated with type 2 diabetes are thought to involve many factors, including high blood pressure, obesity, insulin resistance, and hyperglycemia (abnormally high levels of glucose in the blood). In type 1 diabetes, Seaquist says, the metabolic effect of diabetes on the brain is probably more narrowly related to either hyperglycemia or hypoglycemia (abnormally low blood glucose levels).

In light of this difference, Seaquist and her team have focused their current investigation on type 1 diabetes and the metabolic changes experienced by people who suffer recurrent hypoglycemia. This potentially life-threatening problem is difficult to avoid for people with type 1 diabetes, who are dependent on insulin therapy and must continually keep their blood sugars from rising too high or falling too low.

They’re caught between a rock and a hard place, Seaquist says. They are trying to reduce the risk of eye, kidney, and nerve problems by keeping their blood sugars from going too high. But when blood sugars frequently fall too low, the brain adapts and people fail to know they have hypoglycemia. “So they don’t get the warning symptoms like shakiness that you or I would experience, and they become unconscious,” she explains.

How exactly does the brain become unaware? That’s what Seaquist wants to know.

“If we can understand why people become unaware of hypoglycemia, how brain metabolism changes in people who are exposed to recurrent hypoglycemia and the regions of the brain that are involved, then we can develop therapies so that people can avoid it,” she says. “That’s the hope.”

This knowledge, in turn, should help investigators understand the risk of brain disorders faced by all people who have diabetes—type 1 and 2.

“We must not wait to see whether dementia is the expected outcome in people growing old with diabetes,” Seaquist says. “Diabetes is a huge disease, and these incremental steps we are taking are critically important.”

Extraordinary by any measure

The University of Minnesota’s Center for Magnetic Resonance Research (CMRR), where Elizabeth Seaquist, M.D., studies brain metabolism in people who have diabetes, is home to the world’s largest human scanning device. The 10.5 Tesla, whole-body human magnetic resonance imaging (MRI) magnet is nearly 10 times stronger than most medical MRI scanners.

Seaquist collaborator and CMRR director Kamil Ugurbil, Ph.D. (left), says the giant magnet should enable investigators to reach and exploit the kind of detailed information previously unattainable with even the most advanced scanners. This includes helping Seaquist and her team to understand—the impact of long-term diabetes on the brain.
Great minds think collaboratively

Together, U researchers are testing a simple means to combat vision loss related to diabetes

Neuroscientist Eric Newman, Ph.D., is on a mission. With colleagues in endocrinology and ophthalmology, he is testing a simple chemical that could help reverse vision loss related to diabetes.

Eye disease is a well-known complication of diabetes. High blood glucose and high blood pressure cause the blood vessels in the eye to swell and leak liquid into the retina. This leads to blurred vision and, over time, can cause blindness. This sequence of events, known as retinopathy, is typically thought of as a disease of the microvasculature. But the central nervous system (CNS) also plays a role, says Newman, who has studied the retina for more than 35 years.

The retina is part of the CNS and when it is stimulated by light, neurons in the retina tell the blood vessels to get bigger. This makes way for an increase in blood flow that brings extra oxygen and fuel—in the form of glucose—to the neurons so they can function properly.

“If you stimulate the eye with a flickering light, you can see that the blood vessels get bigger,” Newman says. “But if you do this in a diabetic patient, the vessels do not dilate nearly as much.” Eventually, the eye becomes starved for oxygen, or hypoxic.

This loss of the vascular response happens well before any physical signs of retinopathy occur. “So we think hypoxia could be a triggering factor for retinopathy,” Newman says.

Together with Elizabeth Seaquist, M.D., and Erik van Kuijk, M.D., Ph.D., Newman is testing an over-the-counter chemical that may reverse this loss of vessel dilation in human patients. It’s already been tested and proved effective in diabetic rats, reversing the loss of the blood vessel response in as little as 15 minutes.

Newman and his colleagues hope that eventually a similar type of drug could be used to slow the progression of diabetic retinopathy in people.

Newman received a $100,000 award for the project from Research to Prevent Blindness, a philanthropic organization that supports high-potential investigators. The grant was enough to conduct the experiments, but not enough to buy the special fundus camera needed to make the measurements. The camera, which looks at the retina, presents flickering light and automatically measures blood vessel diameter.

Fortunately, van Kuijk, chair of the Department of Ophthalmology and Visual Neurosciences, was able to obtain funding for the camera, approximately $160,000, from the Minnesota Lions, steadfast supporters of eye research and care at the University for more than 50 years.

Newman, who typically conducts laboratory research, says he is enjoying his first chance to work directly with patients and is excited about his collaboration with physicians Seaquist and van Kuijk.

“The University of Minnesota is a fantastic place to be to do this kind of collaborative work,” he says.

You’re invited to a breakfast briefing with our faculty

Please join us to learn more about diabetes research at the U of M from Elizabeth Seaquist, M.D., on October 14, and David Bernlohr, Ph.D., on November 12. Both events will be from 8 to 9 a.m. at the McNamara Alumni Center on the University’s East Bank Campus.

Register for one or both events at www.rsvp.umn.edu/DiabetesBreakfast or by contacting Kerry Lengeling at kerryl@umn.edu or 612-624-6128.
Finding a cure for diabetes is a longtime passion for immunologist Brian Fife, Ph.D. It’s also deeply personal. He has a cousin with diabetes and for more than 40 years Fife has observed the impact of this devastating autoimmune disease on her life firsthand. “Statistics would say that my chances of developing diabetes were equal to my cousin’s,” Fife says soberly. “But I was lucky. I only got allergies.”

Although unassuming in manner, Fife is already making a name for himself in the world of science. Earlier this year, he was honored with the Medical School 2014 Young Investigator Award, the latest in a series of honors and awards he has earned. The award is made possible by the Carole J. Bland Fund for Faculty Development and is given to a young faculty member who has already proven to be “an outstanding researcher with great potential” in an area of biomedical, behavioral, clinical, or medical research.

Fife joined the U of M faculty in 2008. His interest in autoimmune diseases took hold during graduate school at Northwestern University, where he studied multiple sclerosis. He started his diabetes research as a postdoctoral fellow at the University of California, San Francisco.

“I’ve always been fascinated by how the body understands what is self and what is foreign,” Fife says. “In type 1 diabetes, the body mistakenly sees its own insulin-producing beta cells as foreign and attacks them. My goal is to identify the rogue, diabetes-causing T cells and turn them off or eliminate them while allowing the rest of the immune system to function normally.”

He admits this is no easy task.

“It’s like finding a needle in a haystack. The immune system is a huge, very complex system with trillions of cells.”