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PREVENTION

Nipped in the bud

While type 1 diabetes might be promising ground for a vaccine, the most effective way to avoid type 2 remains good old-fashioned diet and exercise.

BY SCOTT P. EDWARDS

They share a name, are characterized by elevated blood glucose levels, and carry potentially devastating complications if left uncontrolled. But beyond that, type 1 and type 2 diabetes could not be more dissimilar, says diabetes researcher John Buse, director of the Diabetes Care Center at the University of North Carolina. And perhaps the biggest difference of all, he says, is in their preventability. "With type 1 diabetes, there's an immune process at play," says Buse, "and we don't have effective ways to prevent it. Type 2 diabetes (T2D) has classic risk factors that can be modified to either delay the onset of the disease or prevent it completely."

In the United States, 90–95% of the 17.9 million people diagnosed with diabetes have T2D. Before developing the disease, most people almost always have a related condition, called prediabetes, in which their blood has higher concentrations of glucose than is considered normal, but not high enough to signify diabetes. The American Diabetes Association estimates that 79 million people in the United States have prediabetes and thus are at high risk for developing T2D. Similar to T2D, one of the top risk factors for prediabetes is excess body weight, especially when fat is carried around the abdomen, indicative of physical inactivity and overconsumption. In general, says Buse, people with prediabetes have several problems, including insulin resistance and impaired insulin secretion, so "the train has left the station, and unless these people make changes to reduce their risk, many will keep hurtling down the tracks" towards T2D.

CHANGING LIFESTYLES

Scientists and clinicians have long known that people who change their lifestyle, such as by eating a healthier diet, losing weight and exercising more, lower their chances of developing T2D. Ten years ago, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the US National Institutes of Health, confirmed this point of view when it released the findings of the Diabetes Prevention Program (DPP). This multi-centre clinical research study aimed to determine if lifestyle modifications or treatment with an oral diabetes drug (metformin) could prevent or delay the onset of T2D. The answer was an unequivocal yes to both: according to the NIDDK, "millions of high-risk people can avoid developing type 2 diabetes" by losing 7% of their body weight — and maintaining that loss — by eating less fat and fewer calories, and by exercising for at least 150 minutes per week. The study found that diet and exercise interventions reduced the risk of a person developing T2D by 58%. Lifestyle changes were shown to be particularly effective in older people; those 60 years and older reduced their risk by 71%. The study also found that metformin, an oral drug widely used for the treatment of T2D, can help forestall onset of the disease and reduced risk by 31%, most effectively in young, overweight people.

More recently, researchers in China studied the long-term effects of intensive lifestyle

interventions on the incidence of T2D in those with impaired glucose tolerance, another precursor of T2D (ref. 1). Six years of consuming a diet rich in vegetables and low in alcohol and simple sugar, as well as 20 minutes of moderate exercise, delayed the onset of T2D for as long as 14 years, although the majority of participants still developed T2D.

STOPPING THE UNSTOPPABLE

The evidence is clear on T2D prevention, but the picture with type 1 diabetes (T1D) is opaque. "At this point," says Jay Skyler of the Diabetes Research Institute, part of the University of Miami, Florida, "there is no known way to prevent or lower the risk of developing type 1 diabetes." Studies in animals in which oral insulin is given before diabetes develops, however, have been shown to delay the onset of disease. Given that the immune system reacts differently to drugs whether given in oral form or injected subcutaneously (the normal route of delivery for insulin), Skyler and other scientists suspect that cells in the digestive tract might play an important role in delaying or mitigating the immune response. "When an antigen, in this case insulin, is presented across a mucosal barrier like the digestive tract," Skyler says, "the immune system forms protective immunity [against disease] rather than destructive immunity [such as an autoimmune disorder]."

This hypothesis is supported by recent human research at the University of South Florida in Tampa. Treatment with oral insulin was found to delay the onset of disease in high-risk relatives of people with T1D (ref. 2). The study also showed that oral insulin could postpone the onset of T1D in those with insulin autoantibodies for as long as four years, but once treatment ceased, patients developed T1D at the same rate as those taking a placebo. The task now, says Skyler, is to determine the mechanisms involved. Once the process is better understood, clinicians can assess the proper dosage at which oral insulin becomes an effective preventive therapy.

The South Florida study was a follow-up to the Diabetes Prevention Trial-Type 1, or DPT-1, which ran from 1994 to 2003 under Skyler's direction. The original DPT-1 study helped to establish how to predict T1D risk and provided insight into the immune events that lead to the development of the disease, but it brought scientists no closer to a prevention strategy. One result, for example, was that low-dose insulin injections do not prevent T1D in people who have a high risk of developing the disease within five years.

