Scoring Tools Predict Progression to Diabetes

One CDC-developed system doesn't even require a blood test.

BY ROBERT FINN

LONG BEACH, CALIF. — Identifying patients most at risk for progression to diabetes in 5-10 years may become easier with the development of several scoring systems for quantifying risk.

About 57 million Americans have prediabetes, as judged by impaired fasting glucose level, but only about 10% of them will go on to develop type 2 diabetes within 5 years. Because it's impractical to target all of those 57 million people with intensive interventions, several strategies have emerged to identify those most at risk.

According to speakers at a conference on diabetes sponsored by the Centers for Disease Control and Prevention, some of these strategies appear to get good results. Investigators at the CDC, for example, have developed two simple scoring systems—one of which doesn't even require a blood test—that quantify an individual's chance of developing diabetes within 10 years. And researchers at a private company, Tethys Bioscience of Emeryville, Calif., have developed an algorithm based on seven biomarkers that can categorize individuals as being at high, medium, or low risk for progressing to diabetes within 5 years.

"I think in the U.S. population, our user-friendly scoring systems can really help us to target individuals, at least among blacks and whites, who will benefit most from a prevention program," said Dr. Henry S. Kahn of the CDC. "Our basic system could be used to identify those maybe who should just be escalated … to a simple blood test. You could use the basic scoring system through elementary examinations to find out which subsets of your community are in the greatest need of prevention resources."

Dr. Kahn and his colleagues used 10-year follow-up data from the Atherosclerosis Risk in Communities (ARIC) study, which involved 12,729 U.S. adults who did not have diabetes at baseline. The investigators randomly selected 75% of that cohort to derive their scoring systems, reserving the other 25% to demonstrate that the systems work.

The basic scoring system uses only easily obtainable data, and the enhanced scoring system adds information from simple blood tests. Both systems yield a diabetes prediction score (DPS) from 0 to 100 that represents the chance that an individual would develop diabetes within 10 years.

The basic DPS assigns point values to hypertension, family history, black race, age 55-64 years, smoking history, waist circumference, height, resting pulse rate, and weight. Among the validation cohort, basic DPS scores in the lowest quintile corresponded to a 10-year incidence of diabetes of 5%, while scores in the highest quintile corresponded to a 10-year incidence of 32%.

The enhanced DPS eliminates smoking history and weight from the scoring system and adds point values for height and for levels of blood glucose, triglycerides, HDL cholesterol, and uric acid. Among the validation cohort, scores in the lowest quintile corresponded to a 10-year incidence of diabetes of 4%, while scores in the highest quintile corresponded to a 10-year incidence of 46%.

Dr. Kahn said that if incorporated within public health surveys, either scoring system would likely identify some adults with undiagnosed diabetes and some at elevated risk for cardiovascular disease.

The Tethys test employs a different strategy. After analyzing several large European cohorts, investigators identified seven biomarkers that together form a fingerprint identifying individuals likely to develop diabetes within 5 years. Those biomarkers are levels of fasting glucose, hemoglobin A_{1c}, insulin, adiponectin (associated with obesity), ferritin (associated with cell death, especially in the liver), and C-reactive protein and interleukin-2 receptor–alpha (both associated with inflammation and cardiovascular risk).

Michael McKenna, Ph.D, chief scientific officer at Tethys, explained that physicians interested in ordering the test need only request a blood draw and have a standard 3-mL red-cap tube of serum sent to Tethys's CLIA-approved laboratory.

The test, which is called PreDx, yields a score between 0 and 10 that corresponds to the risk of incident diabetes within 5 years. Among the overall test cohort, 5.7% developed diabetes within 5 years. But that was about 2% among the 54% of individuals judged to be at low risk based on their PreDx score, 7% among the 36% judged to be at medium risk, and 20% among the 10% evaluated as high risk. Individuals with high scores were 16.7 times as likely to develop diabetes as those with low scores.

Dr. Eric Book, Tethys's chief medical officer, said that a report describing these results in Northern European populations was to be published in the June 2009 issue of the journal Diabetes Care. But in order to persuade American health plans to cover PreDx, the company will need to demonstrate that the results hold up in multiethnic populations. Those studies will be conducted during summer and fall 2009, with results being published late in 2009 and in spring 2010.

Dr. Kahn reported that he had no conflicts of interest. Dr. McKenna and Dr. Book are both employees of Tethys Bioscience. ■

Investigational Drug Bests Exenatide in Glucose Control

BY DOUG BRUNK

NEW ORLEANS — Patients with type 2 diabetes who were treated with once-daily liraglutide experienced significantly greater improvements in glycemic control, compared with patients who were treated with twice-daily exenatide, results from an open-label, multicenter trial showed.

