

A Report From the 45th Annual Meeting of the European Association for the Study of Diabetes

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The 45th Annual Meeting of the European Association for the Study of Diabetes (EASD) attracted an estimated 17,000 participants to the Messe Praten Center located in downtown Vienna. The annual meeting of the EASD is the most important European forum for the exchange of diabetes information. EASD was founded in 1965 to encourage and support diabetes research, to rapidly diffuse acquired knowledge, and to facilitate its application. Its more than 7000 members include scientists, physicians, nurses, laboratory workers, and students. The association publishes the journal *Diabetologia*.

This year's meeting included scientific and clinical papers and posters, special lectures, and symposia presenting updates in clinical care and basic science, as well as important controversies in diabetes medicine. Highlighted in this paper are presentations concerning insulin therapy, other therapeutic advances, and analyses of trends in diabetes care.

Do Diabetes Drugs Affect Cancer Risk?

The idea that diabetes drugs may influence cancer risk is not a new one, but the issue came to prominence after several observational studies, suggesting a link between insulin therapy and cancer risk, were published in *Diabetologia* in June 2009. New data defending the safety of long-acting insulin analogues and research showing anticancer effects of metformin were presented at a symposium entitled "Diabetes Therapy and Cancer."

Reviewing the mechanisms for these effects, Dr. Ulf Smith of Gothenburg University, Sweden, said that, unquestionably, insulin does not cause cancer. However, new research suggests insulin can promote the growth of cells that have already undergone malignant transformation. Transformed cells express both insulin receptors and the highly homologous receptors for insulin-like growth factor-1 (IGF-1), a target for new cancer treatments. Insulin is active at both receptor sites, and insulin resistance causes the alternative IGF-1–promoting pathway to be favored. Metformin appears to have a protective effect and, although the mechanisms for this effect are not fully known, metformin appears to inhibit an important tumor growth-promoting pathway. In a separate presentation, Dr. Jeffrey A. Johnson of the University of Alberta, Edmonton, said that epidemiologic studies indicate that other oral agents may also mediate the relationship between diabetes and cancer—specifically, the glitazones may be associated with reduced cancer incidence, while the sulfonylureas may be associated with increased incidence. The evidence is limited to observational studies, whose limitations are well-known; but clinical trials of thiazolidinediones as possible adjuvant therapy for cancer have begun.

New data on metformin, insulin, and cancer were presented by Dr. Craig Currie of the University of Cardiff in the United Kingdom. An analysis based on The Health Improvement Network (THIN), a large UK primary care database, aimed to establish a dose-relationship between insulin exposure and cancer risk. The analysis included data from ~5000 patients with type 2 diabetes mellitus (DM) on insulin monotherapy, a similar number on insulin plus metformin, and ~30,000 on metformin alone. Insulin dosage was classified by quartiles based on the number of prescriptions per year. In a multivariate analysis that adjusted for other risk factors, cancer incidence was lowest in patients on metformin monotherapy. Compared with the metformin-only group, risk was increased in patients taking insulin plus metformin only at the highest insulin dose level (>15 prescriptions per year, odds ratio [OR] 3.20). In those taking insulin alone, risk increased with every quartile increase in insulin exposure, reaching a maximum OR of 5.73. These findings support but do not prove a causal relationship between insulin and cancer. The data also suggest that metformin may attenuate any potential risk conferred by insulin.

Two speakers presented new analyses of existing data to defend the safety of the 2 major basal insulin analogues—glargine and detemir. The manufacturers of these insulin formulations permitted analyses of their own clinical trial data in response to the *Diabetologia* papers and the resulting adverse media coverage. Dr. Jay Skyler of the University of Miami, Florida, presented information from the sanofi-aventis adverse event database for insulin glargine. The database comprises 31 controlled trials with ~11,000 patients exposed to glargine or comparator drugs for a median of 6 months, including 1 study with 5 years of exposure. Neutral protamine Hagedorn (NPH) insulin was the major comparator drug. The overall relative risk for all cancers in patients taking insulin glargine versus other treatments was 0.90 (not statistically significant). Relative risks with glargine varied for specific cancer types, but none differed significantly from control groups. Twenty-six uncontrolled trials of glargine, with >68,000 exposed patients, were also identified. An analysis of these studies found no difference in overall cancer incidence compared with age- and sex-adjusted Surveillance Epidemiology and End Results (SEER) data on the general US population.

Preclinical studies and limited evidence from clinical trials support the safety of insulin detemir, said Dr. David Russell-Jones of the University of Surrey in the United Kingdom. Clinical data from the Novo Nordisk database include trials in

which detemir was compared with NPH or glargine insulins in patients with type 1 or type 2 DM. In the trials with NPH, after a median 24 weeks of exposure, cancer rates were 0.36 per 100 patient-years with detemir and 0.92 per 100 patient-years with NPH ($P < 0.05$). After a median of nearly 1 year of exposure, cancer incidence with detemir and glargine did not differ statistically.

Other preclinical evidence also supports the safety of detemir, including a ratio of binding to insulin and IGF-1 receptors similar to that of human insulin, as well as low in-vitro mitogenicity in several cell lines.

