

## Bittersweet breakthroughs in diabetes research

As the number of diabetes cases worldwide skyrockets, progress toward understanding the complex disease has been painstakingly slow. But promising new research on the links between obesity, the metabolic syndrome and diabetes could bring new treatments into the fray, experts say.

According to the World Health Organization, more than 176 million people worldwide have diabetes—nearly 95% of which is non-insulin-dependent type 2 diabetes—and the number is expected to more than double in 25 years.

Because diabetes is a complex, polygenic disease, progress has been slow, but steady, says Alan Saltiel, director of the Life Sciences Institute at the University of Michigan. “We are starting to learn about the complex networks of hormones and metabolic states that link diabetes to obesity.”

Researchers increasingly see the fat cell as an endocrine organ that secretes hormones such as leptin, adiponectin and resistin, which have an effect on insulin sensitivity, Saltiel says.

Since the discovery of leptin in the mid-1990s (*Nat. Med.* 10, 116; 2004), scientists have been scrambling to understand how neural brain circuits comprising neuropeptides, various receptors and other molecules influence eating and metabolism. Existing evidence suggests that these circuits send out signals that influence insulin



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sensitivity, says Jeffrey Flier, chief academic officer at Beth Israel Deaconess Medical Center. There are also indications that diabetes is associated with problems in mitochondrial function, and some of the molecules involved are being identified, Flier says. “That holds a lot of promise,” he says.

Another promising avenue of research is investigating whether the metabolic syndrome (see below) is a result of fat deposits in tissues—such as muscles and liver—where they do not belong, says Michael Schwartz, head of clinical nutrition at the University of Washington. Researchers are also studying the beta-cell defect associated with type 2 diabetes, Schwartz says. “If you can figure out

what causes the cells to die and intervene, if you can prevent the progressive deterioration, it would be a breakthrough as well,” he says.

In the meantime, diabetes is still largely treated with insulin injections. Other drugs in use stimulate the pancreas to make more insulin, decrease the amount of glucose produced by the liver, increase insulin sensitivity or slow down starch absorption.

Two of the newer, more promising, drugs target glucagon-like peptide-1 (GLP-1). GLP-1 stimulates insulin secretion, reduces food intake and suppresses the hormone glucagon. One GLP-1 analog (*Nat. Med.* 9, 1228; 2003) is being developed by Amylin Pharmaceuticals, which plans to submit a new drug application to the US Food and Drug Administration in mid-2004. The Novartis Institutes for BioMedical Research’s LAF237, which increases levels of GLP-1, is in phase 3 clinical trials. Other companies such as Merck have similar drugs in clinical trials.

Despite the multiple avenues of research, experts say it will take time to unravel the complex mechanisms underlying diabetes. “I think we are marching steadily forward but it is going to be a long journey,” says Steve Bloom, professor of medicine at Imperial College London. “A lot of metabolic research is going to lead to advances but it will take a decade or two longer.”

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## Experts give metabolic syndrome heavy consideration

Obesity-rated illnesses are set to overtake smoking as the leading cause of death in the US, warned a recent study. As the overwhelming statistics call for urgent action, however, many scientists are questioning the clinical standards for diagnosing the disorders.

For public health purposes, the body mass index (BMI)—albeit an imperfect measure—is used to assess risk of diabetes and cardiovascular disease (see page 325). But several studies now suggest that the ‘metabolic syndrome’ is a better clinical benchmark for those diseases (*Circulation* 109, 42–46 and 706–713; 2004).

Among physicians, “I think the word [about metabolic syndrome] is buzzing around,” says Prakash Deedwania, chief of cardiology at the Veterans Administration Central California Health Care System in Fresno. Studies suggest that more than 20% of Americans and about 45% of those over 50 have the syndrome (*JAMA* 287, 356–359; 2002). But most people

who have it don’t know about it, Deedwania says. “I think there needs to be more of a unified public health message,” he says.

Even among scientists, there is confusion about the exact criteria for the syndrome, says Gerald Reaven, professor of medicine at Stanford University. Reaven in 1988 coined the term ‘Syndrome X’ to define a similar constellation of symptoms associated with cardiovascular risk.

Definitions of the metabolic syndrome continue to change nearly as rapidly as the average waist size in the US. One definition established by a panel of experts in 2001 describes the syndrome as a large waist circumference combined with hypertension, low levels of high-density cholesterol, and high levels of glucose and triglycerides. The World Health Organization’s definition uses the BMI instead of waist circumference, and some other researchers feel that neither the BMI nor waist circumference is particularly useful.

There is increasing evidence that rather than a high BMI or an expansive waist, other components of the metabolic syndrome—such as high triglycerides—are more predictive of cardiovascular risk. Indeed, many people with the syndrome appear healthy, and many are not overweight.

For instance, the metabolic syndrome is closely related to insulin resistance, but the risk for insulin resistance is highly dependent on genetics, Reaven says. About 25% of the risk comes from a lack of exercise, and only 25% from being overweight. Individuals from specific ethnic groups—such as Asian Indians—have the highest risk of developing insulin resistance, although many appear thin.

“People need to look beyond the scale,” says Oscar Marroquin, a cardiologist at the University of Pittsburgh. “Is [the culprit] really obesity or metabolic abnormalities associated with obesity?”

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