As diabetes emerges, researchers track disease's first steps

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Scientists have taken a remarkably detailed look at the initial steps that occur in the body when type 1 diabetes mellitus first develops in a child or young adult.

The analysis comes from a team of researchers and physicians at the University of Rochester Medical Center who have expertise both in the laboratory and in treating patients. The team studied children from ages 8 to 18 within 48 hours of their diagnosis with type 1 diabetes, an autoimmune disease where the body's immune system attacks the cells in the pancreas that make insulin.

The incidence of the disease is rising quickly and has roughly doubled during the last 20 years or so. Approximately 30,000 children each year in the United States are diagnosed with the disease, according to the American Diabetes Association.

The trend is noticeable to pediatrician Nicholas Jospe, M.D., chief of Pediatric Endocrinology at Golisano Children's Hospital of the University of Rochester Medical Center, and his colleagues nationwide. His group now sees about 90 new cases of type 1 diabetes per year, compared to approximately 25 annually 20 years ago.

Every day, at the eastern end of the medical center, Jospe counsels families and children coping with the condition. At the same time, in a labyrinth of laboratories situated nearly half a mile to the west under the same roof, immunologists like Deborah J. Fowell, Ph.D., use an array of

high-tech equipment to interrogate the likes of T-cells and macrophages for answers about the workings of the immune system.

For the current study, published in the journal *Diabetes*, Fowell and Jospe pooled their strengths to look at the disease in a way impossible to do alone. While scientists know diabetes is becoming more common, they don't understand what factors trigger it, why some children are more prone to getting it, or even why it's becoming more common.

Important clues lie within the so-called "honeymoon phase" in newly diagnosed patients, a period when the disease is more easily controlled in patients than at any other time.

While diabetes never fully goes away – unlike other autoimmune diseases that cycle through remissions and relapses – it is marked by a single, early remission phase that starts within weeks of diagnosis and lasts a year or two. During this time, patients are healthy and don't need much insulin to control the disease. This honeymoon period is central to today's efforts to develop new treatments: Most current new treatments in development are aimed at these crucial first months.

"This is a period of great interest," said Jospe. "During this period, blood glucose levels actually normalize more than at any other time, and patients do not require that much insulin; it's as though the body were still producing insulin. But we do not understand the nature of this remission, and that is holding the field back.

"If we knew what was happening, perhaps we could replicate it or prolong it for the benefit of the patient. Most treatments today attempt to do just that – prolong the honeymoon period. But there has not been much success thus far," added Jospe.

In a hunt for answers, Jospe teamed with Fowell, associate professor of

Microbiology and Immunology and a scientist in the Center for Vaccine Biology and Immunology. For Fowell, the corresponding author of the team's report, an important dimension of her research is translating its findings on the basic regulation of immune cells into a better understanding of immunity in human autoimmune disease.

"Making research relevant for patients – improving their lives through new research findings – is not as straightforward as making a finding in the lab, then trying it out in people," said Fowell. "Rather, it involves analyzing laboratory findings and then taking a closer look in people, while simultaneously studying patients and bringing those observations to the laboratory to help shape experiments there. This is what Nick and I are doing – learning from each other as we go to learn more about diabetes."

Fowell's group analyzed several measures of the immune system during the year after diagnosis in 21 children with type 1 diabetes, as well as in 22 healthy children and 70 healthy adults.

The team focused on immune cells known as T-regulatory cells, powerful cells that control how many other immune cells work. They help determine how the body responds to infection and vaccination, and they play the role of super cops of the immune system, disarming immune cells that mistakenly attack the body's own tissues. Fowell is an expert on "T-regs" and highlighted their role in a recent paper in the Proceedings of the National Academy of Sciences.

Since T-regulatory cells are among those charged with suppressing errant immune cells, exploring their function is an important part of understanding autoimmune diseases like diabetes, where the immune system is out of control.

The team found a great deal of variability among the children. In some,

T-regulatory cells appeared to function normally throughout the remission period, while in others, activity appeared low throughout. In still other children, activity dipped during the honeymoon phase but then bounced back.

At the same time, the team witnessed an increase in activity of immune-boosting "effector cells," and increases in cytokines for interleukin 17 and tumor necrosis factor. Such chemical signaling molecules play a key role protecting us from pathogens, but in autoimmune diseases they have a hand in causing tissue damage – in diabetes, for instance, helping to incite the immune attack that destroys the insulin-producing cells in the pancreas.

The mix of results can be interpreted in many ways, said Jospe. One possibility is that the immune system is producing rogue immune cells that can't be well controlled by the T-regulatory cells. Another possibility is that the function of the T-regulatory cells is not up to par, giving wayward cells the opportunity to harm the body.

Jospe and Fowell are hopeful that the results, a series of molecular snapshots of immune activity in patients, will contribute to a better understanding of the disease.

"One hope, of course, is to create better treatments for patients. Another possibility is to find biomarkers to identify children who are at extra risk of developing type 1 diabetes," said Jospe.

Provided by University of Rochester Medical Center