Discovery may point to better treatments for type 1 diabetes

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Justin Gregory, MD, left, Jordan Smith, RN, and colleagues are studying a possible new treatment that could lead to better health and longer lives for patients with Type 1 diabetes. Credit: John Russell

Researchers at Vanderbilt University Medical Center led by an assistant professor of Pediatrics have made a paradigm-shifting discovery that could lead to new treatments, better health and longer life for patients with type 1 diabetes.

The discovery by Justin Gregory, MD, and his colleagues, reported this month in the journal *Diabetes*, started with an observation, a hunch and an innovative research effort aimed at revealing the true nature of the disease.

First the observation: While people with type 1 diabetes have high blood glucose because they don't make insulin, they're also "resistant" to replacement insulin. They require more insulin than healthy people to move the same amount of glucose from the bloodstream into muscle, where it's burned as fuel.

Conventional scientific wisdom holds that the major complications of type 1 diabetes, which include blindness, heart disease and kidney failure, are caused primarily by high blood glucose. Gregory, who was diagnosed with the disease 19 years ago, wasn't so sure about that.

"There's more to treating type 1 diabetes than just bringing down high blood sugar," he said.

Epidemiological studies show that high insulin levels and insulin resistance are "tightly entwined with" cardiovascular disease, Gregory said. While the precise cause isn't known, insulin-resistant blood vessels make more inflammatory and clotting factors that contribute to coronary artery disease.

What causes insulin resistance in type 1 diabetes? Gregory's hunch was that it had to do with the way insulin is delivered to muscle. Insulin produced normally by the pancreas first travels through the liver, which cuts the amount of insulin in half before sending it off to the muscle.

That doesn't happen when insulin is injected under the skin in people with type 1 diabetes.

As a result, "I have too much insulin at muscle and not enough at liver—all because I'm putting insulin in the wrong place," he said. "Restoring that balance is important toward helping people with type 1 diabetes reduce their risk of heart disease."

To prove that insulin resistance and its consequences in patients with type 1 diabetes was caused not by high levels of glucose but by high levels of insulin, Gregory and his colleagues compared them to patients with another form of diabetes called GCK-MODY—maturity-onset diabetes of the young.

This form of MODY is caused by a genetic defect in glucokinase (GCK), an enzyme that normally regulates blood glucose levels. People with GCK-MODY can produce insulin, but due to the defective enzyme their blood glucose levels are as high as those who have type 1 diabetes.

Using what are called "clamp" techniques, the researchers adjusted blood glucose to the same level in the two groups then compared their insulin levels. Patients with GCK-MODY had the same level of insulin as did normal healthy controls, indicating that their muscle tissues were equally sensitive to circulating insulin.

But the patients with type 1 diabetes had insulin levels that were two-and-a-half times higher than either the GCK-MODY group or the healthy controls, indicating their tissues were resistant to insulin and required a lot more of it to move glucose out of the bloodstream.

The study "brings to light the need to develop therapeutic strategies to keep the appropriate balance of insulin between the liver and peripheral insulin-sensitive tissues," Gregory said. "We need to come up with ways of delivering insulin that replicate that normal balance of insulin."

One way might be to change the replacement insulin molecule so that

upon injection it goes preferentially to the liver. Another potential way is to implant an insulin pump inside the abdominal space, the area around the intestines. Insulin produced there will also go to the liver first.

A third possibility is to develop an oral insulin with a protective coating that prevents it from being degraded in the stomach and intestines until it can reach the liver.

Gregory said he was guided in his research by his mentors, Alan Cherrington, Ph.D., and Naji Abumrad, MD, who are listed as co-authors on his paper.

Abumrad is professor of Surgery and the John L. Sawyers Professor of Surgical Sciences. Cherrington is the Jacquelyn A. Turner and Dr. Dorothy J. Turner Professor of Diabetes Research and professor of Molecular Physiology and Biophysics.

Researchers at the University of Chicago including Louis Philipson, MD, Ph.D., director of the Kovler Diabetes Center and current president, Medicine and Science, of the American Diabetes Association, were instrumental in helping to identify people with MODY2 to participate in the study.

Others at Vanderbilt who participated included Gregory's research nurse, T. Jordan Smith, who also has type 1 diabetes; Daniel Moore, MD, Ph.D., assistant professor of Pediatrics; James Slaughter, DrPH, associate professor of Biostatistics; Holly Mason; Curtis Hughey; and Marta Smith.

Funding from the National Institutes of Health, including a feasibility grant from the National Institute of Diabetes and Digestive and Kidney Diseases (DK020593), made the study possible. So did the unique resources of the Vanderbilt Clinical Research Center, where insulin

resistance in people with type 1 diabetes was compared to those with MODY2 and normal controls.

"It was such a great dynamic," Gregory said. "Having a group of people with the same purpose but with diverse skills was enormously helpful in being able to get the study off the ground."

Yet Gregory, whose four young children so far are diabetes-free, feels the pressure to do more. In general, Caucasian children have a 1 in 250 to 1 in 500 chance of developing type 1 diabetes. But if one of their parents is diabetic, their risk rises sharply, to 1 in 20.

"That literally hangs over my head all the time," he said. "I feel fortunate that I have a direct stake in what I do, but there are things beyond my control right now. This is one of them."

Provided by Vanderbilt University