Because T1D is an autoimmune disease, one option to prevent disease could be vaccines. Many people with T1D have antibodies to an enzyme found in the brain and pancreas called glutamic acid decarboxylase (GAD). Among other things, GAD is an autoantigen, which activates a subset of T cells that react to GAD as an ally rather than an enemy. In T1D, these friendly T cells can quell the attack against the beta cells. However, results of a recent trial using a GAD-based vaccine were less than promising: treatment with an alum-formulated GAD vaccine, which contains an adjuvant to boost the body's response to antigens, did not preserve beta-cell function in patients with T1D (ref. 3). Nevertheless, a phase II trial of another GAD vaccine, called Diamyd (produced by a company of the same name in Stockholm, Sweden), is set to evaluate whether preventive treatment with the vaccine can delay or halt the progression of T1D in children with a high risk of developing T1D.

Preliminary results of another diabetes vaccine study show that it might be possible to reverse T1D using an inexpensive and long-used tuberculosis vaccine. In animal studies, the Bacillus Calmette-Guérin (BCG) vaccine prevented T cells from destroying insulin-producing cells and allowed the pancreas to once again ramp up insulin production. BCG is an attractive vaccine candidate because it raises levels of tumour-necrosis factor (TNF), an immune protein that can suppress the attack on the pancreas. Autoimmunity specialist Denise Faustman of Massachusetts General Hospital in Boston reported at a 2011 American Diabetes Association meeting in San Diego, California, that low doses of the BCG vaccine temporarily increased insulin production in patients who have had T1D for more than 20 years. In a recent study, Faustman showed that the pancreas actually slowly declines over decades, rather than weeks or months[4]. "This is the first clue we've got about how to kill bad T cells in humans with long-term disease and in which the pancreas kicked in to produce insulin," Faustman says. In a phase II trial, which has begun pre-screening subjects, Faustman and her colleagues will see just how far they can encourage the pancreas to re-establish insulin secretion.

"Millions of high-risk people can avoid developing type 2 diabetes" by losing 7% of their body weight.

If Faustman's vaccine can truly restore insulin production, it could in theory serve as the basis for a prophylactic T1D vaccine. "At all stages of diabetes," she says, "we need to slow or prevent the deterioration of the pancreas' ability to produce insulin or, even better yet, restore insulin secretion to higher levels as we have started to do." ■

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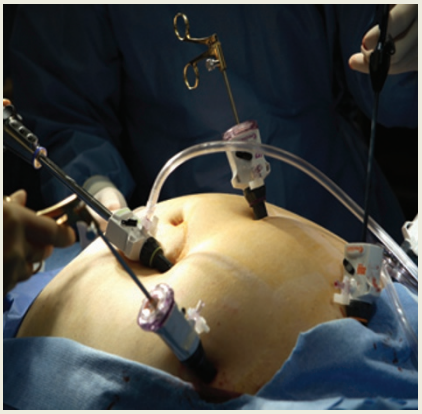
THE SURGICAL SOLUTION

Shrinking the stomach



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Is weight-loss surgery the next step in diabetes prevention? Two new studies reported in the *New England Journal of Medicine* suggest it might be in obese people with type 2 diabetes (T2D).

A team at the Catholic University in Rome compared two weight-loss surgery procedures with typical diabetes treatment[5]. After two years, 95% of patients receiving a biliopancreatic diversion and 75% of those receiving a Roux-en-Y gastric bypass were in disease remission with normal blood glucose levels. Both procedures shrink the stomach to the size of a chicken's egg and bypass portions of the small intestine, restricting food absorption; in addition, biliopancreatic diversion removes part of the stomach. None of the patients in a group receiving only medical treatment — consisting of oral diabetes drugs or insulin, modified diet, and increased physical activity — went into remission.

The second study, conducted at the Cleveland Clinic in Ohio, compared patients who had either gastric bypass or sleeve gastrectomy, which cuts the stomach to the size of a banana, to those who received intensive treatment with diet, exercise and medication[6]. One year after surgery, 42% of the gastric-bypass patients and 37% of those having sleeve surgery were in remission, compared with only 12% of the patients treated but not operated on.

Previous observational studies have shown a connection between weight-loss surgery and reduced incidence of T2D, but there was until now no solid evidence making the connection. "This is an important result," says John Buse, a diabetes researcher at the University of North Carolina. "As a randomized study, it is the first proof of the clinical observations that had previously been made." — *S. P. E.*