The findings of the Effect of Liraglutide or Exenatide Added to an Ongoing Treatment on Blood Glucose Control in Subjects With Type 2 Diabetes (LEAD-6) were reported at the annual scientific sessions of the American Diabetes Association by Dr. John B. Buse, chief of the division of endocrinology at the University of North Carolina, Chapel Hill. They were simultaneously published online (Lancet 2009 [doi:10.1016/S0140-6736(09)60659-0]).

Liraglutide is an investigational human glucagon-like peptide-1 (GLP-1) analogue, developed by Novo Nordisk Inc., that is undergoing Food and Drug Administration review for approval. Its proposed indication is as an adjunct to diet and exercise and for use in combination therapy with oral antidiabetic agents to improve glycemic control in patients with type 2 diabetes.

Exenatide (Byetta, Amylin Pharmaceuticals Inc.) is an exendin-based GLP-1 receptor agonist approved for use by people with type 2 diabetes who are unsuccessful in controlling their blood sugar levels. Both agents are delivered via subcutaneous injection.

Between August 2007 and April 2008, 464 patients aged 18-80 years with type 2 diabetes were randomized to receive liraglutide 1.8 mg once daily or exenatide 10 mcg twice daily at 132 office-based sites in 15 countries. Patients were eligible for the trial if their hemoblobin A_{1c} levels were 7%-11%, if their body mass index was 45 kg/m^2 or less, and if they were on maximally tolerated doses of metformin, sulfonylurea, or both.

Mean reduction in HbA_{1c} was 1.12% in the liraglutide group, compared with 0.79% in the exenatide group.

DR. BUSE

The primary end point of LEAD-6 was the difference in HbA_{1c} values between the two treatment groups from baseline to week 26.

At baseline, the mean age of the patients was 56 years, 92% were white, mean BMI was 33 kg/m^2, and their mean HbA_{1c} level was 8.2%. Of the 464 patients, 231 received exenatide and 233 received liraglutide.

At 26 weeks, the mean reduction in HbA_{1c} was 1.12% among patients in the liraglutide group, compared with 0.79% among patients in the exenatide group, a statistically significant difference. In addition, significantly more patients in the liraglutide group achieved HbA_{1c} levels of less than 7%, compared with their counterparts in the exenatide group (54% vs. 43%, respectively).

The researchers also found that patients in the liraglutide group achieved significantly greater drops in levels of fasting plasma glucose, compared with those in the exenatide group (1.61 mmol/L vs. 0.60 mmol/L). However, exenatide reduced plasma glucose levels more than did liraglutide after breakfast and dinner meals, which suggests that liraglutide exerts more of its effects in the premeal or fasting period.

Weight reductions in both groups were similar, at about 3 kg.

Both drugs were well tolerated, but patients in the liraglutide group experienced less persistent nausea and less frequent rates of hypoglycemia, compared with those in the exenatide group.

In a commentary accompanying the study, Dr. Christophe E.M. DeBlock and Dr. Luc F. Van Gaal of Antwerp University Hospital, Belgium, expressed concerns about FDA reports of increased rates of pancreatitis associated with liraglutide treatment. "Whether the association is causal and whether it is a class effect of GLP-1 analogues is not clear," they wrote (Lancet 2009 [DOI:10.1016/S0140-6736(09)60942-9.]) "We recommend not to give GLP-1 analogues to patients at risk for pancreatitis (e.g., with cholecystolithiasis, alcoholism, or hypertriglyceridemia)."

The commentators also pointed to an FDA briefing noting that the risk rate of frequency of papillary thyroid cancer in patients taking liraglutide is 1.6% per 1,000 patient-years of exposure, compared with 0.6% per 1,000 patient-years of exposure in patients taking exenatide. They recommended that future long-term studies of the agents include careful monitoring of thyroid abnormalities.

At the meeting, Dr. Buse said that there were no signs of elevated calcitonin levels (a marker of medullary thyroid carcinoma) in the study participants. "The calcitonin levels were very low on average and indistinguishable between the two groups," he said.

Dr. Buse disclosed that he has been an investigator, consultant, or speaker for several pharmaceutical companies, including Amylin and Novo Nordisk, the trial's sponsor. Dr. Van Gaal is an adviser to Novo Nordisk and Eli Lilly. Dr. DeBlock declared that he had no conflicts of interest. ■