Costs of Glycemic Control Versus Costs of Complications

The increased costs of maintaining good glycemic control in type 2 DM may be offset by the reduced cost of diabetes complications, according to an analysis of a managed care database by M. Bron of Takeda Pharmaceuticals North America, Inc. Total health care costs were analyzed for >41,000 patients with no history of diabetes complications and no recent medication changes. During up to 3 years of follow-up, ~27% and 45% of patients developed macrovascular and microvascular complications, respectively. The risk of these complications increased by 2% to 3% with each 1% increase in glycosylated hemoglobin (A1C) level. However, overall costs for treatment (ie, facility, provider, and pharmacy costs) did not differ by A1C level. Costs related to treating diabetes complications were highest in patients with the highest A1C levels—up to \$6451 with A1C $\geq 9.0\%$ compared with \$4500 or less with A1C $\leq 7.9\%$. The higher costs for treating complications were balanced by higher initial provider costs in patients who achieved better glycemic control.

Replacing Premeal Insulin With Exenatide

Intensive insulin therapy combining basal insulin with premeal insulin may achieve better glycemic control but at the expense of weight gain and increased risk for hypoglycemia. K. Cusi of the University of Texas, San Antonio, described an open-label trial in which twice-daily exenatide was substituted for premeal insulin in 24 patients with well-controlled type 2 DM who were also taking insulin detemir. Glycemic control (A1C) was similar before and 6 months after the substitution. Patients lost an average of 4.6 kg of body weight. Metabolic laboratory studies at the end of 6 months showed reduced plasma glucose and insulin secretion after a 4-hour mixed meal, improved second-phase insulin secretion, reduced systemic inflammation (C-reactive protein), and reduced steatosis.

Long-term Efficacy of Standard Diabetes Care: The FIELD Study

It is assumed that insulin resistance and impaired α -cell function worsen over time in patients with type 2 DM. However, long-term follow-up of patients maintained on standard therapies suggests this may not be the case, according to J.D. Best of the University of Melbourne, Australia. Members of the placebo control group of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study were followed for 5 years. Fenofibrate is a peroxisome proliferator-activated receptor (PPAR)- α antagonist. The 4900 patients in the control group received standard therapy with metformin, sulfonylureas, and insulin. About 27% of patients were treated with lifestyle measures only at baseline. Use of oral agents increased from 67% at baseline to 77%, and insulin use increased from 14% at baseline to 28%. Median A1C levels in the study cohort were 6.9% at baseline and 7.0% at the end of the study. Median fasting glucose improved significantly over the course of the study, and patients did not gain weight on average. These results suggest that the glycemic benefits of newer treatments should be judged against what is achievable with standard diabetes care.

Clinical Trials: Novel Oral Blocker of Renal Glucose Reabsorption

Two speakers presented the results of clinical trials of dapagliflozin, a novel oral agent that blocks glucose reabsorption from the kidneys. A multinational placebo-controlled trial investigated 3 doses of dapagliflozin as add-on therapy in 546 patients who had inadequate glycemic control on metformin, according to a report by C.J. Bailey of Aston University, Birmingham, in the United Kingdom. After 26 weeks of treatment, average reductions in A1C with dapagliflozin were superior to placebo (0.67%–0.84% vs 0.30%, respectively), and larger proportions of patients achieved the A1C target of <7.0% (33%–40.6% vs 25.9%). The new agent was also associated with clinically significant weight loss (2.7–3.4 kg). Compared with placebo, dapagliflozin was not associated with changes in markers of renal impairment, increases in creatinine, or more hypoglycemic episodes.

Dapagliflozin was also the subject of a pilot study in insulin-resistant patients presented by J.P.H. Wilding of University Hospital, Aintree, in the United Kingdom. This study included 71 persons with type 2 DM poorly controlled with insulin (≥ 50 units/d) plus oral agents. Study subjects were randomly assigned to 12 weeks of treatment with 1 of 2 doses of dapagliflozin or placebo added to their baseline oral agent and with insulin reduced by 50% from the baseline dose. A1C was reduced by a mean of 0.61% and 0.69% for the 2 doses of active drug versus 0.09% with placebo. Dapagliflozin was also associated with decreases in fasting and postprandial plasma glucose and systolic and diastolic blood pressure. Patients lost an average of ~4.4 kg with dapagliflozin and 1.9 kg with placebo.

Liraglutide May Reverse Prediabetes

Prediction and prevention of type 2 DM was the subject of a scientific session at which N. Finer of University College in London described results of a controlled trial of liraglutide. The study was undertaken to investigate the use of liraglutide for weight loss in obese nondiabetic subjects. The effect of liraglutide on prediabetes was a secondary end point. Of 564 study subjects, 175 had prediabetes based on the criteria published by the American Diabetes Association in 2003. By random assignment, patients received 1 of 4 liraglutide doses, an active comparator (open-label orlistat), or placebo for 20 weeks. All patients were advised to exercise more and reduce their caloric intake. Of the patients with prediabetes, 88% to 96% of those randomized to the 3 highest doses of liraglutide reverted to normal glucose tolerance versus 41% with orlistat, 46% with placebo, and 69% with the lowest dose of liraglutide. The proportion of patients progressing from normal glucose tolerance to prediabetes was 2% to 6% with the 4 liraglutide doses, 19% with orlistat, and 23% with placebo. Dr. Finer concluded that treatment with liraglutide may delay the onset of type 2 DM.

This is just a brief highlight of the many topics discussed and papers presented at the 2009 EASD. The 46th Annual Meeting will take place in Stockholm, Sweden, from September 20 to 24, 2010. Information on this upcoming meeting is available at www.easd.org.